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REVIEW

Advances in immune cell-based therapeutic agents for the treatment of inflammation-related diseases

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Abstract Inflammation-related diseases account for over 50% of global disease-associated mortality; the core pathological mechanisms of these diseases are closely linked to functional dysregulation of immune cells such as macrophages and T cells. Aberrantly activated immune cells excessively secrete inflammatory mediators, which drive chronic inflammatory cascades and trigger irreversible tissue damage. In recent years, immune cell-based therapeutic agents (ICTAs) have garnered significant attention due to their inherent targeting specificity and immunomodulatory capabilities, encompassing whole immune cells, cell membranes, or extracellular vesicles serving as active therapeutics or delivery carriers. This review systematically elaborates on strategies for constructing ICTAs through nanoengineering, genetic engineering, and membrane-fused engineering, while outlining their integrating applications with other delivery devices. Furthermore, we summarize the preclinical and clinical trial advancements of ICTAs in various diseases such as tumors, rheumatoid arthritis, diabetes, atherosclerosis, Alzheimer's disease, inflammatory bowel disease, ischemia/reperfusion injury, sepsis, and hemophagocytic lymphohistiocytosis. These insights establish an interdisciplinary design framework for developing clinically applicable ICTAs and propose novel therapeutic approaches for inflammation-related diseases.

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1. Introduction

Inflammation, a central trigger for major diseases including tumors, metabolic disorders, cardiovascular diseases, and neurodegenerative disorders, is responsible for over half of global disease-related mortality[1]. Under normal conditions, physiological inflammation is a critical defense mechanism for the body to eliminate pathogens and repair damaged tissues[2,3]. However, under persistent genetic predisposition or environmental stress, dysregulated release of pro-inflammatory mediators such as IL-1β and TNF-α disrupts inflammatory homeostasis, driving a vicious cycle of "inflammation−immune dysregulation−tissue fibrosis" and leading to severe inflammation-related pathologies, including tumors, rheumatoid arthritis (RA), diabetes mellitus (DM), atherosclerosis (AS), Alzheimer's disease (AD), inflammatory bowel disease (IBD), ischemia/reperfusion injury (IRI), sepsis, and hemophagocytic lymphohistiocytosis (HLH)[2,4-6]. Inflammation is classified based on the nature of its stimulus into infectious inflammation and sterile inflammation. Infectious inflammation is triggered by the invasion of pathogens such as bacteria, viruses, fungi, and parasites. Its core initiating signal arises from pathogen-associated molecular patterns (PAMPs). These PAMPs are recognized by pattern recognition receptors (PRRs) on innate immune cells, leading to the activation of the inflammatory response. Conversely, sterile inflammation results from non-infectious tissue damage, including causes like physical trauma, ischemia−reperfusion injury, chemical insults, or the accumulation of autoantigens and abnormal metabolic products. Its core initiating signal consists of endogenous "danger signals" known as damage-associated molecular patterns (DAMPs), which are released during cell injury or stress. Similar to PAMPs, DAMPs are recognized by PRRs expressed on innate immune cells, subsequently triggering inflammatory cascades[7,8]. Tumors, RA, DM, AS, AD, IRI and HLH are driven by chronic sterile inflammation, while sepsis and IBD are driven by infectious inflammation. Regardless of the initiating cause, inflammation can be divided into three phases (Fig. 1). i) Initiation phase, PAMPs and DAMPs activate cells with immune function, including tissue-resident macrophages, endothelial cells, and dendritic cells (DCs), which recognize pathogen-derived and tissue-damage signals. Tissue-resident macrophages release chemokines (*e.g.*, CCL2, CXCL8) and pro-inflammatory cytokines (*e.g.*, IL-1β, TNF-α, IL-6), and inflamed endothelial cells upregulate adhesion receptors such as P-selectin and E-selectin while secreting pro-inflammatory mediators (*e.g.*, IL-8, CCL2). Together, these cytokines recruit circulating neutrophils and monocytes to infiltrate the inflamed site. Infiltrating monocytes differentiate into pro-inflammatory macrophages, synergizing with neutrophils to clear pathogens or debris *via* phagocytosis. Neutrophils further eliminate pathogens through NETosis, releasing neutrophil extracellular traps (NETs). In addition, PAMPs and DAMPs trigger DCs' maturation, activating $CD8^+$ T cells *via* MHC-antigen peptide-TCR signaling to induce perforin- and granzyme-mediated cytotoxicity. B cells recognize antigens directly *via* the B cell receptor (BCR), internalize and process them, and present the processed antigens to follicular helper T (Tfh) cells through MHC-II. With the help of co-stimulatory molecules such as CD40/CD40L and cytokine signals like IL-21, B cells differentiate into plasma cells and memory B cells, producing high-affinity antibodies. DCs serve as a bridge between innate and adaptive immunity, ensuring the specificity of the immune response and preventing damage to self-tissues. Additionally, by generating memory T cells and memory B cells, they establish long-term immune protection. Collectively, these processes establish a self-reinforcing inflammatory microenvironment. ii) Resolution phase, upon pathogen or debris clearance, macrophages, neutrophils, epithelial cells, and platelets collaboratively synthesize specialized pro-resolving mediators (SPMs), such as lipoxins and resolvins. SPMs suppress NF-κB signaling to induce neutrophil apoptosis and promote macrophage polarization toward an anti-inflammatory phenotype, enhancing their capacity to engulf apoptotic cells and necrotic tissues, thereby preventing excessive inflammation. iii) Post-resolution phase, after inflammation subsides, tissue-resident DCs and macrophages persist for months, modulating the magnitude of subsequent immune responses to maintain homeostasis. Dysregulation at any phase may drive the transition from acute to chronic inflammation, and ultimately contribute to major diseases such as tumors, RA, DM, AS, AD, IBD, IRI, sepsis and HLH[9]. Traditional therapeutic approaches relying on chemotherapeutic agents, nonsteroidal anti-inflammatory drugs (NSAIDs), or glucocorticoids have been limited by their non-selective targeting, often resulting in suboptimal efficacy. This has spurred the exploration of more precise and targeted therapeutic strategies.

Immune system homeostasis disruption represents a shared pathological hallmark of inflammation-related diseases, and immunotherapy has emerged as a promising method. Immune cell-based therapeutic agents (ICTAs) refer to therapeutic agents derived from whole cells, cell membranes, or extracellular vesicles (EVs), which have delivery capabilities or therapeutic functions, and can be engineered *via* nanoengineering, genetic engineering, or fusion engineering. ICTAs, which leverage their superior biocompatibility, diverse surface receptor expression, and unique physiological barrier-penetrating capabilities, have shown the potential to cure a variety of refractory diseases and are currently widely recognized as the most clinically promising treatment strategy. ICTAs are categorized into three classes based on cellular components: i) Whole immune cells as active therapeutics or delivery carriers. These cells migrate to inflamed tissues upon sensing damage signals, enabling targeted pathogen defense while overcoming the limited specificity of traditional nanotherapeutics and enhancing biocompatibility[10-12]. ii) Immune cell membranes as delivery carriers. Through hypotonic lysis, mechanical disruption, freeze-thaw cycles, or sonication, cell membranes are isolated and purified *via* differential or density gradient centrifugation to remove intracellular components (*e.g.*, DNA, mitochondria), retaining targeting functionality while minimizing immunogenicity[13,14]. iii) Immune cell-derived EVs, including exosomes (30−150 nm), microvesicles (200−500 nm), and apoptotic bodies (1−5000 nm), as therapeutics or delivery carriers. EVs inherit parental cell functionalities while their submicron size facilitates them to cross the vascular endothelial barrier and significantly prolong their circulation time *in vivo* by

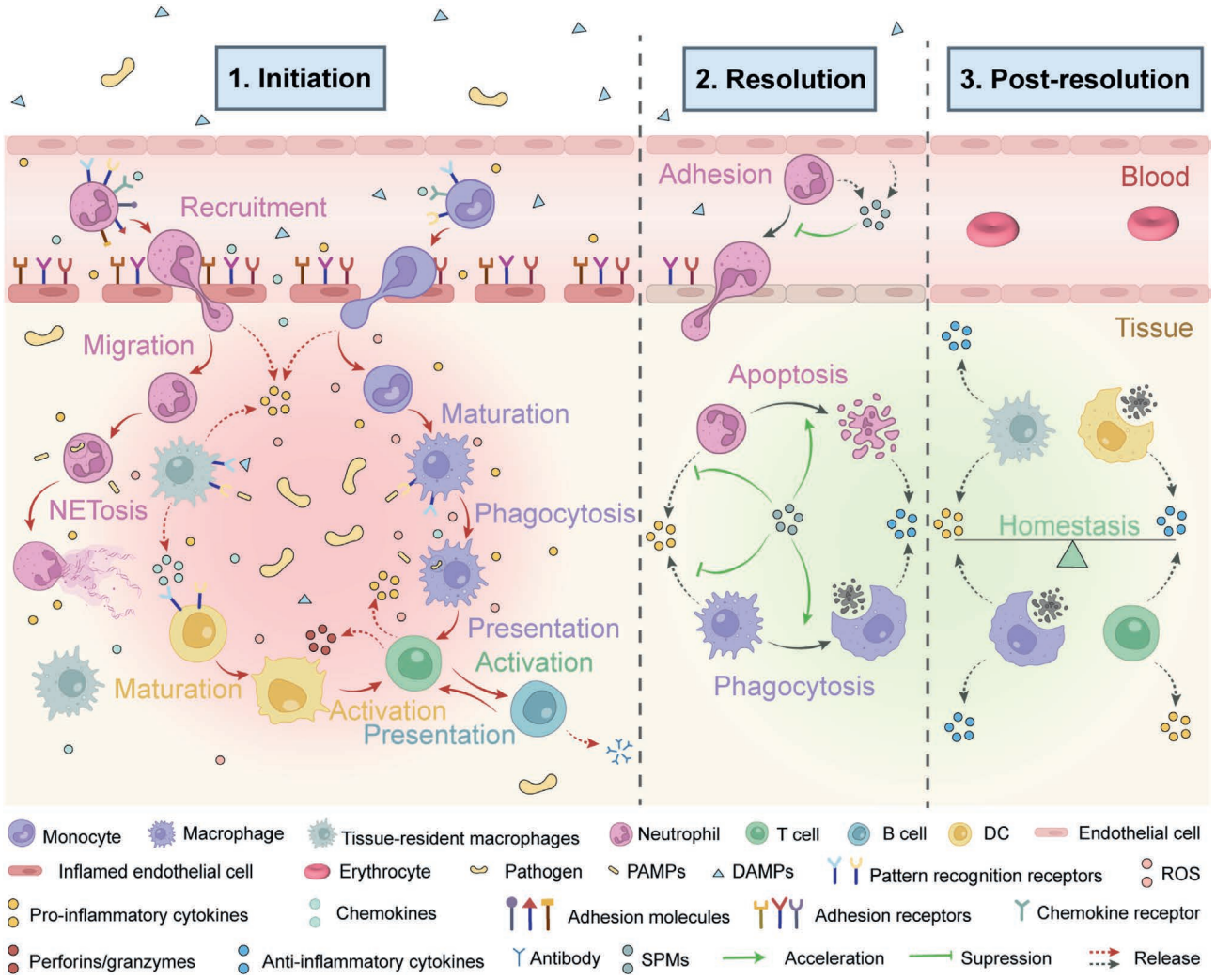

Figure 1 Immune cells mediate inflammation onset and regression. During the initiation phase, tissue-resident macrophages and DCs are activated by PAMPs and DAMPs. These cells then release inflammatory factors (*e.g.*, TNF-α and IL-6) and chemokines, which recruit neutrophils and monocytes to the site of inflammation. Neutrophils and inflammatory macrophages, which are derived from monocytes, collaborate to clear pathogens and debris. Meanwhile, activated DCs trigger the cytotoxicity of $CD8^+$ T cells and the differentiation of $CD4^+$ T cells, $CD8^+$ T cells directly eliminate infected cells, while follicular helper T (Tfh) cells migrate into B cell zones to initiate critical T−B cell collaboration. Together, these actions build and amplify the inflammatory microenvironment. In the resolution phase, after the pathogen has been removed, macrophages, neutrophils, and others synthesise SPMs. SPMs promote neutrophil apoptosis by inhibiting the NF-κB pathway and driving macrophage polarisation towards an anti-inflammatory phenotype, which enhances their ability to remove apoptotic cells. This proactively terminates inflammation and prevents over-reaction. In the post-resolution phase, resident DCs and macrophages persist for a long time, modulating subsequent immune responses to maintain homeostasis. The gray vertical dashed line indicates the division of the inflammatory process into three stages.

escaping capture by the mononuclear phagocyte system (MPS)[15,16]. Crucially, immune cells and their derivatives (cell membranes and EVs) possess the innate ability to precisely sense inflammatory signals, dynamically engage across inflammation stages and actively orchestrate its timely resolution.

This review systematically examines the pivotal role of immune cells in inflammatory cascades. It highlights innovative strategies, including nanoengineering, genetic engineering, and membrane-fused engineering for ICTAs development, alongside their applications with advanced delivery systems (Fig. 2). Furthermore, we summarize the current landscape of ICTAs in treating inflammation-related diseases and outline both opportunities and challenges in clinical translation. We aim to establish a theoretical foundation and technical roadmap for rational ICTAs design, accelerating their transition into safe, effective, and accessible mainstream therapies for inflammation-related diseases.

2. Immune cells associated with inflammation

Inflammation, a critical defense mechanism against pathogen invasion and tissue injury, relies on a sophisticated regulatory network of immune cells to maintain its dynamic equilibrium[17]. Based on the progression characteristics of disease processes, inflammatory responses can be broadly categorized into two distinct types: acute inflammation and chronic inflammation[6]. The former is typically self-limiting in nature, while the latter has been closely associated with the pathogenesis and progression of various major diseases[3,18]. A deeper understanding of immune cell

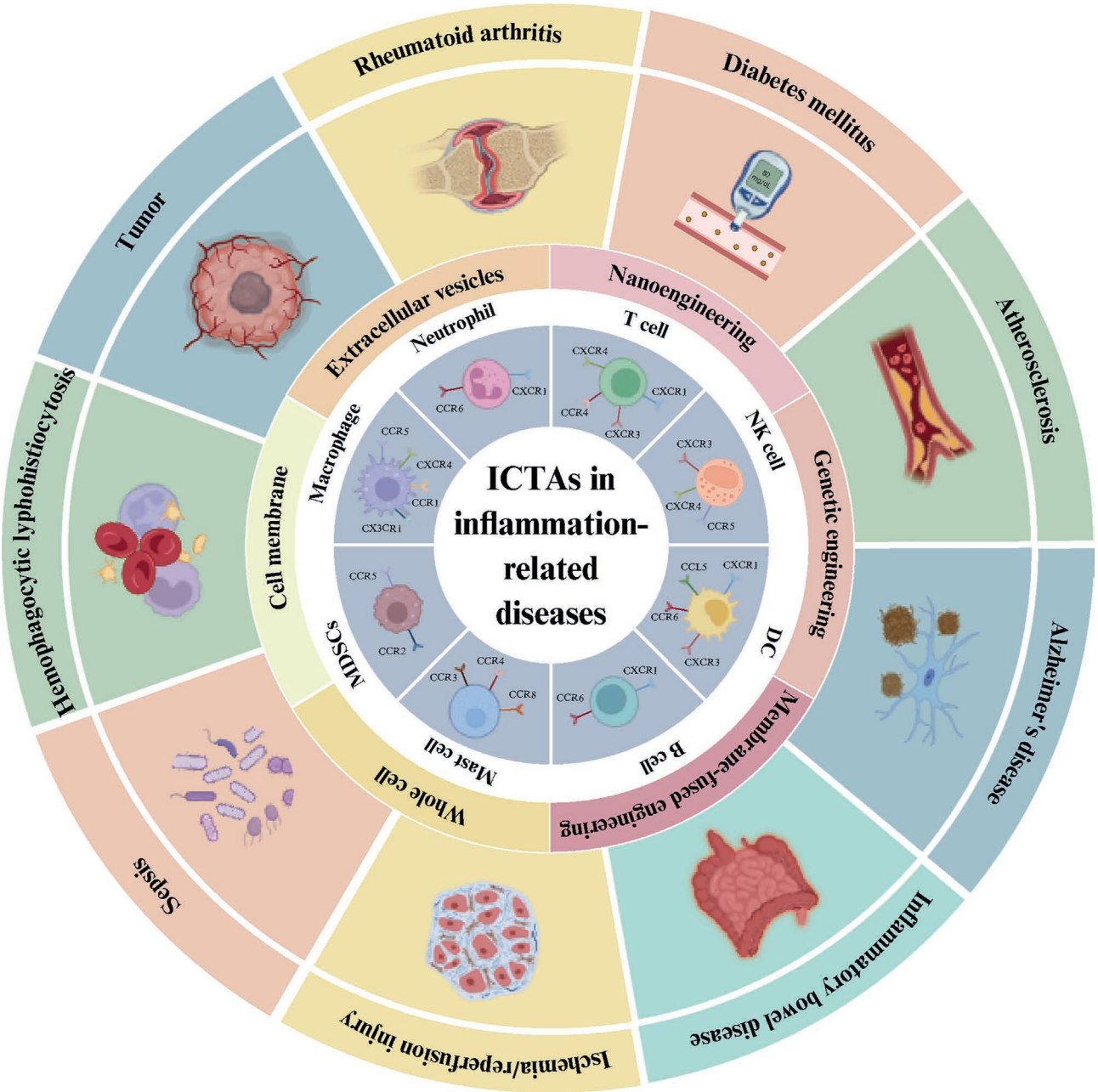

Figure 2 ICTAs for the treatment of inflammation-related diseases. Immune cells, including macrophages, neutrophils, T cells, natural killer (NK) cells, DC, B cells, mast cells, and myeloid-derived suppressor cells (MDSCs), express a variety of chemokine receptors and possess natural inflammatory tropism, enabling them to be engineered as active therapeutic agents or drug delivery vehicles. Through strategies such as nano-engineering, genetic engineering, and membrane fusion engineering, intact cells, cell membranes, or extracellular vesicles can be engineered to construct ICTA systems with specific functions.

regulatory mechanisms across different inflammatory phases holds significant scientific value for elucidating the pathological progression of inflammation-related disorders and developing novel therapeutic strategies.

This section summarizes the biological properties and functions of key immune cells, macrophages, neutrophils, T cells, NK cells, DCs, B cells, MDSCs, and mast cells, and their roles in inflammation-associated pathologies (Table 1), providing a theoretical foundation for precise modulation of inflammatory processes.

2.1. Macrophages

Macrophages, often known as "sentinels" of the immune system, play pivotal roles in eliminating pathogens, apoptotic cells, and metabolites while modulating other immune cells to maintain tissue homeostasis[19,20]. They also possess mature antigen-presenting capabilities, which are crucial in bridging innate and adaptive immunity and driving the progression of inflammatory diseases. For example, macrophages present antigens to naive $CD8^+$ T cells *via* MHC-I molecules and to naive $CD4^+$ T cells *via*

Table 1 Summary of the main immune cell types, and their biological properties, functions, advantages and challenges.

Cell type	Size (μm)	Marker	Lifespan	Function	Advantage	Challenge
Monocytes	10–20	Mouse: $Ly6C^{hi}CD43^{lo}CD11b^{+}CD115^{+}CD62L^{+}$(classical); $Ly6C^{hi}CD43^{hi}CD11b^{+}CD115^{+}$ (intermediate); $Ly6C^{lo}CD43^{hi}CD11b^{+}CD115^{+}CD11c^{+}$(nonclassical); Human: $CD14^{hi}CD64^{+}CD62L^{+}TNFR1^{+}TNFR2^{lo}$(classical); $CD16^{+}CD14^{hi}CD64^{+}$HLA-$DR^{hi}TNFR1^{hi}$ $TNFR2^{+}$(intermediate); $CD14^{lo}CD16^{hi}TNFR1^{lo}TNFR2^{hi}$ (nonclassical)	$CD14^{+}CD16^{-}$: ~1 day; $Ly6C^{hi}CCR2^{+}CX3CR1^{int}$: ~4 days; $Ly6C^{lo}$ $CCR2^{-}CX3CR1^{hi}$: ~7 days	Differentiate into macrophages and DCs; phagocytosis; inflammation tendency; antigen presentation	Differentiability; a specific phagocytic capacity	Differential uncertainty; limited function
Macrophages	10–30	Mouse: $CD11b^{+}F4/80^{+}$; Human: $CD11b^{+}CD11c^{+}CD68^{+}$; $CD86^{+}CD80^{+}iNOS^{+}$(M1-like); $CD163^{+}CD206^{+}$(M2-like)	Several months	Phagocytosis; inflammation tendency; pro-inflammatory and anti-tumor (M1-like); tissue repair, angiogenesis and remodeling (M2-like); antigen presentation	Powerful phagocytic capacity; different functional phenotypes; large volume	Complex phenotype; reprogramming risks; unstable or uncontrolled drug release
Neutrophils	10–15	Mouse: $CD11b^{+}CXCR4^{+}$MHC II^{-} $Gr\text{-}1^{+}Ly\text{-}6G^{+}Siglec\text{-}F^{-}$; Human: $CD11b^{+}CD15^{+}CD16^{+}CD32^{+}CD44^{+}CD66b^{+}$	12–24 h	Degranulation, phagocytosis, releasing reactive oxygen species (ROS) and NETs, inflammation tendency	Rapid response; the most abundant immune cells in circulation	Short life; reprogramming risks; low drug loading efficiency;
T Cells	8–10	Mouse, human: $CD3^{+}$; $CD8^{+}$ (Cytotoxic T Cells); $CD4^{+}$ (helper T Cells, Th); T-Bet $^{+}$ $IFN\gamma^{+}$(Th1); $GATA\text{-}3^{+}IL\text{-}4^{+}$(Th2); $ROR\gamma t^{+}$ $IL\text{-}17^{+}$(Th17); $FoxP3^{+}CD25^{+}$(Treg)	2 weeks after activation	Antiviral; antitumor; immune suppression (Treg); activated antigen-presenting cells (Th1, Th2, Th17); triggering differentiation of biochemical center B cells into antibody-secreting plasma cells and memory B cells (Tfh)	Direct kill; high specificity; immunological memory; multifunctional	Restricted by MHC; exhaustion; autoimmune risk; tumor microenvironment inhibition; cytokine release syndrome (CRS)
NK	12–15	Mouse: $NK1.1^{+}NKp46^{+}NKG2D^{+}CD3^{-}$; Human: $CD56^{+}CD3^{-}$; $CD56^{lo}/CD16^{hi}$ (PB cytotoxic NK cells); $CD56^{hi}CD16^{lo}$ (PB immature NK cells)	1 week	Antiviral; antitumor; inflammation tendency; releases perforin and granzyme	Powerful killing ability; the alloreactivity is relatively low.; resistance to immunosuppression; eliminate senescent cells	Small quantity; difficult to achieve *in vivo* amplification
DCs	10–15	Mouse: $CD11c^{+}$MHC II^{+} (Conventional dendritic cells, cDCs); Siglec $H^{+}CD317^{+}$ (Plasmacytoid dendritic cells, pDCs); Human:	Immature: ~10 h; mature: >100 h	Uptake, processing, and presentation of antigens	Strong antigen presenting ability;	Small quantity; poor targeting; immunoregulation

		$CD11c^+HLA\text{-}DR^+$(cDCs); HLA-DR^+CD123^+(pDCs)				
B Cells	7–10	Mouse, human: $CD19^+$	Immature: 1–5 days; mature: ~40 days	Generate high-affinity antibodies; generate immune memory; act as antigen-presenting cells	Antibacterial and toxin-neutralizing; immunological memory;	Not common as a carrier
MDSCs	10–20	Mouse: $CD11b^+Ly6G^+Ly6C^{lo}$; Human: $CD11b^+Ly6G^-Ly6C^{hi}$	Several days	Immunosuppression	Limiting excessive inflammatory responses	Core immunosuppressive drivers (chronic inflammation/tumor)
Mast cells	10–20	Mouse, human: $Fc\varepsilon R1\alpha^+CD117^+$	Several months	Release histamine; immune tolerance; host defense against toxins and parasitic infections	Early warning and recruitment; immune tolerance	Pro-inflammatory and sensitizing properties

MHC-II molecules. $CD8^+$ cytotoxic T cells induce apoptosis and necrosis in target cells through cytotoxins or cytokines, thereby accelerating progression within AS plaques. $CD4^+$ T cell subsets can influence AS progression through mechanisms such as immune activation or immunosuppression[21-23]. Except for tissue-resident macrophages (*e.g.*, microglia in the brain and Kupffer cells in the liver), which originate from embryonic precursors, most inflammation-associated macrophages derive from blood monocytes. During acute inflammation initiation, PRRs recognize PAMPs and DAMPs, thus activating NF-κB and MAPK signaling pathways in macrophages, and driving the release of pro-inflammatory cytokines (*e.g.*, TNF-α, IL-1β, IL-6), chemokines (*e.g.*, CCL1, CCL2, CXCL8), and oxidative enzymes (*e.g.*, NADPH oxidase, inducible nitric oxide synthase). Further, these mediators recruit neutrophils and monocytes to inflamed sites. In the killing of pathogens, NADPH oxidase-derived superoxide anions synergize with inducible nitric oxide synthase-generated nitric oxide (NO) to form peroxynitrite ($ONOO^-$), directly disrupting pathogen structures. TNF-α further upregulates endothelial expression of adhesion molecules (*e.g.*, ICAM-1, VCAM-1) to facilitate leukocyte extravasation, while IL-1β, IL-6, IL-12, and IL-23 can activate adaptive immunity[24]. During early inflammation resolution, macrophages adopt a "hyperactivated" state, forming gasdermin D (GSDMD) pores on their membranes to release specialized lipid mediators like 11,12-epoxyeicosatrienoic acid (11,12-EET), promoting tissue repair[25]. However, in chronic inflammation, monocytes/macrophages lose repair function, exacerbating tissue damage[26-28].

Under distinct environmental stimuli, macrophages undergo phenotype switching between pro-inflammatory M1-like and anti-inflammatory M2-like states through NF-κB signaling pathway-mediated polarization mechanisms. The pathogenesis of inflammation-related diseases frequently involves dysregulated M1/M2 balance, which provides a mechanistic foundation for developing targeted therapeutic strategies that modulate macrophage polarization[29,30]. Tumor-associated macrophages (TAMs), typically M2-like, secrete immunosuppressive factors to foster tumor progression; shifting TAMs toward M1-like phenotypes has shown therapeutic potential[31-33]. However, the simple M1-like and M2-like category paradigm is not strictly applicable to the *in vivo* situation, and it is particularly important to focus on phenotypic markers beyond the M1-like and M2-like category[34]. Ly6C is a glycoprotein expressed in the middle stages of macrophage direct precursor development, and bone marrow-derived monocytes differentiate into $Ly6C^{hi}$ and $Ly6C^{lo}$ macrophages based on differential expression of Ly6C[35]. In liver injury, $Ly6C^{hi}$ monocytes are recruited and gradually transformed into $Ly6C^{lo}$ macrophages that promote fibrotic regression[36]. Intriguingly, the canonical neutrophil marker Ly6G has been demonstrated to serve as a phenotypic identifier for monocyte-derived macrophage subsets with reparative functions under specific pathophysiological conditions. $Ly6G^+$ macrophages promote alveolar type II epithelial cell proliferation and alveolar epithelial repair through the secretion of soluble factors, including IL-10 and IL-1α, thereby providing a novel therapeutic target for pulmonary injury recovery[37].

2.2. *Neutrophils*

Neutrophils, one of the most abundant leukocytes in peripheral blood, serve as the "infantry" of the immune system, patrolling the bloodstream to defend against pathogens[26,38-40]. Their recruitment to inflammatory sites follows a precisely coordinated process

involving sequential stages of tethering, rolling, adhesion, crawling, and transmigration[41]. During the acute inflammatory phase, PRR-mediated pathogen surveillance triggers vascular endothelial cells to upregulate adhesion molecules P-selectin and E-selectin, which interact with glycoproteins on neutrophil surfaces. However, this interaction has a low affinity (K_d ~100 μmol/L). Under shear stress, this dynamic "tether-release" cycle drives neutrophil rolling along the vessel wall. With continued enhancement of inflammatory signaling, integrin family members on neutrophils, including lymphocyte function-associated antigen 1 (LFA-1), very late antigen 4 (VLA-4), and macrophage-1 antigen (Mac-1), bind to endothelial integrin ligands (*e.g.*, ICAM-1, VCAM-1) expressed on the endothelium to stabilize adhesion. Once fully adherent, neutrophils crawl toward sites with high chemokine concentrations, as regulated by the PI3K pathway. Finally, through ERK pathway-mediated cytoskeletal remodeling, neutrophils cross the endothelial barrier in a deforming movement, completing the process of transmembrane migration to inflammatory tissues[26,41-43].

Similar to macrophages, neutrophils can be categorized into pro-inflammatory N1-like and anti-inflammatory N2-like phenotypes based on surface markers (CD66b/CD11b) and secretion profiles[44]. Untreated neutrophils may be reprogrammed to the N2-like phenotype in the tumor microenvironment (TME) after infusion, exacerbating immunosuppression and posing an additional risk to patients[45]. Under normal conditions, neutrophils undergo apoptosis after phagocytosing necrotic cells to resolve acute inflammation. However, in chronic inflammatory diseases, the overactivation of N1-like neutrophils promotes disease progression, which is associated with dysregulation of NETs[46,47]. NETs are an extracellular web-like structure formed after pro-inflammatory signaling, consisting of DNA, histones, and cytotoxic granule-derived proteins, and their formation is tightly regulated by multimodal receptors, including receptor for advanced glycation end products (RAGE), P-selectin glycoprotein ligand 1 (PSGL-1), Toll-like receptors (TLRs), low-affinity immunoglobulin gamma receptors (FcγR), and sialic acid-binding immunoglobulin-type lectins (Siglecs)[48,49]. In RA, systemic lupus erythematosus (SLE), and coronavirus disease 2019 (COVID-19), myeloid inhibitory C-type lectin-like receptor (MICL) directly recognizes NET-associated DNA to restrain neutrophil activation. However, MICL deficiency or inhibition triggers uncontrolled NETs *via* the ROS−PAD4 axis, fueling autoinflammatory loops and disease progression. Conversely, MICL blockade to enhance NETosis may protect against fungal infections[50]. These insights reveal that targeting key nodes of NETs formation promises to be a therapeutic strategy for NETs-mediated inflammation-related diseases.

2.3. T cells

T cells, derived from bone marrow hematopoietic stem cells, are often hailed as the "main force" of the immune system. After positive and negative selection in the thymus, these hematopoietic stem cells differentiate into naïve $CD4^+$ or $CD8^+$ T cell subsets. Antigenic stimulation drives naïve T cell activation into effector differentiation programs. During the middle-to-late stages of acute inflammation, $CD4^+$ T cells differentiate into multiple subsets: Th1, Th17, Tfh, Th9, Th22, and regulatory T (Treg) cells, orchestrated by combinatorial transcription factors and cytokines. Th1, Th2, Th9, Th22, and Th17 cells orchestrate inflammatory and anti-pathogen responses, while Tfh cells migrate into B cell zones to promote humoral immunity through CD40L and IL-21. Treg cells, however, secrete immunosuppressive factors such as IL-10 and TGF-β to regulate inflammation resolution[51,52].

$CD8^+$ T cells, upon activation, bifurcate into short-lived terminally differentiated effector (TE) cells ($KLRG1^+CD127^-$) and long-lived memory precursor (TMP) cells ($KLRG1^-CD127^+$). TE cells directly eliminate infected or malignant cells *via* perforin- and granzyme-mediated apoptosis, whereas TMP cells further mature into long-lived memory $CD8^+$ T (Tmem) cells, enabling rapid effector differentiation upon antigen re-exposure[53,54]. In chronic inflammatory diseases, $CD8^+$ T cells are gradually depleted and lose their effector function due to continuous antigenic stimulation. At this point, $CD4^+$ T cells counteract this exhaustion by providing help signals through co-stimulatory molecules (*e.g.*, CD27, CD28, 4-1BB, OX-40) and cytokines (*e.g.*, IL-2, IL-21), thereby sustaining $CD8^+$ T cell functionality and memory formation[51]. Notably, the interplay between T cells and the gut microbiota critically influences inflammatory progression[55]. Dysregulated T cell activity in the intestinal mucosa compromises barrier integrity, facilitating bacterial translocation into systemic circulation and triggering systemic inflammation[56].

2.4. NK cells

NK cells, accounting for approximately 1% of total immune cells, are often called the "special forces" of the immune system[57]. Unlike other immune cells, NK cells do not rely on MHC molecules to recognize target cells and depend primarily on the balance between activation and inhibition signals. NK cells retain their killing capacity even in immunosuppressive microenvironments[58]. Under normal conditions, MHC-I molecules on healthy cells bind to inhibitory receptors (*e.g.*, KIR, NKG2A) on NK cells, and inhibitory signaling predominates, suppressing their activation. When inflammation occurs, MHC-I is absent or down-regulated in aberrant cells, activation signals mediated by activating NK receptors (*e.g.*, NKG2D, NKp44, NKp30, and NKG2C) predominate, and NK cells kill aberrant cells[59,60].

CD56, CD16, CD27, CD57, and perforin markers can distinguish their maturation states. Immature NK cells in lymph nodes primarily regulate immune responses, whereas in the circulation, about 90% of NK cells are in a mature state and mainly perform killing functions[61,62]. When in an inflammatory state, mature NK cells are activated to produce cytotoxic responses, releasing perforins and granzymes or killing target cells by inducing death signals, such as TNF-associated apoptosis-inducing ligand (TRAIL)/TRAIL-R and Fas ligand/Fas, effectively eliminating diseased cells. Reduced NK cell numbers or dysfunction correlate with inflammatory diseases such as RA and SLE[63].

2.5. DCs

DCs, derived from hematopoietic bone marrow progenitors, act as the immune system's "liaison officers"[64]. Most DCs remain immature in normal physiology, excelling in antigen capture and processing. By capturing molecular signals released by pathogens or aberrant cells through the PRR, they can initiate maturation programs. Mature DCs have a diminished ability to intake and process antigens and a progressively enhanced ability to present antigens, efficiently presenting pathogen information to $CD4^+$ T cells *via* MHC-class II molecules, as well as developing a unique

cross-presentation ability to load exogenous antigens onto MHC-class I molecules to activate $CD8^+$ T cells, initiating an adaptive immune response. They also secrete pro-inflammatory mediators (*e.g.*, antimicrobials, chemokines) to recruit immune cells to infection sites. DCs are categorized into three subsets: conventional DCs (cDCs), plasmacytoid DCs (pDCs), and Langerhans cells (LCs). cDCs are further divided into cDC1 (specialized in priming $CD8^+$ T cells) and cDC2 (implicated in Treg, Th1, and Th17 activation). pDCs are the primary producers of type I interferons, rapidly suppressing viral replication by releasing large amounts of IFN-α/β within hours of viral infection. LCs, residing in epidermal and mucosal layers, represent a macrophage−DC hybrid population critical for cutaneous immune surveillance[65]. Remarkably, the function of DCs is dynamically regulated by the metabolic microenvironment. In TME, intratumoral glutamine supplementation enhances cDC1-mediated $CD8^+$ T cell immune responses *via* the follicular protein (FLCN), thereby suppressing tumor growth[66].

2.6. B cells

B cells, key players in adaptive immunity, primarily mediate immune responses through antibody secretion. Their development and maturation occur in the bone marrow, where immature B cells expressing IgM-type BCRs undergo central tolerance mechanisms (*e.g.*, clonal deletion) to eliminate autoreactive B cells. Upon antigen stimulation, B cells mature and migrate to peripheral lymphoid organs (*e.g.*, lymph nodes, spleen), differentiating into antibody-secreting plasma cells or long-lived memory B cells, clearing pathogens *via* neutralization, opsonization, phagocytosis, and complement activation[67]. When the tolerance mechanism of immature B cells is defective or mature B cells are abnormally activated, it leads to autoimmune diseases characterized by chronic inflammation[68,69]. For instance, in RA, mature B cells produce autoantibodies such as rheumatoid factor (RF) and anti-citrullinated protein antibodies (ACPAs), driving immune dysregulation[70]. In addition, in some inflammation-related diseases (*e.g.*, tumors), there are tertiary lymphoid structures (TLS), which are structures similar to secondary lymphoid organs (*e.g.*, lymph nodes) formed by the aggregation of local immune cells in non-lymphoid tissues, are mainly associated with mature B cells, and can promote immune cell activation, and closely correlate with disease progression and prognosis[71,72].

2.7. MDSCs

MDSCs are immature myeloid cells, are categorized into polymorphonuclear MDSCs (PMN-MDSCs) and monocytic MDSCs (M-MDSCs). Despite phenotypic and functional differences, both subsets exhibit potent immunosuppressive activity, with PMN-MDSCs being particularly linked to tumor metastasis[73]. During early inflammation, MDSCs suppress T cell activity through multiple mechanisms, thereby mitigating excessive inflammation and tissue damage[74,75]. Growth factors such as GM-CSF, G-CSF, and CSF1 promote the accumulation of MDSCs. Dysregulation of the production of these growth factors and the persistence of inflammatory mediators lead to the amplification and accumulation of MDSCs, thereby triggering chronic inflammation[76]. Cytokines at sites of inflammation, including IL-1β, IL-4, IL-6, IL-13, TNF, and IFN-γ, promote MDSCs expansion while further activating these cells, greatly exacerbating their immunosuppressive function[74].

2.8. Mast cells

Mast cells reside in connective tissues and maintain stable numbers under homeostasis, but expand significantly during inflammation[77,78]. These cells express nine TLRs subtypes, which induce pro-inflammatory mediator production upon activation. For example, TLR2 triggers TNF, IL-4, IL-5, IL-6, and IL-13 secretion, while TLR4 activation upregulates TNF, IL-6, IL-13, and IL-1β[79]. Mast cell-derived factors (*e.g.*, IL-6, CCL3, CCL5, TNF-α)

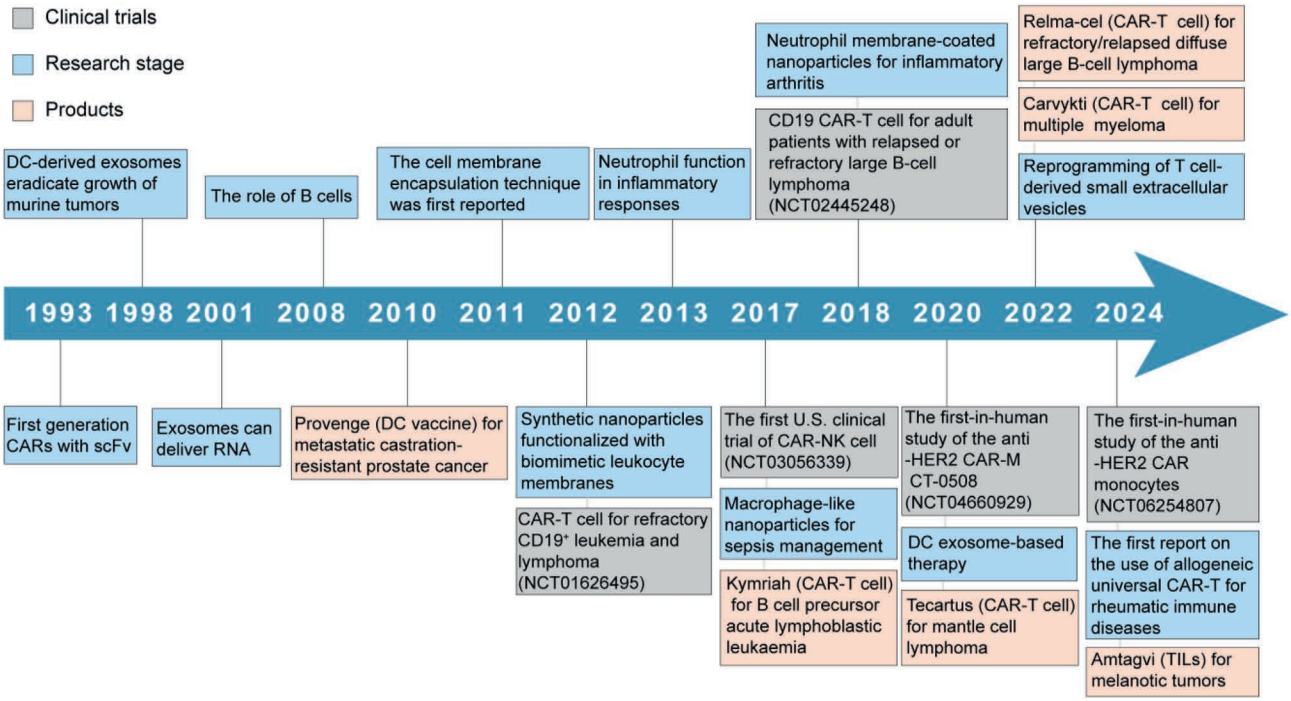

Figure 3 Timeline for the development of ICTAs in inflammation-related diseases.

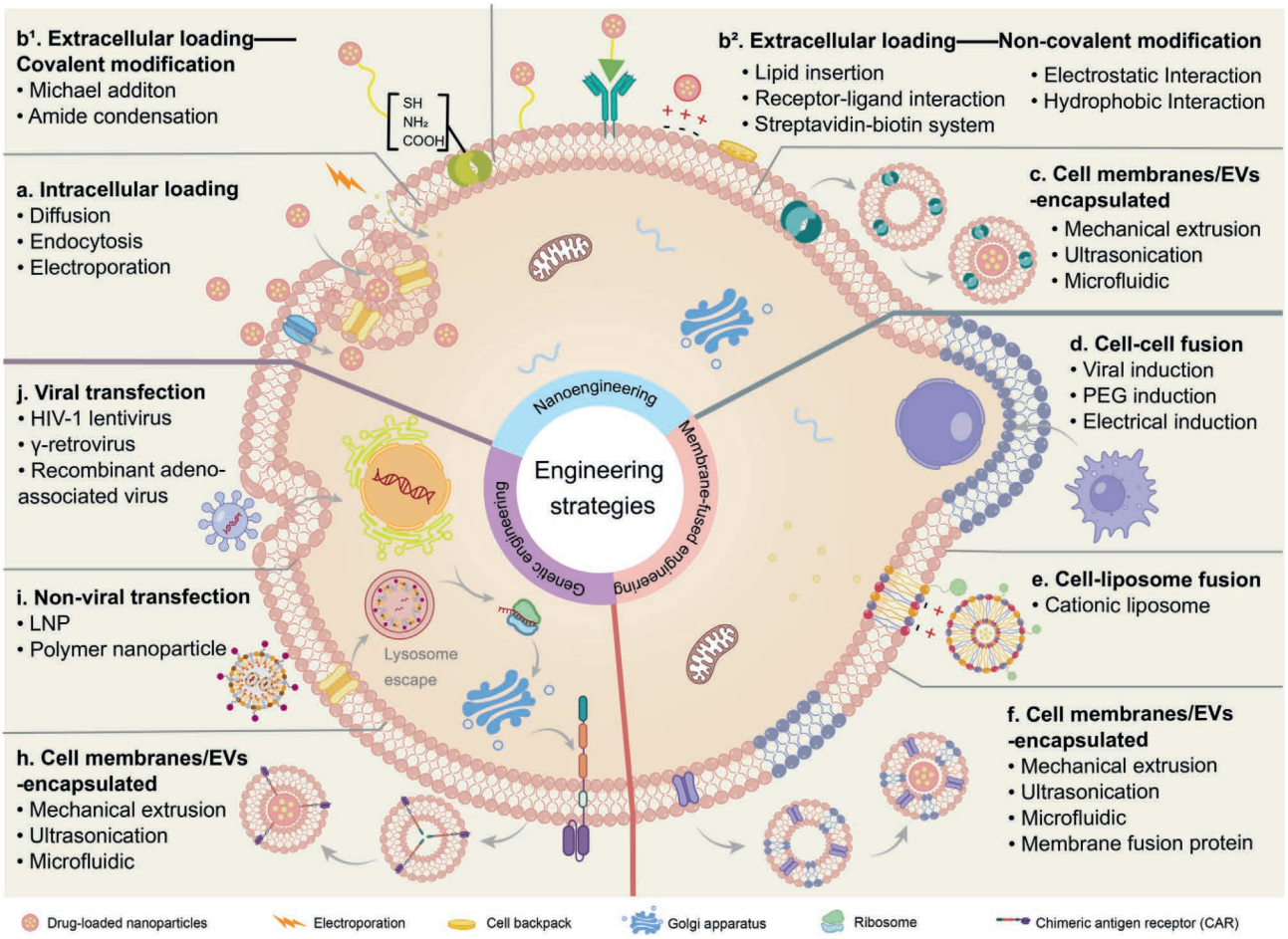

Figure 4 Schematic diagram of the main engineering strategies of ICTAs. These strategies mainly include nanoengineering, genetic engineering, and membrane-fused engineering, which can load drugs in the intracellular space, load drugs on the cell membrane based on covalent and non-covalent interactions, load drugs in the cytoplasm by membrane-fused, and load genetic drugs in the nucleus based on viral and non-viral vector systems. Engineered cell-derived membranes and EVs can also act as active therapeutics or delivery carriers.

critically regulate adaptive immune cells, including B cells, T cells, and neutrophils[80,81]. Although best known for their role in allergies and asthma *via* high-affinity IgE receptor (FcεRI) signaling, mast cells contribute to non-allergic pathologies, especially in autoimmune diseases and cancer[82-84]. Yet, their role in tumors remains controversial, varying by tumor type as well as mast cell localization[85].

3. Engineering strategies of ICTAs

ICTAs have been studied for more than 30 years and have shown potential for important applications in the treatment of tumors and immune-related diseases (Fig. 3). To date, immune cells, including macrophages, neutrophils, T cells, NK cells, and DCs, along with their membranes or EVs, have been engineered as active therapeutics or delivery carriers of active pharmaceuticals[86].

Whether utilizing whole immune cells, cell membrane, or EVs, it is possible to enhance the function and viability of ICTAs through nanoengineering, genetic engineering, and membrane-fused engineering, to further improve the effectiveness and safety, and to continue to advance the basic research and clinical translation of ICTAs (Fig. 4). Table 2 summarizes the application paradigms of these engineering strategies in ICTAs development, the selection of the strategies can be found in Table 3.

3.1. Nanoengineered ICTAs

Nanoengineered ICTAs are formed by loading nanomedicines onto the interior or surface of whole cells, cell membranes, or EVs. On the one hand, the nanomedicines can improve the stability of the loaded drug and reduce the effect of free drug on the physiological function of the cells; on the other hand, they can effectively integrate the natural chemotaxis ability of the immune cells and their components, and significantly increase the active target accumulation of the drug. Nanomedicine refers to agents made from nanomaterials that are used for the prevention, treatment, and diagnosis of diseases. To date, diverse nanomaterials, including lipid nanoparticles, polymeric nanoparticles, gold nanorods, upconversion nanoparticles, nanocrystals, quantum dots, silica nanoparticles, and nanodiamonds, have been widely integrated into ICTAs, effectively inhibiting disease progression in inflammation-related diseases without compromising immune carrier functionality[87-93].

It is important to note that, the inflammatory tissue microenvironment often exhibits weak acidity (pH 5.0−6.5), upregulated proteases (*e.g.*, matrix metalloproteinases (MMPs), cathepsins), and elevated glutathione (GSH) levels, providing endogenous

Table 2 Application of different engineering strategies.

Engineering strategy	Types of ICTAs	Strategy	Cell source	Active composition	Application	Ref.
Nanoengineering	Whole cell	Intracellular loading	BMDNs	IR780 molecules and TRP-2 peptide liposome	Melanoma	215
	Whole cell	Extracellular loading	Th17 cells	Aminooxy-acetic acid	Multiple sclerosis	216
	Whole cell	Extracellular loading	NK-92MI cells	IL-21 nanoparticles	Burkitt's lymphoma tumor	126
	Whole cell	Extracellular loading	BMDNs	Urokinase-coupled silver nanoparticles	Thrombotic diseases	123
	Whole cell	Extracellular loading	RAW246.7 cells	*E. coli* Nissle 1917	Breast tumor	217
	Whole cell	*In vivo* loading	Circulating monocytes	DOX·HCl	Glioblastomas (GBMs)	131
	Whole cell	*In vivo* loading	Circulating neutrophils	DNase I	Ischemic stroke	218
	Cell membrane	Membrane-encapsulated	Macrophages	Polylysine-modified BSA NPs	Type 2 diabetes (T2D)	219
	Cell membrane	Membrane-encapsulated	Circulating neutrophils	Celastrol	RA	220
	Cell membrane	Membrane-encapsulated	CTLL-2 cells	Curcumin	Melanoma	221
	Cell membrane	Membrane-encapsulated	BMDCs	Rapamycin	Glioma	222
	Cell membrane	Membrane-encapsulated	BMDCs, cancer cell	PLGA nanoparticles	Melanoma, HCC, cervical cancer	223
	EVs	Exosomes-encapsulated	NK-92MI cells	Cisplatin	Ovarian cancer	224
	EVs	Exosomes-encapsulated	RAW246.7 cells	Silibinin	AD	225
	EVs	Microvesicle-encapsulated	RAW246.7 cells	TNF-α and IL-6 siRNAs and PB nanoparticles	RA	226
	EVs	Surface-modified exosomes	BMDNs	Sub-5 nm ultrasmall PB nanoparticles	RA	227
	EVs	Surface-modified exosomes	DC2.4 cells	DOX and gefitinib	Lung cancer	228
Genetic engineering	Cell	Viral transfection	Tregs	Insulin-specific CAR	T1D	229
	Cell	Non-viral transfection	Peripheral blood B cells	Alpha-L-iduronidase	Mucopolysaccharidosis type I	230
	EVs	Viral transfection	hPB-T cells	EGFR and HER2 CAR	Breast tumor	190
Genetic engineering & nanoengineering	Whole cell	Extracellular loading	Splenic T cells	CD19 CAR	Burkitt's lymphoma tumor	231
	Whole cell	Extracellular loading	T Cells	Human interleukin-15 super-agonist	Melanoma	232
	Cell membrane	Membrane-encapsulated	CTLL-2 cells	IFN inducer ORY-1001	Triple-negative breast cancer, melanoma, and colon cancer	233
	Cell membrane	Membrane-encapsulated	hPB-T cells	Glypican-3 CAR, IR780 loaded mesoporous silica materials	HCC	234
Membrane-fused engineering	Whole cell	Cell-cell fusion	DC2.4 cells, Hepa1-6 cells	Tumor-associated antigens in HCC	HCC	199
	Cell membrane	Cell-liposome fusion	RAW264.7 cells, lipidated peptides	Simvastatin	AS	235
Membrane-fused engineering & nanoengineering	Cell membrane	Membrane-encapsulated	RAW264.7 cells, BMDNs	Rapamycin-loaded PLGA nanoparticles	Glioma	236

BMDNs, bone marrow-derived neutrophils; TRP-2, tyrosinase-related protein 2 peptide; DOX, doxorubicin; BMDCs, bone marrow-derived DCs; CAR, chimeric antigen receptor; PLGA, poly (lactic-*co*-glycolic acid); DNase I, deoxyribonuclease I; BSA NPs, bovine serum albumin nanoparticles; PB, prussian blue nanoparticles; hPB-T cells, human peripheral blood T cells; HCC, hepatocellular carcinoma.

Table 3 Advantages and limitations of engineering strategies.

Strategies	Characteristics	Methods	Applications	Advantages	Limitations
Nanoengineering	Improve the stability and increase the active target accumulation of the nanomedicines	Intracellular loading	Load nanomedicines inside cells	Achieve targeted drug delivery, penetration of biological barriers, and evasion of systemic clearance	Possibilty of drug degradation after phagoctytosis; potential toxicity to cell vector
		Extracellular loading	Load nanomedicines on the surface of cells	Enable stable loading of nanomedicines to the cell surface (covalent/non-covalent), protecting drug stability from intracellular degradation and preserving cell viability.	Easy to be engulfed, degraded and cleared, uncontrollable release, high cost
		In vivo loading	Load nanomedicines *in vivo* by hijacking immune cells	Rapid administration, established technology, easy fabrication	Limited loading efficiency, potential toxicity
		Membrane/EVs-encapsulated	Coat the membrane/EVs onto the outer layer of the nanoparticle	Biocompatible, crossing biological barriers	Limited extraction, limited loading efficiency, uncontrollable release, complex manufacturing process
		Surface-modified membrane/EVs	Achieve simultaneous drug loading inside and outside the membrane	Enhance targeting	The stability of the membrane structure may be compromised.
Genetic engineering	Selective gene depletion or expression	Viral transfection	Mainly used for *ex vivo* cell therapies, especially cells that are hard to transform	High transfection efficiency, long-term stable and transient expression	Insertion mutation risk, immunogenicity, carrier capacity limit
		Non-viral transfection	Mainly used for *in vivo* cell therapies, superior biosafety and clinical translational potential	Transient high expression, deliver large segments,	Low transfection efficiency, off-target effect,
Membrane-fused engineering	Rapidly combine the functional properties of distinct membranes	Fusion protein induction	Achieve functional proteins or nucleic acids delivery to cell membranes or the cytoplasm	High efficiency	Immunogenicity
		PEG induction and other chemical fusogens	Fuse diverse cell types, extensively applied in tumor vaccines	Non-selective fusion	Low efficiency
		Electrical induction and other physical methods	Fuse diverse cells and cell membranes	Moderate fusion efficiency, requires fewer cells	Rely heavily on specialized instrument
		Cationic liposomes	Achieve surface modification while directly delivering drugs into the cytoplasm	Fuse both *in vitro* and *in vivo*	Unintended intracellular responses

triggers for stimuli-responsive drug release. At the same time, exogenous stimuli (*e.g.*, temperature, light, magnetic field, electrical, mechanical, and ultrasound) can precisely modulate the spatiotemporal release of drugs. Yu et al.[94] have loaded the anti-tumor drug decitabine and the photothermite IR820 *via* disulfide-bonded cross-linking of bovine serum albumin and surface-modified anti-CD11b antibody to target neutrophils in the blood circulation to form drug-loaded neutrophils (ANP nanovehicle) *in vivo* (Fig. 6A), the ANP nanovehicle can be tracked in real time by IR820-mediated near-infrared fluorescence imaging. When reaching the tumor area, 808 nm laser irradiation triggers neutrophils to release ANP by cellular pyrolysis, and under the stimulation of high glutathione content in TME, the disulfide bond is broken, thus releasing the drug, which can play a synergistic efficacy of photothermal-chemotherapeutic. Such strategies combining endogenous responsiveness and exogenous energy modulation

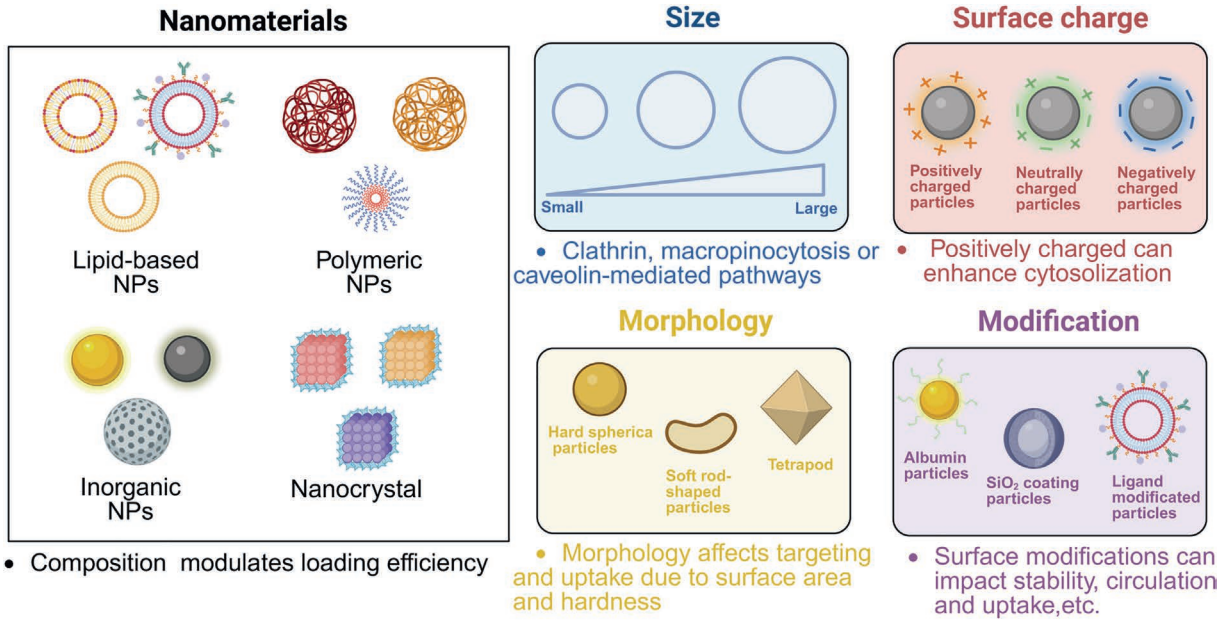

Figure 5 Main physicochemical properties that affect the delivery efficacy of nanomaterials. Composition, size, surface charge, morphology and modification can influence the intracellular delivery efficacy of nanomaterials.

highlight the potential of nanoengineering ICTAs for precise, visualized therapies. Nevertheless, current challenges include optimizing immunogenicity control, preserving cellular functionality, and ensuring long-term biosafety. Overall, nanoengineering ICTAs has opened new frontiers in treating inflammation-related diseases.

3.1.1. Nanoengineering of whole immune cells

Nanoengineered formulations based on whole immune cells are prepared *via* intracellular loading, extracellular surface conjugation, or *in vivo* loading. These approaches preserve the native viability and chemotactic functions of immune cells while achieving efficient drug encapsulation in the cytoplasm or on the cell membrane.

Intracellular loading strategies: Intracellular loading strategies primarily employ passive diffusion, protein-mediated endocytosis, or electroporation for drug encapsulation. Passive diffusion relies on concentration gradients between intra- and extracellular environments, only applicable to small molecules or lipophilic substances with limited loading efficiency[95]. Protein-mediated endocytosis, driven by clathrin or caveolin pathways, offers higher selectivity and efficiency[96]. Conventional electroporation generates micron-sized pores in cell membranes *via* high-intensity electrical pulses, but risks membrane damage[97]. In contrast, cellular nanoporation (CNP) uses low-intensity pulses to transiently form nanopores, enabling high-efficiency loading of diverse cargoes (*e.g.*, mRNA) with minimal cytotoxicity[98]. Currently, protein-mediated endocytosis is the most widely adopted strategy to load nanomedicines. Hou et al. [99] have engineered M1-like macrophages (M1/SLNP) to internalize sorafenib-loaded lipid nanoparticles (SLNPs) *via* caveolae-mediated and clathrin-mediated uptake, achieving a drug loading of 38.18 ± 0.80 μg/10^6 cells (Fig. 6B). The M1/SLNP demonstrates an 85.02% tumor suppression rate *in vivo*, outperforming free SLNPs (54.04%) and M1-like macrophages alone (42.49%), thus pioneering a novel paradigm for ICTAs-based chemoimmunotherapy.

The intracellular delivery efficacy of nanomedicines depends on nanoparticle size, surface charge, morphology, and composition (Fig. 5). Normally, particles between 20 nm and 1 μm are rapidly internalized[100]. When the particle size is larger than 100 nm, endocytosis mainly relies on clathrin or macropinocytosis, whereas particles smaller than 100 nm utilize caveolin-mediated pathways[101,102]. Owing to the cell membrane is negatively charged, positively charged nanoparticles can enhance cytosolization by electrostatic adsorption, and thus their internalization efficiency is significantly higher than that of neutral or negatively charged particles[103]. Morphological studies of nanomedicines have shown that hard spherical particles are more likely to be phagocytosed compared to soft rod-shaped particles due to their wider contact surface with the cell membrane and the fact that they do not require significant actin remodeling[104]. Lipid composition also modulates loading efficiency. For instance, inverse-phospholipid liposomes (*n*-DOCPs) expose hydrophobic regions by rearranging phospholipid headgroups, enabling targeted adsorption of inflammatory opsonins (*e.g.*, C3b complement fragments) and achieving 70.4% of *n*-DOCPs targeting activated neutrophils[105]. Surface modifications or structural design also affect loading efficiency: BSA-coated nanoparticles reduce nonspecific protein adsorption of serum proteins while promoting neutrophil recognition *via* Fc or complement receptors[106]. Modification of nanomedicines with cell-penetrating peptides or ligands can further enhance cellular uptake efficiency. For example, R8-modified PEGylated liposomes (R8-Lip) showed a total drug payload of 63 μg/10^6 cells in macrophages[107]. Furthermore, asymmetrically arranged nanostructures are more susceptible to phagocytosis than symmetric nanoparticles due to rough surfaces that activate the complement alternative pathway[108]. These insights provide multidimensional design principles for precise nanomedicine−cell interactions.

Also, the intracellular loading strategy must consider whether the drug can be released from the cell as expected. For instance, macrophages require at least 6 h to migrate to the site of

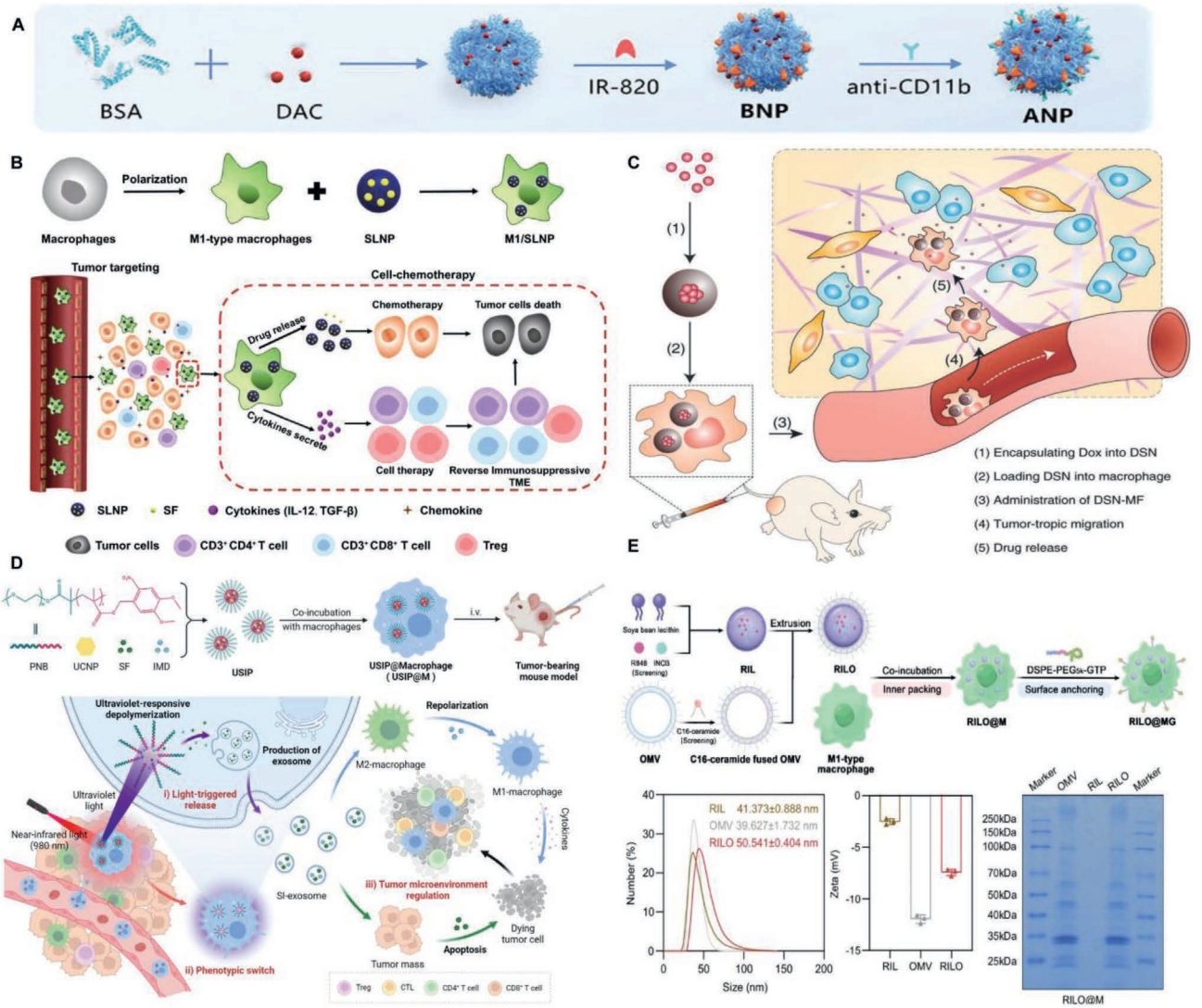

Figure 6 Examples of intracellular loading strategy in nanoengineered whole immune cells. (A)The preparation of anti-CD11b-nanoparticles (ANP) nanovehicles. Reprinted with the permission from Ref. 94. Copyright©2023, John Wiley and Sons. (B)M1/SLNP enhance the therapeutic efficiency of HCC. Reprinted with the permission from Ref. 99. Copyright©2020, Springer Nature. (C) Schematic illustration of DSN-MΦ for tumor targeting delivery. Reprinted with the permission from Ref. 109. Copyright©2018, John Wiley and Sons. (D) Localized light-controlled USIP@M induced the polarization of macrophage carriers and the apoptosis of tumor cells. Reprinted with the permission from Ref. 115. Copyright©2024, Elsevier. (E) Schematic illustration of the preparation process of RILO@MG.Reprinted with the permission from Ref. 116. Copyright©2024, Springer Nature.

inflammation following intravenous injection. Zhang et al.[109] have developed a drug-silica nanocapsule platform that delays drug release by increasing silica coating thickness to address this (Fig. 6C). The nanocapsule-loaded macrophages (DSN-MΦ) maintain functional homeostasis (viability >95%, unimpaired migration efficiency) for 24 h and achieve sustained release of over 50% doxorubicin (Dox) within 48 h, precisely aligning with therapeutic time windows. Drugs can be released by cell damage, transcellular diffusion or exocytosis and through tunneling nanotubes[110-113]. Xue et al.[114] have engineered neutrophils internalized with paclitaxel (PTX)-loaded cationic liposomes (PTX-CL/NEs). These PTX-CL/NEs become hyperactivated upon sensing elevated pro-inflammatory cytokines (*e.g.*, IL-6, TNF-α) in postoperative gliomas, triggering NETs formation to destroy the cells and release PTX-CL. In terms of responsive release, Liu et al.[115] have synthesized ultraviolet-responsive amphiphilic block copolymers (PNB) containing *ortho*-nitrobenzyl groups. These polymers are co-loaded with sorafenib (SF, a multi-target tyrosine kinase inhibitor), IMD-0354 (a macrophage polarizing agent), and upconversion nanoparticles (USIP) to form a nanotherapeutic system. Further co-culture with macrophages generates a photoactivatable drug delivery system (USIP@M) (Fig. 6D). USIP@M macrophages target tumors *via* the CCL2/CCR2 axis, and upon near-infrared irradiation, the upconversion nanoparticles emit ultraviolet light to disassemble PNB, stimulate drug release in the form of exosomes, while preserving macrophages' immunotherapeutic activity. In mouse skin melanoma cells B16F10 tumor-bearing mice, USIP@M achieves a tumor suppression rate of 92.82 ± 1.75%, significantly outperforming the macrophage-only (23.44 ± 3.79%) and USIP-only (49.15 ± 3.43%) groups.

It is of concern that nanomedicines that rely on endocytosis for intracellular loading usually undergo lysosomal degradation to release the drug, and this would affect cellular activity or disrupt the drug combination ratio. To circumvent this, Liu et al.[116] have developed a nanoengineered macrophage formulation (RILO@MG) with surface-anchored glypican-3-targeting peptides and tumor-therapeutic drug payloads (Fig. 6E). Surface-anchored glypican-3-targeting peptides enhance tumor cell recognition, boost specific targeting and the phagocytosis of glypican-3-overexpressing cancer cells. The RILO@MG carries a cargo of the TLR7/TLR8 agonist R848 and 2,3-dioxygenase 1 (IDO1) inhibitor INCB024360, wrapped in C16 ceramide-enriched outer membrane vesicles derived from FimH-positive *E. coli* MG1655 (RILO). Just as FimH-positive *E. coli* evades macrophage clearance by binding to the glycosylphosphatidylinositol-anchored protein CD48 on macrophages, RILO similarly avoids lysosomal degradation within these cells. Furthermore, RILO exhibits strong colocalization with the Golgi apparatus, supported by a Pearson correlation coefficient of 0.78, indicating that the majority of RILO is trafficked to the Golgi. At tumor sites, C16 ceramide induces negative curvature in phospholipid bilayers, triggering membrane invagination and intraluminal vesicle formation, which facilitates drug release from macrophages in the form of exosomes. This study pioneers the regulation of drug-carrying exosome generation, revealing a new form of drug release from nanoengineered whole immune cells and laying a key theoretical foundation for the development of cytopharmaceuticals for the treatment of solid tumors.

Extracellular loading strategies: The cell membrane, enriched with lipids, polysaccharides, and proteins, possesses functional groups (*e.g.*, amines, thiols, carboxyls) and unique surface properties (*e.g.*, negative charge, phospholipid bilayer, ligand-binding sites). These features enable stable covalent or non-covalent loading of nanomedicines onto the cell surface, minimizing adverse effects of intracellular environments on drug stability while preserving cellular viability[117].

Covalent modification refers to the stable binding of functional molecules (*e.g.*, targeting ligands, fluorescent probes, therapeutic drugs, etc.) and their nanomedicines to the surface of the cell membrane through chemical bonds (*e.g.*, amide bonds, thioester bonds, click chemistry bonds, etc.)[118]. Yang et al.[119] have utilized the azide-dibenzocyclooctyne (DBCO) click chemistry to covalently modify a glycopolymer on the surface of azide-labeled DCs, which interact with T-cell surface receptors (*e.g.*, mannose-6-phosphate receptor, the family of NK cell-associated receptors, NK-like C-type lectin-like receptor, and the family of sialic acid-binding immunoglobulin-like lectins) to enhance adhesion between DCs and T cells significantly. Thanks to the stability of the covalent bonds, the glycopolymer modification can be maintained on the DCs' surface for more than 48 h, sufficient to fully activate the anti-tumor response of $CD8^+$ T cells.

Non-covalent modification of the cell surface refers to the loading of functional molecules onto the cell membrane surface by lipid insertion, affinity/streptavidin-biotin system, electrostatic, hydrophobic forces or receptor−ligand interaction, which provides a simple and mild modification strategy for the functionalization of the cell surface. Wang et al. [120] have utilized the property of long hydrophobic lipid chains to anchor and insert into cell membranes. The DSPE-PEG-modified cucurbituril (CB) artificial receptor is inserted into macrophages by co-incubation to obtain a supramolecular artificial receptor macrophage (SAR-Macrophage). The host-guest interaction between CB and adamantane (ADA) ligand is used to significantly enhance the macrophages' recognition and capture of ADA-pre-modified *Escherichia coli*. However, the hydrophobic lipid-anchoring strategy, which relies solely on inserting lipid tails into cell membranes, significantly limits drug-loading capacity. Xu et al.[121] have engineered RAW264.7 murine monocytic leukemia cells by inserting the prodrug DMPE-PEG-GPARC-S-S-DM4 into their outer membrane, creating the RDM system (Fig. 7A). The lipid-conjugated molecules cover only $8.82 \pm 6.99\%$ of the cell surface, achieving a total drug payload of 0.39 ± 0.02 μg/10^6 cells, which results in limited therapeutic efficacy. Specific immune cells can also be targeted with the help of receptor−ligand interactions[122].

In addition, the binding of affinity/streptavidin to biotin, although dependent on a variety of non-covalent forces, is close to covalent in strength and stabilizes the anchoring molecule for long periods of time. Using this system, Zheng et al.[123] have asymmetrically immobilized urease on natural neutrophil surfaces, creating urease-modified neutrophils (UM-NEs) (Fig. 7C). UM-NEs generate CO_2 and NH_3 upon contact with endogenous urea, propelling neutrophils toward thrombotic sites. At these sites, pro-inflammatory cytokines trigger NETs formation, releasing urokinase (UK)-conjugated silver nanoparticles (AgNPs) to induce thrombolysis and inhibit thrombus formation. Remarkably, UM-NEs exhibit a prolonged elimination half-life ($t_{1/2} = 12$ h), vastly exceeding that of free UK ($t_{1/2} = 0.18$ h), thus, UM-NEs show long-time circulation.

It is essential to note that the "cell backpack" technology is a soft, disc-shaped biodegradable microparticle that adheres to cell surfaces to avoid phagocytosis of the drug while maintaining cellular activity and even phenotype, and serves as a repository for drugs or other regulatory molecules, which has been studied in macrophages, neutrophils, and NK cells[124-127]. Zhang et al.[43] have used cationic liposomes of hyaluronic acid-maleimide (HAMal) encapsulated STING agonist (STING-Mal-NP) as a backpack, and subsequently load the liposomes onto neutrophil cell surface sulfhydryl groups (NEs-SH) *via* the reaction between the maleimide and thiol groups(NEs@STING-Mal-NP) (Fig. 7B). In the TME, hyaluronidase (HAase) degrades the HA-Mal shell, releasing STING agonists. Transwell assays and *in vivo* imaging confirm that NEs@STING-Mal-NP preserve neutrophil migratory capacity and biodistribution. After 48 h, NEs@STING-Mal-NP, the amount of STING agonist at the tumor site is significantly increased to 3.5-fold that of the STING-MAL-NP group, ultimately enhancing the therapeutic efficacy against breast cancer. Specifically, utilizing metal-polyphenol networks enables the construction of single-cell coatings on cell surfaces. These coatings exhibit pH responsiveness and tunable size and stiffness, thereby achieving precise control over cellular behavior and effective regulation of biological processes[128].

In vivo loading strategies: This strategy utilizes the inherent mechanism of immune cells in the body to clear pathogens, to achieve nanomedicines targeting specific circulating immune cells *in vivo*. Thus, these nanomedicines evade immune clearance, overcome endothelial barriers, prolong systemic circulation, and reduce off-target toxicity. This approach bypasses the laborious *ex vivo* processes of cell isolation, expansion, and reinfusion, effectively addressing the limitations of conventional cell therapies in allogeneic compatibility, scalable manufacturing, and clinical accessibility. Due to their natural abundance in circulation and inherent phagocytic functions, neutrophils and monocytes serve as primary carriers for this strategy[129-132].

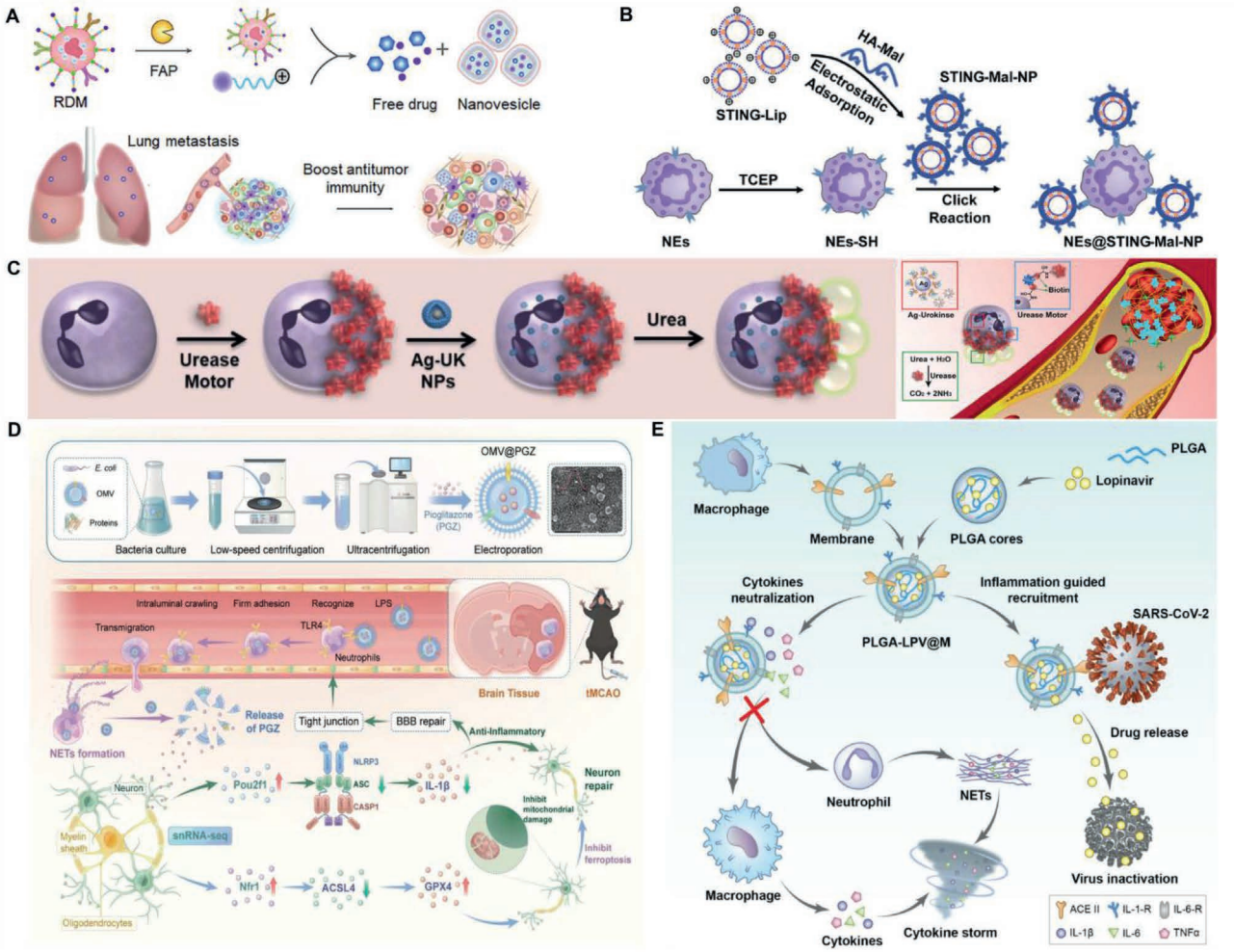

Figure 7 Examples of extracellular and *in vivo* loading strategies in nanoengineered whole immune cells. (A) RDM targets lung metastasis and potentiates the antitumor immunity. Reprinted with the permission from Ref. 121. Copyright©2023, American Chemical Society. (B) Liposomes are loaded onto neutrophil cell surface *via* the reaction between the maleimide and thiol groups. Reprinted with the permission from Ref. 43. Copyright©2023, American Chemical Society. (C) UM-NEs (Ag-UK) system targets thrombus sites. Reprinted with the permission from Ref. 123. Copyright©2022, American Chemical Society. (D) OMV@PGZ hijacks neutrophils in circulation and accumulates in ischemic regions. Reprinted with the permission from Ref. 133. Copyright©2023, John Wiley and Sons. (E) PLGA nanoparticles coated with THP-1 cell membranes block proinflammatory substances to reduce the production of cytokines and NETs. Reprinted with the permission from Ref. 135. Copyright©2021, Springer Nature.

Non-covalent modifications and intracellular internalization represent the most widely utilized approaches for *in vivo* drug loading. Pan et al.[133] have developed the OMV@PGZ nanosystem (Fig. 7D), wherein the neuroprotective agent pioglitazone (PGZ) is encapsulated within *E. coli* outer membrane vesicles (OMVs). By leveraging the surface LPS on OMVs for specific recognition by TLR4/TLR2 receptors on neutrophils, this system hijacks neutrophils in circulation to traverse the blood−brain barrier (BBB) and accumulate in ischemic regions. Subsequent release of PGZ within the target site suppresses inflammatory responses, achieving neuroprotection. Feng et al.[134] have employed artificially damaged/senescent red blood cells (RBCs) to carry the antitumor drug vincristine (VIN). Taking advantage of the innate clearance function of monocytes/macrophages toward damaged cells, they achieve tumor-specific accumulation of VIN-loaded biotinylated erythrocyte-poly(lactic-*co*-glycolic acid) nanoparticles. This approach ingeniously combines the innate functions of RBCs and monocytes/macrophages, offering a novel perspective for *in vivo* loading strategies. However, as precursors to macrophages, monocytes undergo a dynamic differentiation process (involving transendothelial migration, increased cell volume, elevated organelle content, and enhanced phagocytic capacity) that may trigger abnormal drug release. Consequently, the interplay between monocyte differentiation and drug-carrier stability must be carefully considered when designing monocyte/macrophage-based therapeutic formulations.

3.1.2. Nanoengineering of cell membranes

Nanoengineering based on immune cell membranes usually involves coating the cell membrane onto the outer layer of the nanoparticle to form a core-shell structure. The preparation process generally comprises three key steps: cell membrane extraction, nanoparticle core synthesis, and membrane-core fusion. Membrane-core fusion is commonly achieved *via* mechanical extrusion, sonication, or microfluidics. Mechanical extrusion is one of the most commonly used methods. The cell membrane and

the nanoparticle core are extruded through a polycarbonate membrane several times by an extruder. producing uniform-sized nanoparticles while preserving membrane protein integrity, though scalability remains challenging. Sonication employs high-frequency sound waves to drive the self-assembly of cell membranes and nanoparticle cores into core-shell structures, offering simplicity and low material consumption for batch preparation. Microfluidics, utilizing electric pulses to drive nanoparticle cores into membranes, shows unique potential for industrial-scale applications. Once the preparation is completed, the physicochemical and biological properties need to be characterized through multiple dimensions, including morphological analysis, particle size, zeta potential, and membrane protein composition, to ensure that the cell membrane has been successfully coated on the surface of the nanoparticles[136].

Shan et al.[135] have encapsulated the antiviral drug lopinavir (LPV) within poly(lactic-*co*-glycolic acid) (PLGA) nanoparticles and coated them with THP-1 cell membranes. The membrane-coated nanoparticles increase in size from 85.8 $\pm$ 4.4 nm to 102.2 $\pm$ 4.0 nm (Fig. 7E). These THP-1 membranes retain macrophage surface receptors, enabling competitive uptake of pro-inflammatory mediators to suppress macrophage/neutrophil activation and mitigate cytokine storm syndrome in COVID-19-infected mice. Similar to extracellular loading strategies for nanoengineering of whole immune cells, the surface of the cell membrane can also be modified by lipid insertion to achieve simultaneous drug loading inside and outside the membrane. Sun et al.[137] have coated genistein (GS)-loaded solid lipid nanoparticles with peritoneal macrophage membranes, then modified the surface with DSPE-PEG_{2000}-rabies virus glycoprotein (RVG) and DSPE-PEG_{2000}-triphenylphosphine (TPP), compared to unmodified nanoparticles, DSPE-PEG_{2000}-RVG enhances BBB penetration by 10-fold, while DSPE-PEG_{2000}-TPP targets damaged neuronal mitochondria, which more strongly inhibit mitochondrial ROS in Aβ-treated HT22 neuronal cells, alleviating AD. In various inflammatory diseases, the cells from which membranes are derived may exhibit either anti-inflammatory or pro-inflammatory properties, which must be evaluated on a case-by-case basis. For example, Liu et al. [138] utilized Treg membranes with immunosuppressive functions to coat PLGA nanoparticles, constructing Treg membrane-bionic nanoparticles (TNPs). These TNPs retained the characteristic membrane proteins and immunomodulatory functions of Treg cells, enabling them to interact with overactivated immune cells. They effectively suppressed macrophage differentiation into osteoclasts, hindered dendritic cell maturation, and inhibited the activation of effector T cells, thereby significantly delaying the progression of chronic periodontitis. However, cell membrane drug-loading capacity is limited, in addition to conventional nanocarriers that can increase drug loading, pre-drug strategies also provide a way. Prodrug strategies can weaken intermolecular drug interactions, enhancing nanocarrier drug payloads[139]. Moreover, prodrugs often incorporate stimuli-responsive bonds, such as: i) Redox-responsive: disulfide, trisulfide, diselenide, or ketal bonds; ii) Acid-responsive: hydrazone, Schiff base, or *cis*-aconityl amide bonds; iii) Hypoxia-responsive: azo, quinone, or nitro groups. Zhang et al.[139] have encapsulated a hypoxia-responsive quinone-modified monomethyl auristatin E (MMAE) dimer prodrug (hQ-MMAE2) into PLGA nanoparticles (hQ-PLGA NPs), then coat them with neutrophil membranes to create hQNM-PLGA NPs. This achieves a 93.7% drug-loading efficiency. Leveraging neutrophil membrane tropism, hQNM-PLGA NPs are recruited to inflammatory tumor sites, lysosomes destroy neutrophil cell membrane to release hQ-PLGA cores, and severe tumor hypoxia triggers hQ-MMAE2 degradation for controlled release of MMAE.

3.1.3. Nanoengineering of EVs

EVs can deliver intercellular communication. Nanoengineering based on EVs of immune cells usually loads nanomedicines inside EVs, which can be divided into exogenous loading and endogenous loading.

Exogenous loading methods involve isolating and purifying EVs, followed by drug encapsulation into EVs using techniques such as co-incubation, sonication, extrusion, electroporation, phospholipid bilayer fusion, freeze-thaw cycling, or saponin treatment[140]. These methods vary in loading efficiency and applicability to different drug types. For hydrophilic or protein-based drugs, loading capacity follows an ascending order: co-incubation $<$ saponin treatment $\leq$ sonication $\leq$ freeze-thaw cycling $\leq$ electroporation $<$ fusion $<$ extrusion[141,142]. For hydrophobic drugs, coincubation is the most commonly used method due to their easy interaction with lipids on the surface of EVs[142]. Didiot et al. [143] have conjugated a hydrophobic TEG-cholesterol moiety to the 3′-end of small interfering RNA (siRNA). This hydrophobically modified siRNA is co-incubated with exosomes derived from human malignant glioblastoma U87 cells at 37 °C for 90 min to promote rapid binding of siRNA to the cell membrane with cholesterol. Each exosome is loaded with 1000 to 3000 siRNA molecules, and the size distribution and integrity of the exosomes remain unchanged after loading. In addition, adjusting pH, temperature, or sonication parameters can further optimize load efficiency. For instance, the loading efficiency of doxorubicin (Dox) in macrophage-derived EVs increases about 14-fold when pH is close to the pI of Dox[144].

Endogenous loading means that the drug is first loaded into the cells, and after the drug is sorted into the EVs and released from the donor cells, the drug-loaded EVs are obtained by isolation and purification. Silva et al.[145] have co-incubated magnetic iron oxide nanoparticles and the therapeutic photosensitizer *m*-THPC with human THP-1 cell-derived macrophages, then cultured the cells for 2 days in serum-free medium under starvation conditions to stimulate EVs release, and drug-loaded EVs with magnetic and photo-thermal switching effects are produced by centrifugation and magnetic sorting, where 93.3 ng iron oxide nanoparticles are loaded and 5.6 ng of photosensitizer per 10^8 EVs. However, due to the complex mechanism of drug sorting into EVs, it is difficult to regulate by external means, resulting in the low applicability of the endogenous drug loading strategy.

Similar to the *in vivo* distribution of traditional nanomedicines, systemically administered EVs of nanoscale dimensions exhibit nonspecific accumulation in organs such as the liver, spleen, gastrointestinal tract, and lungs. Studies reveal distinct biodistribution patterns among EVs derived from different cell sources: DC-derived EVs are preferentially taken up by the spleen, while exosomes from M1-like macrophages display unique lymph node tropism[146,147]. To overcome the limitations of natural targeting, EVs can be engineered *via* chemical modification, lipid insertion, or covalent conjugation of targeting ligands. Ivanova et al. [148] have covalently linked trivalent *N*-acetylgalactosamine (GalNAc) to EVs bearing a HaloTag protein label. By utilizing GalNAc's interaction with the asialoglycoprotein receptor 1 (ASGR1), these EVs achieve specific targeting to human primary hepatocytes with high ASGR1 expression. Despite these advantages, the low yield of EVs restricts their clinical scalability. This

challenge has spurred the development of extracellular vesicle mimetics (EVMs), nanoscale vesicles constructed by integrating cellular membrane components with synthetic lipids. Using micron-scale membrane extrusion combined with differential centrifugation, EVMs production increased from 10^8 particles/mL (natural EVs) to 8.4×10^9 particles/mL per 10^6 cells, enabling potential large-scale manufacturing[149,150]. Current EVMs fabrication strategies fall into three categories: i) Cell membrane extrusion: physically extruding whole cells to reshape membranes into nanovesicles. While biocompatible for loading small-molecule drugs, proteins, or nucleic acids, this method faces challenges in large-scale production. ii) Enucleated cell membrane processing: combining hypo-osmotic lysis with ultrasonic homogenization of enucleated cell membranes. This enhances exogenous drug loading capacity but may compromise membrane protein integrity. iii) Hybrid EVM synthesis: fusing natural EVs with synthetic liposomes *via* freeze−thaw cycles or co-extrusion. Though offering flexible drug-loading capabilities, this approach has the risk of inactivation of bioactive components[151,152]. In the future, it is necessary to develop standardized EVMs preparation protocols, quality assessment frameworks and functional validation methods to promote their clinical translation.

3.2. Genetic engineered ICTAs

Genetic engineered ICTAs refer to the targeted modification of whole immune cells, cell membranes, or EVs through genetic engineering technologies to enhance their targeting specificity, killing effect, or longevity. In addition to physical methods such as electroporation and microinjection, current gene delivery systems for such engineering are broadly categorized into viral and non-viral vectors[153]. Viral vectors, relying on their natural infection mechanisms, are mainly used for *ex vivo* cell therapies requiring long-term stable transgene expression. These vectors are further classified into integrating and non-integrating types: integrating vectors (*e.g.*, HIV-1 lentivirus, γ-retrovirus) permanently integrate transgenes into the host genome for sustained expression but carry insertional mutagenesis and tumorigenic potential risks. In the non-integrating vectors, adenovirus is transiently expressed in free form, while the recombinant adeno-associated viruses (rAAVs) predominantly exist as non-integrating episomes, which significantly reduces insertional mutagenesis risks. Compared with viral vectors, non-viral vectors (*e.g.*, lipid nanoparticles, polymer nanoparticles) circumvent the biosafety risks and show superior biosafety and clinical translational potential in delivering mRNA, DNA, or proteins[154-156].

3.2.1. Genetic engineering of whole cells

Chimeric antigen receptor (CAR) cell therapy is a research hotspot in genetically engineered therapeutic agents based on whole immune cells. This therapy involves recombining an antibody's single-chain variable fragment (scFv) targeting a specific antigen with transmembrane and intracellular signaling domains *in vitro* to form a chimeric protein. The engineered CAR construct is transfected into patient-derived immune cells *via* genetic engineering. Upon reinfusion into the patient, these modified cells express CAR and selectively recognize and eliminate diseased target cells. CAR-T cell therapy has achieved groundbreaking clinical success, particularly for hematologic malignancies. The core technology of CAR-T cell therapy is the design and construction of CARs, which have evolved through five generations since their introduction in the 1990s: first-generation CARs contain only a CD3ζ activation domain; second-generation CARs integrate co-stimulatory molecules (*e.g.*, CD28 or 4-1BB); third-generation CARs add cytokine secretion capabilities; fourth-generation CARs introduce logic-gated systems; and fifth-generation CARs incorporate suicide switches for controlled activation. Despite these advancements, CAR-T cell therapy faces challenges in treating solid tumors, including the immunosuppressive TME, off-target toxicity, and T-cell exhaustion[157]. The TME in solid tumors is characterized by insufficient cytokine synthesis (*e.g.*, IL-2) and excessive nutrient depletion, severely restricting CAR activation. To address this, Allen et al.[158] have engineered CAR-T cells with tumor antigen-specific synthetic Notch (synNotch) receptors, enabling autonomous IL-2 production to overcome cytokine limitations. These synNotch-modified T cells exhibit enhanced infiltration into immunosuppressive tumors, whereas conventional CAR-T cells are unable to do so (Fig. 8A). In order to avoid the depletion of CAR-T cells caused by repeated stimulation of tumor antigens and continuous self-activation due to aggregation of CAR structures, shortening the cell culture time, supplementing relevant cytokines like IL-15, or increasing the sodium ion concentration in the culture medium, have shown promise in preserving CAR-T cell functionality[159,160]. In addition, like nanoengineering ICTAs, surface modifications can further optimize CAR-T cells. Siriwon et al.[161] have chemically conjugated maleimide-functionalized cross-linked multilamellar liposomal vesicles (cMLV) to CAR-T cell surfaces. Upon systemic administration, cMLVs release A2a adenosine receptor (A2aR) antagonists to counteract the immunosuppressive microenvironment, restoring T cell proliferation and IFN γ secretion, thereby enhancing the therapeutic effect of CAR-T treatment. To address off-target toxicity, synthetic biology approaches are developing multi-specific, logic-gated, and tunable CAR architectures[162]. A notable example is the light-controllable CAR-T cell system developed by Zhang et al.[163], which employs a FITC-*O*-Folate linker molecule. It connects anti-FITC CAR-T cells to folate-expressing target cells *via* a photocleavable *ortho*-nitrobenzyl ester bond. Under 365 nm light, the bond rapidly breaks, disengaging CAR-T cells and terminating cytotoxicity.

In recent years, CAR cell therapy has been gradually extended to macrophages, NK cells, DCs, and neutrophils[164-167]. Among these, CAR macrophages demonstrate significant potential in solid tumor treatment due to macrophages' unique tumor infiltration and phagocytic capabilities, with second-generation macrophage CAR constructs already developed[168,169]. Traditional engineered cell therapies require multiple steps, peripheral blood cell collection, *ex vivo* expansion, activation/differentiation, CAR genetic modification, and quality control before reinfusion, a cumbersome and time-consuming process driving interest in *in vivo* immune cell engineering. This approach leverages technologies like lentiviral vectors (LV), adeno-associated vectors (AAV), synthetic polymer nanoparticles, lipid nanoparticles (LNP), enveloped carriers, and exosomes to engineer CAR genes into immune cells *in vivo* directly, bypassing *ex vivo* manipulation and reducing technical barriers for clinical translation, with initial applications have been realized in T cells, macrophages and B cells[170-176]. Chen et al.[174] have implanted hydrogels into post-resection GBM cavities to co-deliver macrophage-targeting editing nanomicelles (NP-pCAR) and CD47 antibodies, enabling *in situ* reprogramming of TAMs into CD133 CAR-M cells that effectively target glioma stem cells. This strategy has extended survival beyond 90 days in 83% of tumor-bearing mice without significant organ toxicity. Despite proof-of-concept success, *in*

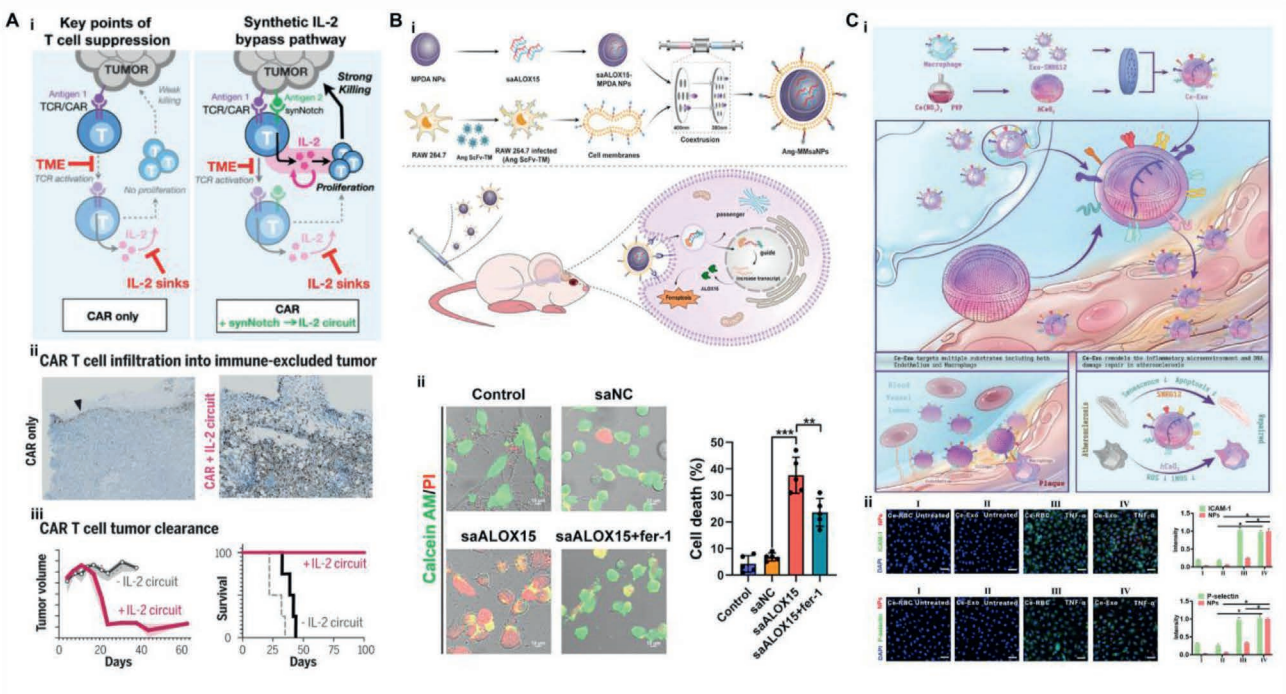

Figure 8 Genetic engineered ICTAs for treating inflammation-related diseases. (A) Engineering therapeutic T cells with synthetic IL-2 circuits drives local T cell proliferation independent of TCR activation. (i) Synthetic synNotch→IL-2 circuits can drive local T cell proliferation, bypassing immune suppression mechanisms. (ii) Engineered therapeutic T cells with tumor-triggered IL-2 production can infiltrate into an immune-excluded tumor. (iii) Engineered therapeutic T cells with tumor-triggered IL-2 production can clear immune-excluded tumors. Reprinted with the permission from Ref. 158. Copyright©2022, The American Association for the Advancement of Science. (B) Biomimetic macrophage membrane-coated nanoparticles induce ferroptosis in glioblastoma. (i) Construction schematic diagram of Ang-MMsaNPs. (ii) SaALOX15 promotes ferroptosis in GBM cells. Reprinted with the permission from Ref. 184. Copyright©2023, American Chemical Society. (C) Ce-Exo preparation and application for atherosclerosis. (i) Schematic illustration of Ce-Exo preparation. (ii) Ce-Exo binds to damaged cells through a ligand-receptor specific recognition mechanism. Reprinted with the permission from Ref. 185. Copyright©2024, John Wiley and Sons.

vivo CAR cell engineering faces challenges such as insufficient delivery specificity, low transfection efficiency, high carrier immunogenicity, and difficulties in dynamically regulating CAR activity. Future advancements require highly precise delivery systems and real-time CAR activity monitoring.

Recently, CAR technology has expanded beyond oncology into autoimmune diseases like type 1 diabetes (T1D), SLE, and autoimmune encephalitis. In anti-*N*-methyl-D-aspartate receptor (NMDAR) encephalitis, NMDAR-specific chimeric autoantibody receptor (CAAR)-T cells precisely eliminated autoreactive B cells without off-target toxicity, laying the groundwork for Phase I/II trials in autoantibody-mediated diseases[177,178]. Notably, the lower antigen burden in autoimmune diseases allows therapeutic doses as low as 1/10 to 1/5 of those used in cancer therapies, reducing risks like cytokine release syndrome[179]. For example, refractory large B-cell lymphoma requires 1×10^8 CAR-T cells[180], whereas studies in SLE and idiopathic inflammatory myopathy show sustained remission with 6×10^7 CD19 CAR-T cells[181,182]. Additionally, CAR-Treg cells, critical for maintaining immune tolerance, exhibit therapeutic potential in modulating excessive immune responses in graft-*versus*-host disease (GvHD), T1D, RA, and IBD[183].

3.2.2. *Genetic engineering of cell membranes*

Genetic engineering of donor cells enables targeted knockout or overexpression of specific membrane proteins to enhance immunomodulatory capacity, disease targeting, and endosomal escape efficiency. These engineered cell membranes can be integrated with nanomedicines. Cao et al.[184] have utilized an adenovirus to overexpress Angiopep-2 (Ang) on RAW264.7 macrophage membranes (Fig. 8B). By fusing these membranes with mesoporous dopamine nanoparticles *via* membrane-coating technology, they obtain an Ang-MM@MPDA delivery system, Ang selectively bound to the lipoprotein receptor-related protein 1 (LRP1) on astrocytes, improving nanoparticle penetration across the BBB. Simultaneously, macrophage surface α4 or β1 integrins further enhance BBB traversal and glioma targeting by interacting with VCAM-1. Given that 15-lipoxygenase (ALOX15) is a key driver gene for ferroptosis in GBM, they designed a small activating RNA targeting the ALOX15 gene (saALOX15). Utilizing the aforementioned Ang-MM@MPDA delivery system, they precisely delivered saALOX15 to glioblastoma lesions. This approach effectively induced significant upregulation of ALOX15 expression within GBM cells, consequently leading to the successful induction of tumor cell ferroptosis. Additionally, functional proteins can be anchored to membrane surfaces *via* fusion with glycosylphosphatidylinositol (GPI) anchor signal peptides or transmembrane domains, enabling precise engineering of membrane protein functionality[186]. Zhu et al.[187] have used Lipofectamine 2000 to transfect the nucleic acid sequence of anti-HER2 scFv and CD80 co-stimulatory molecules carrying GPI-anchored sequences into Chinese hamster ovary (CHO) cells, then extract the CHO membrane and coat with mesoporous silica nanoparticles containing the chemotherapeutic drug DOX (MSN-C), which

significantly reduces tumor volume in the GPI-modified MSN-C-treated mice as compared to the non-GPI-modified group. These advancements highlight the synergistic potential of genetic and nanoengineering. However, the extraction quality and protein structural stability of engineered cell membranes are still the key bottlenecks for clinical translation, and a standardized membrane quality evaluation system needs to be established with the help of emerging technologies such as cryo-electron microscopy, proteomics, AlphaFold prediction, and Fluorescence recovery after photobleaching (FRAP).

3.2.3. *Genetic engineering of EVs*

Exosomes, characterized by their small size (30−150 nm), structural homogeneity, and low immunogenicity (lacking apoptotic signaling molecules on the surface), have emerged as a central focus in extracellular vesicle engineering. Current approaches involve genetically modifying donor cells, followed by isolating and purifying engineered exosomes from cell culture media using differential centrifugation, density gradient centrifugation, or cushion-based ultracentrifugation[188,189]. Fu et al.[190] have isolated CAR-T cell-derived exosomes by differential centrifugation, which do not express PD-1 and overcome the immunosuppressive function of the tumor's PD-1/PD-L1 signaling axis compared to CAR-T. Moreover, granzyme B and perforins are targeted to be released into the intracellular area of the tumor cells through a membrane fusion mechanism, demonstrating a tumor killing efficiency comparable to that of the CAR-T donor cells with in breast cancer models and lower toxicity in preclinical *in vivo* models of cytokine release syndrome. In another study, Wei et al.[185] have used lentivirus to overexpress the long noncoding RNA (lncRNA) SNHG123 on RAW264.7 macrophage surfaces. Exosomes carrying this RNA are isolated *via* differential centrifugation and further loaded with hollow ceria nanoparticles ($hCeO_2$) to construct cerium-macrophage exosomes (Ce-Exo) (Fig. 8C). Ce-Exo selectively delivers lncRNA SNHG123 and $hCeO_2$ to DNA-damaged vascular endothelial cells in AS, synergistically alleviating disease progression by suppressing DNA damage, scavenging ROS, and delaying cellular senescence. These studies emphasize the benefits of engineered exosomes in reducing systemic toxicity, but also provide direct evidence of their use as multifunctional biomaterials.

3.3. *Membrane-fused engineered ICTAs*

Membrane fusion, the process by which two lipid bilayers merge into a single structure, is a ubiquitous phenomenon in nature. However, due to the inherent free energy barrier, membrane fusion usually requires the involvement of fusion proteins. Natural examples include soluble *N*-ethylmaleimide-sensitive factor attachment protein receptors (SNAREs), which mediate fusion between organelles and plasma membranes in eukaryotic cells; gp41, which drives the fusion of the HIV viral envelope with $CD4^+$ T cell membranes; and hemagglutinin (HA), which facilitates fusion between influenza viruses and host cells[191-193]. These naturally occurring fusion mechanisms provide critical insights for engineering ICTAs. Compared to traditional *ex vivo* genetic engineering of ICTAs, fusion-engineering ICTAs overcome limitations such as complex preparation workflows, prolonged timelines, and high costs. Utilizing membrane fusion technology, phospholipid bilayer structures, including cell−cell, membrane−membrane, membrane−liposome, and extracellular vesicle−vesicle systems, can be seamlessly fused to rapidly achieve membrane modifications and cytosolic drug loading in ICTAs.

3.3.1. *Membrane-fused engineering of whole cells*

Common methods for inducing whole cell fusion *in vitro* include virus-mediated fusion, polyethylene glycol (PEG)-based chemical fusion, and electrofusion. Virus-mediated fusion offers high efficiency and rapid kinetics but carries risks of immunogenic contamination[194,195]. PEG, the most widely used chemical fusogen, enables non-selective fusion of diverse cell types and is extensively applied in tumor vaccine development[196-198]. Hu et al.[199] have treated a mixture of mouse bone marrow-derived DCs (DC2.4) and hepatocellular carcinoma cells (Hepa1-6) at a 2:1 ratio with PEG_{1450} for 3 min, successfully generating DC/tumor fusion vaccines. These vaccines co-expressed DC costimulatory molecules (*e.g.*, CD80/CD86) and tumor-associated antigens, significantly enhancing the immune system's ability to recognize and eliminate tumor cells. When combined with a folate receptor-targeted chitosan/mouse interferon-γ-inducible protein-10 (mIP-10) nanodelivery system, the median survival of tumor-bearing mice increases from 75 to 92 days. The efficacy of PEG-mediated fusion depends on factors such as PEG molecular weight, concentration, pH, cell viability, temperature, and incubation time. Optimization of these parameters or integration with auxiliary techniques can further improve fusion outcomes. Gao et al.[200] have pretreated human B-lymphoma cells (Ramos) and acute lymphoblastic leukemia T cells (CCRF-CEM) with 100 nmol/L multivalent DNA ligand clusters for 10 min to promote aggregation, followed by treatment with 50% (*w*/*w*) PEG_{6000} for 3 min, achieving a fusion rate increase from 3.58% to 61.8% (Fig. 9A). Electrofusion, which employs high-voltage pulses to create transient pores in tightly apposed cell membranes, surpasses PEG in efficiency and requires fewer cells but relies heavily on specialized instrumentation[201,202]. These advancements underscore the versatility of fusion technologies in refining the design and delivery of biomaterials.

For lipid-coated nanomedicines, the phospholipid bilayer formed by lipid molecules can fuse with the target cell membrane, enabling surface modification while directly delivering drugs into the cytoplasm. Cationic liposomes containing neutral lipids like 1,2-dimyristoyl-*sn*-glycero-3-phosphocholine (DMPC) or 1,2-dioleoyl-*sn*-glycero-3-phosphoethanolamine (DOPE) and cationic lipids like 1,2-dioleoyl-3-trimethylammonium-propane (DOTAP), in which the molar ratio of neutral lipid: cationic lipids from 1:0 to 1:2 all have the potential to fuse with living cells both *in vitro* and *in vivo*, rely on electrostatic interactions between cationic lipids and negatively charged cell membranes to reduce intermembrane distance and destabilize membrane integrity, while neutral lipids provide mobility similar to cell membranes, thereby driving fusion[203,204]. Zheng et al.[205] have developed a core-shell membrane-fusogenic liposome (MFL) where the core contains PLGA nanoparticles loaded with the sialyltransferase inhibitor P-3Fax-Neu5Ac (PFNAc), and the shell is composed of DMPC, cationic lipid DOTAP, and tumor-targeting Lewis X trisaccharide (LeX)-conjugated DSPE-PEG (DSPE-PEG-LeX). Upon intratumoral injection, the MFL fuses with tumor cell membranes, delivering the PLGA core into the cytoplasm while anchoring LeX trisaccharides on the cell surface to activate NK cells. Subsequent slow release of PFNAc from PLGA downregulates tumor-associated sialic acids and immunosuppressive glycans, amplifying NK-mediated antitumor responses. Similarly, Zheng et al.[206]

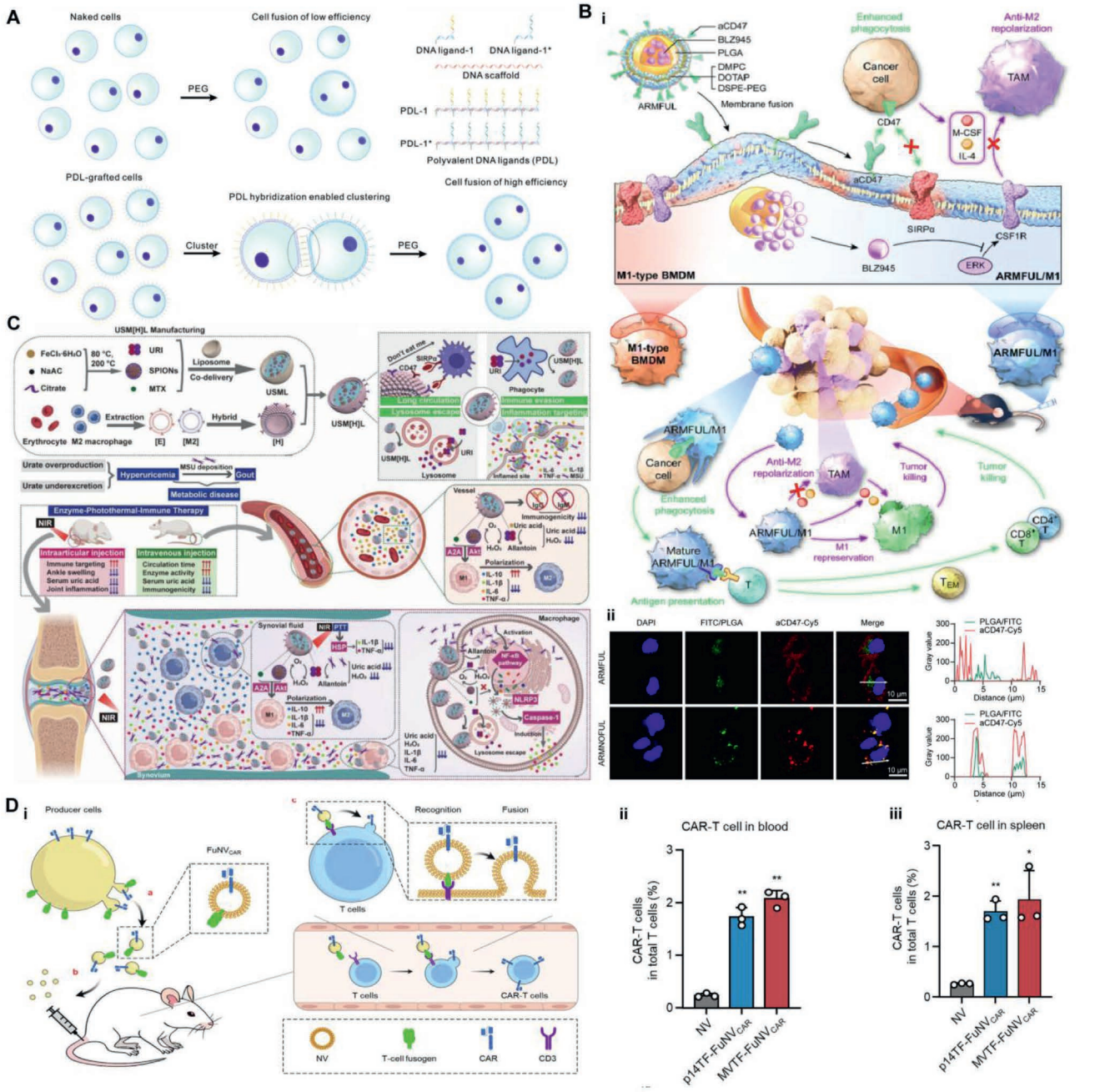

Figure 9 Membrane-fused engineered ICTAs for treating inflammation-related diseases. (A) PDL enables efficient cell clustering for promoting PEG-induced cell fusion. Reprinted with the permission from Ref. 200. Copyright©2022, American Chemical Society. (B) ARMFUL/M1 blocks CD47-SIRPα signaling to enhance macrophage phagocytosis of tumors and maintains the antitumor M1-like of ARMFUL/M1 in the TME. (i) Schematic illustration of *in vitro* engineering of M1-like macrophages using membrane-fusogenic liposomes. (ii) ARMFUL can fuse with M1-like macrophage cell membranes. Reprinted with the permission from Ref. 206. Copyright©2023, The American Association for the Advancement of Science. (C) USM[H]L targets inflammation in gouty arthritis and reduces uric acid levels. Reprinted with the permission from Ref. 207. Copyright©2023, John Wiley and Sons. (D) Production of CAR-T cells *in vivo* with genetic engineering and membrane fusion engineering. (i) Production of CAR-T cells *in vivo* using virus-mimetic FuNVs. (ii) The percentage of CAR-T cells targeting CD19 (CD19 CAR-T) in the blood. (iii) The percentage of CAR-T cells targeting CD19 (CD19 CAR-T) in the spleen. Reprinted with the permission from Ref. 208. Copyright©2023, Elsevier.

have engineered cationic liposomes embedded with anti-CD47 antibodies and encapsulating PLGA nanoparticles loaded with the colony-stimulating factor 1 receptor (CSF1R) inhibitor BLZ945, termed ARMFUL (antibody-releasing membrane-fusogenic liposomes). The ARMFUL fuse with M1-like macrophages *in vitro* to form ARMFUL/M1, delivering BLZ945-loaded PLGA cores into the cytoplasm and anchoring anti-CD47 antibodies on the macrophage membrane (Fig. 9B). After intravenous

injection, the anti-CD47 antibodies block CD47−SIRPα signaling to enhance macrophage phagocytosis of tumors. At the same time, BLZ945 maintains the antitumor M1-like of ARMFUL/M1 in the TME by inhibiting CSF1R tyrosine kinase activity, effectively suppressing B16F10 tumor growth and metastasis in mice. However, it is critical to consider that liposomes may enter cells *via* non-fusogenic pathways, potentially triggering unintended intracellular responses.

3.3.2. Membrane-fused engineering of cell membranes

Membrane-fused engineering hybrid cell membranes combine the functional properties of distinct cellular membranes, enabling multi-targeting or antigen-presenting capabilities. Common methods for fusing different cell membranes and coating nanoparticles include mechanical extrusion, sonication, combined sonication-extrusion, and microfluidics[136,209]. Mechanical extrusion applies physical pressure to wrap nanoparticle cores with cell membranes, which is fast and simple, and can coat nanoparticles of different sizes, though it faces challenges in large-scale production. Sonication minimizes material loss during coating, but it may lead to uneven size and membrane damage from localized overheating. Microfluidics injects distinct cell membranes and nanoparticles into microchannels, leveraging shear forces from channel geometries to fuse membranes and coat nanoparticles with high precision and minimal loss, albeit limited by small production volumes. These methods vary in uniformity, operational complexity, and scalability, enabling tailored choices for specific applications. Chen et al.[207] have isolated erythrocyte and M2-like macrophage membranes *via* hypotonic lysis and differential centrifugation, fused them into vesicles using sonication, and then repeatedly extruded them with nanoliposomes loaded with self-cascading dual enzymes and immunomodulators through polycarbonate membranes to obtain uniform therapeutic nanoparticles (USM [H] L). Because the fused membranes obtain the properties of the erythrocyte and M2-like macrophage membranes, USM [H] L exhibits prolonged systemic circulation and immune evasion capabilities, naturally targeting inflammation-associated macrophages, escaping lysosomal degradation, and reducing uric acid levels while suppressing inflammation in gouty arthritis (Fig. 9C). Notably, hybrid membranes can also be derived from pre-fused cells. Similarly, Pan et al.[210] employed ultrasonic extraction to isolate the cell membranes of OVA-overexpressing mouse melanoma B16 cells and SARS-CoV Spike protein-overexpressing human embryonic kidney HEK 293T cells. These membranes were then fused *via* ultrasonic processing and coated onto the surface of nanoparticles loaded with immune adjuvants, resulting in the development of a dual-antigen display nanovaccine (DADNs). This vaccine effectively promotes the maturation of dendritic cells (DCs), enabling the dual presentation of tumor antigens and viral antigens. It not only intervenes in tumor progression but also demonstrates significant preventive effects against SARS-CoV infection. Liu et al.[211] have fused DCs with mouse breast cancer cells (4T1) using 50% (*w*/*w*) PEG_{4000}, harvested hybrid membranes (FM) *via* freeze-thaw cycles, and coated photosensitizer-loaded Zr-MOF (PCN-224) to create PCN@FM. PCN@FM effectively presents tumor-wide antigens and co-stimulatory molecules, masking the photosensitizer to activate durable immune responses, leading to near-complete tumor elimination in 4T1 tumor-bearing mice.

3.3.3. Membrane-fused engineering of EVs

After isolating and purifying EVs from different donor cells, membrane-fused engineering EVs can be prepared by extrusion. These hybrid EVs retain the low immunogenicity, negative surface charge, and biocompatibility of the parent cells while enabling the loading of diverse bioactive components (*e.g.*, small molecules, nucleic acids, and proteins). They also directly participate in intercellular communication or regulate target cell functions. Tang et al.[212] have isolated M1-like macrophage-derived EVs using differential centrifugation, fused them with liposomes loaded with the chemotherapeutic agent shikonin, photosensitizer IR820, and immunomodulator poly-biguanide *via* sonication-extrusion, and modified the EVs with CD47-targeting peptides using DSPE lipid insertion. These engineered EVs blocked the CD47-SIRPα "don't eat me" signal, promoting infiltration of M1-like macrophages into tumors and enhancing their phagocytic activity, thereby achieving multi-mechanistic synergistic therapy. However, this strategy may compromise membrane protein conformational integrity, and residual heterologous membrane components could trigger immune rejection.

EVs can also be fusion engineered *via* genetic engineering to incorporate viral-like membrane fusion proteins, enabling efficient delivery of functional proteins or nucleic acids to cell membranes or the cytoplasm[213]. Zhao et al.[208] have generated engineered EVs expressing viral fusion proteins, CD3, and CAR proteins by infecting RAW264.7 cells with lentivirus, followed by differential centrifugation. Upon intravenous injection, these EVs preferentially accumulate in the spleen and liver, fusing with blood/splenic T cell membranes to generate CAR-T cells *in situ*, bypassing the complexities of traditional *ex vivo* CAR-T manufacturing (Fig. 9D). Additionally, Liang et al.[214] have linked EV sorting protein CD63, vesicular stomatitis virus G glycoprotein (VSV-G) fusion protein, and cargo proteins (Cre and super repressor of NF-κB) using a cleavable linker peptide derived from *Mycobacterium tuberculosis recA (21)*. This linker peptide dissociates under the multivesicular bodies' low pH (5.5−6), releasing cargo proteins into the lumen of EVs. Engineered EVs derived from HEK 293T cells *via* polyethyleneimine (PEI)-mediated plasmid transfection and tangential flow filtration achieve cytoplasmic delivery efficiencies of 66% and 98% in human cervical cancer cells (HeLa) and breast ductal carcinoma cells (T47D), respectively, after 48 h of co-culture.

4. Novel delivery devices promote the development of ICTAs

Currently, ICTAs primarily rely on intravenous injection for systemic administration. Researchers can employ high-performance liquid chromatography (HPLC), ultra-performance liquid chromatography (UPLC), and similar methods to quantify drug concentrations in specific tissues, track fluorescently labeled therapeutic agents *via* flow cytometry or confocal imaging, and utilize high-resolution magnetic resonance imaging (MRI), highly sensitive positron emission computed tomography (PET), and safe photoacoustic imaging (PAI) for real-time, systemic monitoring of therapeutic agents. While these formulations significantly improve targeting efficiency compared to free drugs, they remain constrained by biological barriers such as intravascular barriers, endothelial barriers, and the extracellular matrix, leaving substantial room for improvement in targeting efficacy[237]. Integrating ICTAs with novel delivery devices like scaffolds and microneedles

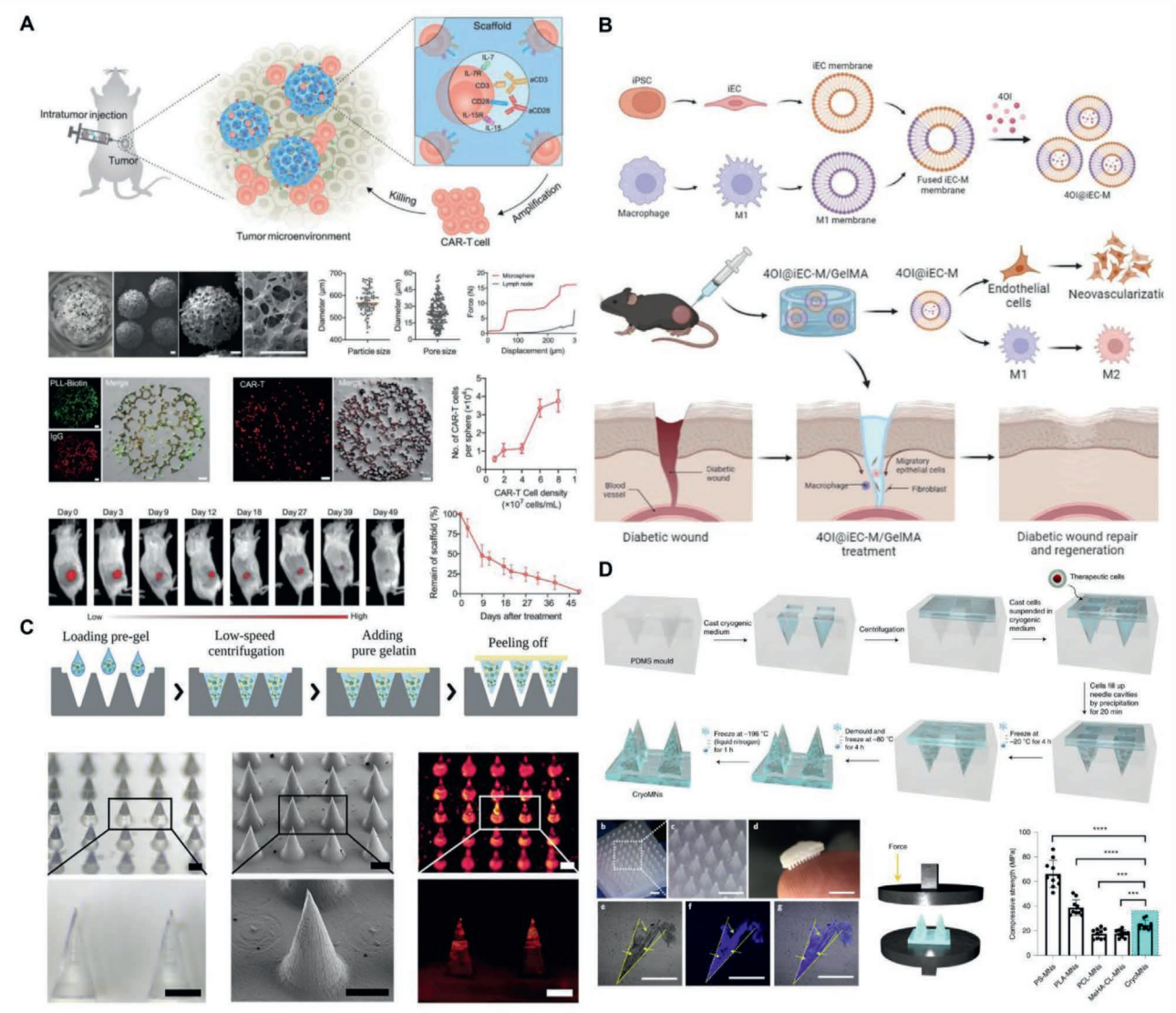

Figure 10 Existing delivery devices to promote the development of ICTAs. (A) The artificial lymph node-like scaffold maintains the proliferation and killing of CAR-T cells. Reprinted with the permission from Ref. 239 Copyright©2024, Oxford University Press. (B) 4OI@iEC-M are incorporated into a multifunctional gelatin methacryloyl (GelMA) hydrogel. Reprinted with the permission from Ref. 243 Copyright©2023, Springer Nature. (C) Methacrylated hyaluronic acid (HAMA)-based hydrogel microneedles enable minimally traumatic delivery of cells and biomolecules to resilient diabetic foot wounds. Reprinted with the permission from Ref. 244 Copyright©2022, John Wiley and Sons. (D) CryoMN preserves cell viability and proliferative capacity for up to one month. Reprinted with the permission from Ref. 245 Copyright©2021, Springer Nature.

can overcome these biological barriers, enabling precise targeting, sustained-release therapy, and enhanced patient compliance.

4.1. Scaffolds

Scaffolds are a 3D network implant composed of hydrophilic or amphiphilic polymers, characterized by suitable biocompatibility, tissue compatibility, and biodegradability. Their porous structure provides optimal support for cell attachment, proliferation, differentiation, and migration, enabling the co-delivery of ICTAs and other therapeutic agents. Natural materials (*e.g.*, alginate, collagen, gelatin, and fibrin) or synthetic polymers (*e.g.*, polyvinyl alcohol (PVA) and polyglycolide (PGA)) can serve as scaffold materials. Stephan et al.[238] have embedded CAR-T cells into an alginate-based scaffold along with the STING agonist cyclic di-GMP (cdGMP), effectively recruiting and stimulating antigen-presenting cells (APCs) to prime T cells. Compared to intratumoral injection of T cells and STING agonists, this scaffold improves survival in pancreatic cancer mice by 4.6-fold and dissolves within one week, eliminating the need for surgical removal. Likewise, Gu et al.[239] have developed a PLGA-based porous microsphere scaffold, where each microsphere accommodates approximately 3.8×10^4 CAR-T cells. By decorating the scaffold with anti-CD3 and anti-CD28 antibodies to mimic lymph node APCs, CAR-T cells exhibit 15-fold proliferation in subcutaneous tumor models while maintaining robust cytotoxic activity post-expansion (Fig. 10A). Such scaffolds can also integrate with *in vivo* cell engineering. Brudno et al.[240] have engineered a

multifunctional alginate scaffold for T Cell engineering and release (MASTER), first modifying alginate with azide groups, then loading anti-CD3, anti-CD28 antibodies, and IL-2 *via* DBCO-azide click chemistry, and finally incorporating T cells and retroviral vectors. The MASTER's 100−200 μm pores ensure efficient T cell-virus interactions, creating an *in vivo* "depot" for CAR-T generation. However, the viability of cells within these scaffolds is limited over time due to restricted oxygen and nutrient supply[241].

Hydrogels are the most widely used for ICTAs delivery among various scaffold types. Composed of crosslinked hydrophilic polymers forming a 3D network, hydrogels exhibit high water content (>90%) and a porous structure that mimics the extracellular matrix (ECM), mimicking the mechanical properties of natural tissues and preserving ICTAs activity. Monotherapy often has limited efficacy in combating complex diseases, particularly tumors, due to the immunosuppressive tumor microenvironment, the difficulty in maintaining drug activity, and the lack of synergistic effects among therapeutic agents. Therefore, it is crucial to develop combination treatment strategies that enable multi-mechanistic synergy and enhanced efficacy. Hu et al.[242] have developed a hyaluronic acid hydrogel-based composite system (CAR-T-P-aPDL1@gel) co-loaded with anti-PD-L1 antibody-modified platelets, IL-15 cytokine-encapsulated nanoparticles, and CAR-T cells. The anti-PD-L1-modified platelets alleviate immunosuppression by blocking the PD-1/PD-L1 immune checkpoint pathway, IL-15 sustains CAR-T cell viability, and the hydrogel enables sustained CAR-T release over 4 weeks. In a post-surgical melanoma model, the CAR-T-P-aPDL1@gel group shows a 6.4-fold reduction in tumor bioluminescence intensity compared to the CAR-T@gel + P-aPDL1 group and a >60-fold reduction compared to the CAR-T + P-aPDL1 group.

Furthermore, certain hydrogels possess intrinsic wound-healing properties. Zhang et al.[243] have fused membranes from induced pluripotent stem cell-derived endothelial cells (iECs) and M1-like macrophages to create hybrid membranes (iEC-Ms). iEC-Ms are wrapped with the anti-inflammatory drug 4-octyl itaconate (4OI), and then incorporated into a multifunctional gelatin methacryloyl (GelMA) hydrogel to construct 4OI@iEC-M/GelMA (Fig. 10B). This design induces M2-like macrophage polarization *via* 4OI, while the co-expressed CCR2 (macrophage) and CXCR4 (endothelial cells) receptors on iEC-M conferred dual inflammatory-vascular targeting. The GelMA hydrogel promotes cell migration and angiogenesis by mimicking the ECM's 3D environment, and its RGD sequences further enhance cell adhesion, ultimately accelerating diabetic wound healing. Notably, *in vivo* implantation of scaffolds may trigger foreign body reactions, leading to fibrous capsule formation that isolates the scaffold from surrounding tissues and impedes cargo release, potentially compromising therapeutic efficacy[241].

4.2. Microneedles

Microneedles, composed of micron-sized needle tips arranged in arrays on a base, directly traverse the stratum corneum to deliver therapeutics into the microcirculation, offering a minimally invasive and pain-free drug delivery strategy. Microneedle materials include silicon-based substrates (*e.g.*, porous silicon), natural polymers (*e.g.*, hyaluronic acid (HA), gelatin, chitosan), and synthetic polymers (*e.g.*, PLGA, polymethyl methacrylate (PMMA)). Li et al.[246] have developed porous PLGA microneedles that achieved a 20% loading efficiency when incubated with CAR-T cells at a density of 10^7 cells/mL, without compromising cell viability. In melanoma models, CAR-T cells delivered *via* these microneedles exhibit threefold greater proliferation compared to intratumoral injection, enabling deeper and broader infiltration within solid tumors.

Based on their structural features, microneedles are categorized into solid microneedles, hollow microneedles, coated microneedles, dissolvable microneedles, and hydrogel microneedles[247,248]. Xu et al.[244] have engineered a methacrylated hyaluronic acid (HAMA)-based hydrogel microneedle loaded with human adipose-derived stem cells (ADSCs) and bioactive platelet-derived growth factor-D (PDGF-D), enabling minimally traumatic delivery of cells and biomolecules to resilient diabetic foot wounds (Fig. 10C). Innovatively, Xu et al.[245] have pioneered cryomicroneedles using ice as the microneedle material, supplemented with cryoprotectants (dimethyl sulfoxide and sucrose). These microneedles deliver DCs loaded with tumor antigen (OVA) into the dermis, with the patch dissolving upon skin penetration to enable DCs-based immunization. The cryogenic fabrication process preserves loaded cell viability and proliferative capacity for up to one month (Fig. 10D). This approach both establishes a simple, safe, and minimally invasive strategy for ICTA delivery and provides a breakthrough solution for long-term cell preservation, laying the critical technical groundwork for clinical translation.

5. ICTAs in inflammation-related diseases

Currently, ICTAs strategies entering clinical trials primarily focus on genetically engineering of whole cells, while therapeutic agents developed through nanoengineering or membrane-fused engineering remain largely in the preclinical exploration stage. From a therapeutic mechanism perspective, ICTAs enable disease intervention through bidirectional regulation of immune balance. This section summarizes existing ICTAs for treating inflammation-related diseases (Fig. 11).

In pro-inflammatory therapeutic areas requiring immune activation (*e.g.*, tumor), research focus on functionally enhancing ICTAs like macrophages, neutrophils, T cells, NK cells, and DCs (Table 3). Key strategies employed include genetic modification (*e.g.*, CAR engineering) and engineered cell membranes encapsulated nanoparticles. These strategies aim to disrupt the tumor immunosuppressive microenvironment. As Table 3 demonstrates, these whole cell-based strategies, particularly those incorporating CAR modifications, have shown promising clinical advancements in various tumors, evidenced by outcomes like tumor regression and prolonged survival. However, significant challenges persist, including CRS and neurotoxicity (common with CAR-T therapies), limited *in vivo* persistence and function of therapeutic cells (particularly exhaustion in solid tumors), and the long manufacturing times, high costs, and limited accessibility associated with autologous cell products.

For anti-inflammatory applications targeting conditions like RA, DM, AS, AD, IBD, IRI, sepsis, and HLH, researchers primarily explore nanoengineering strategies. These include using macrophage- or neutrophil-membrane-encapsulated carriers and engineered exosomes to confer ICTAs with inflammation-suppressing capabilities or the ability to deliver therapeutic payloads. The goal is to restore microenvironmental homeostasis. As Table 4 indicates, significantly fewer anti-inflammatory ICTAs have entered clinical trials compared to pro-inflammatory

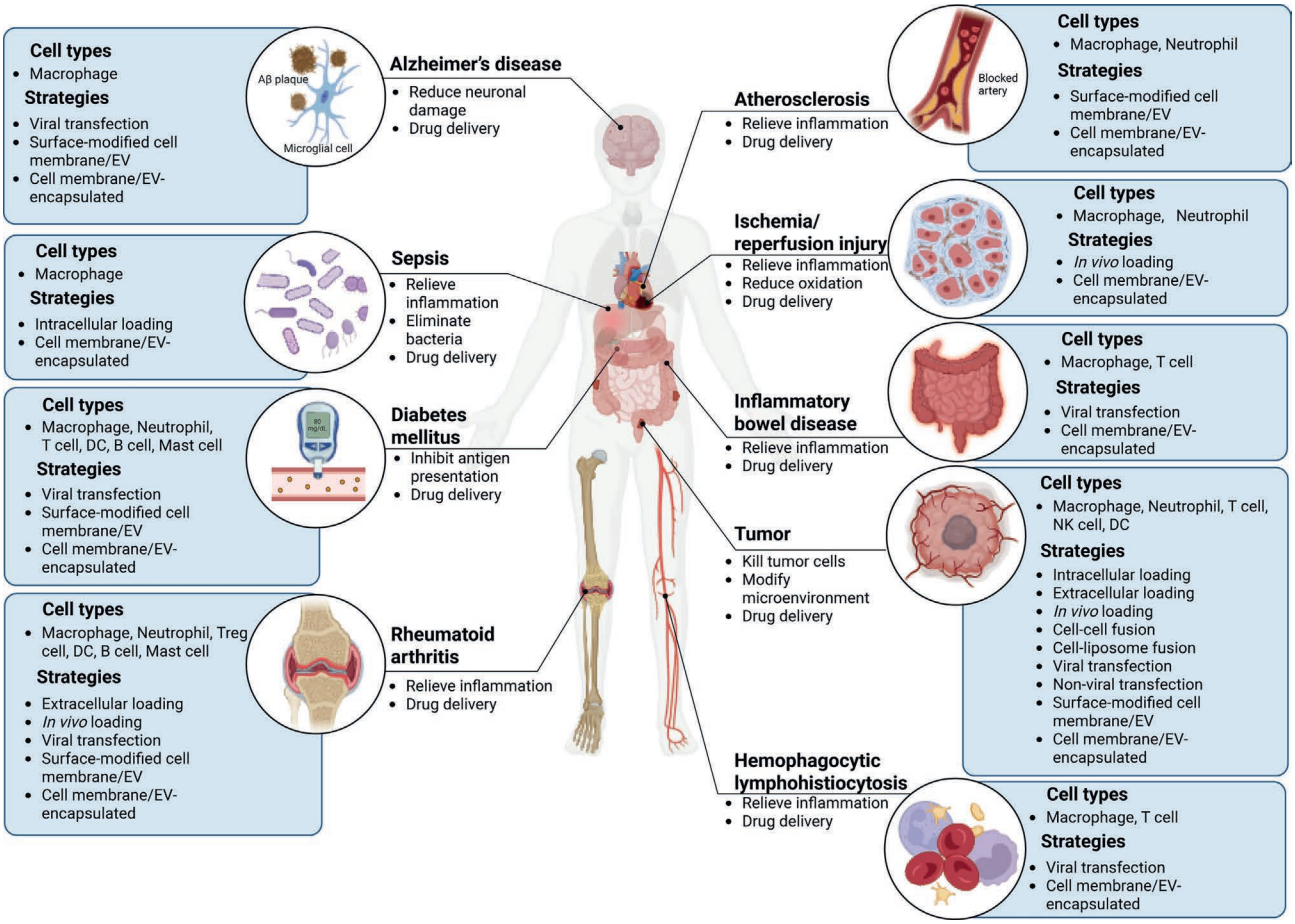

Figure 11 Existing ICTAs for inflammation-related diseases. ICTAs utilize nanoengineering, genetic engineering, and membrane-fused engineering. They act as active therapeutics or delivery carriers to restore homeostasis in pathological microenvironments, specifically targeting inflammation-related diseases.

cellular therapies, and those that have are generally at much earlier stages. Critical hurdles include achieving moderate immunosuppression, enhancing the efficiency of crossing biological barriers like the BBB for AD therapy. Consequently, the vast majority of these anti-inflammatory strategies remain in the preclinical exploration phase, lacking a mature clinical development pipeline comparable to the established CAR therapies in oncology.

5.1. Treatment of tumors by pro-inflammatory

Innate and adaptive immune responses during inflammation play critical roles in tumor initiation, progression, and metastasis. Tumor cells exhibit activation of multiple classical inflammatory signaling pathways, including NF-κB, mitogen-activated protein kinase (MAPK), IL-6/JAK/STAT3, and phosphatidylinositol-3 kinases/Akt/mammalian target of rapamycin (PI3K/Akt/mTOR)[2,249]. In acute inflammation, immune cell-derived stimuli and inflammatory cytokines typically activate the immune system to exert anti-tumor effects. However, prolonged acute inflammation leads to hypoxia, low pH, and accumulation of abnormal metabolites, which disrupt immune cell function and drive the transition to chronic inflammation. Chronic inflammatory cytokines promote tumorigenesis by inducing genetic mutations, suppressing apoptosis, stimulating angiogenesis, and recruiting immunosuppressive cells (*e.g.*, TAMs, MDSCs, and Tregs), thereby establishing an immunosuppressive TME and accelerating tumor progression[250]. Monocytes, macrophages, neutrophils, T cells, NK cells, and DCs are common cell types utilized in ICTAs.

5.1.1. Whole-cell-based pro-inflammatory therapy

When therapeutic approaches require harnessing the dynamic biological functions of cells themselves, whole cells are the preferred delivery vehicle. For instance, when it is necessary to reverse the immunosuppressive microenvironment in solid tumors, macrophages are critical carriers due to their substantial infiltration within the TME, often exhibiting a tumor-promoting M2-like phenotype[31]. Reprogramming TAMs to an M1-like can remodel the immunosuppressive microenvironment. Song et al.[251] have developed M1-like macrophages derived from RAW 264.7 cells, loaded with nanospheres (CpG-ASO-Pt, CAP@M) containing functional nucleic acid therapeutics (CpG-ASO) and chemotherapeutic drug cisplatin (Pt). Compared to macrophage-only or cisplatin monotherapy groups, CAP@M treatment increases the proportion of M1-like macrophages to 29.8% and reduces M2-like macrophages to 22.3% in tumors, lowering the M2/M1 (%) from 5% to 1%, effectively reversing immunosuppression. Neutrophils represent a critical component infiltrating the TME, abundant CXCL1/CXCL2 within the TME functions as a primary recruiter of neutrophils. This cell type possesses the innate capacity to cross the BBB or blood−brain tumor barrier and infiltrate the

Table 4 Overview of selected clinical trials utilizing ICTAs in inflammation-related diseases.

Cell types	Therapeutic agents	Diseases	Phases	Status	NCT number	Country
Macrophages	HER2 CAR-macrophages	Gastric cancer	I	Not yet recruiting	NCT06224738	China
	HER2 CAR-macrophages	HER2 overexpressing solid tumors	I	Active, not recruiting	NCT04660929	USA
Monocytes	HER2 CAR monocytes	HER2 overexpressing solid tumors	I	Recruiting	NCT06254807	USA
T Cells	Mesothelin/PSCA/CEA/HER2/MUC1/EGFRvIII CAR-T	Pancreatic cancer	I	Unknown status	NCT03267173	China
	CD33 CAR-T	Acute myeloid leukemia	II	Completed	NCT04835519	China
	Claudin18.2 CAR-T	Gastric adenocarcinoma	I	Recruiting	NCT06353152	China
	BCMA CAR-T	Multiple myeloma	III	Recruiting	NCT04287660	China
	GD2 CAR-T	Osteosarcoma, neuroblastoma	I	Active, not recruiting	NCT01953900	USA
	CD19 CAR-T	B Cell lymphoma	I	Completed	NCT02659943	USA
	HER2 CAR-T	Metastatic malignant neoplasm, breast cancer	I	Recruiting	NCT03696030	USA
	IL13Ralpha2 CAR-T	Ependymoma, GBM	I	Recruiting	NCT04661384	USA
	CD19 CAR-T	Rheumatoid arthritis	II	Not yet recruiting	NCT06475495	Germany
	COVID-19 specific T Cell derived exosomes (CSTC-exo)	Corona virus infection, pneumonia	I	Unknown status	NCT04389385	Turkey
	Tumor-infiltrating lymphocytes (TIL) engineered with membrane-binding cytokine	Advanced gynecologic tumors	I	Recruiting	NCT05468307	China
	T Cell membrane-anchored tumor-targeted IL12 -modified TIL	Metastatic soft-tissue sarcoma	I	Not yet recruiting	NCT06474676	USA
	Peripherally-derived autologous T cell loaded with IL-15 cell backpack	Solid tumors and lymphomas	I	Terminated	NCT03815682	USA
NK cells	NKG2D CAR-NK	Multiple myeloma	I	Not yet recruiting	NCT06379451	China
	GD2 CAR-NKT	Neuroblastoma	I	Recruiting	NCT03294954	USA
	CD30 CAR-NK	T-cell lymphoma, classical hodgkin lymphoma	I	Recruiting	NCT04288726	USA
DCs	CAR-DC	Solid tumor, adult lymphoma	I	Recruiting	NCT05631886	China
DCs, macrophages and tumor cells	Chimeric exosome	Recurrent or metastatic bladder cancer	I	Recruiting	NCT05559177	China
Myeloid-derived supressor cell	MDSCs	Systemic inflammatory response syndrome	Not applicable	Completed	NCT02902939	Russian Federation
Blood samples	Circulating EVs	Chronic pancreatitis, diabetes mellitus	Observational	Recruiting	NCT05989867	China
	Circulating EVs	Insulin resistance diabetes mellitus	Observational	Recruiting	NCT06401876	USA

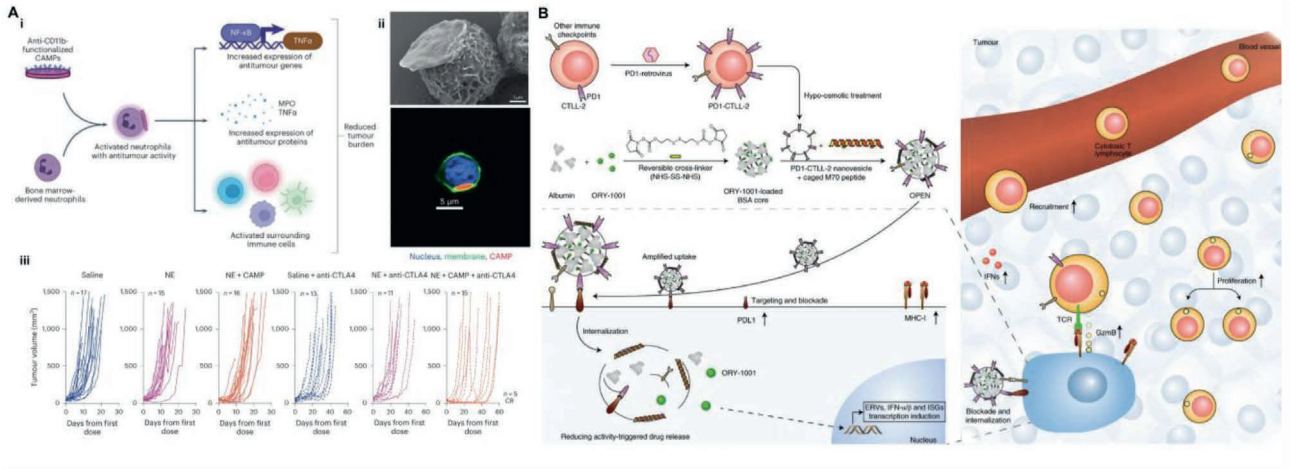

Figure 12 Examples of ICTAs treating a disease by promoting inflammation. (A) Scheme of the neutrophil-CAMP concept. (i) Neutrophils are activated upon attachment to anti-CD11b Fab-functionalized CAMP. (ii) Confocal microimaging and the scanning electron micrograph confirmed the successful loading of anti-CD11b-modified CAMP structures on the neutrophil surface. (iii) Neutrophil-CAMP in combination with the anti-CTLA4 group achieves complete tumor regression on Day 60. Reprinted with the permission from Ref. 125. Copyright©2024, Springer Nature. (B) OPEN suppresses tumor growth in breast cancer models, outperforming control therapies. Reprinted with the permission from Ref. 233. Copyright©2021, Springer Nature.

glioblastoma parenchyma. Notably, a unique neutrophil subpopulation exists in GBM, the disease-specific suppressive granulocytes (DSSGs), which directly promote tumor progression and induce T cell exhaustion. Consequently, utilizing neutrophils as a delivery vehicle for GBM therapy holds promise: by enabling the sustained recruitment of circulating neutrophils and replacing DSSGs, this strategy has the potential to reverse the immunosuppressive balance[252,253]. Notably, neutrophil polarization within the TME impacts therapeutic efficacy, in such cases, it can be engineered to polarize toward an anti-tumor N1 phenotype. Kumbhojkar et al.[125] have used anti-CD11b Fab-modified cyto-adhesive micropatches (CAMPs) to crosslink surface receptors, driving neutrophils isolated from mouse bone marrow toward an N1 phenotype (Fig. 12A). Combining neutrophil-CAMPs with anti-cytotoxic T-lymphocyte-associated protein 4 (anti-CTLA4), intravenous administration suppresses B16F10 tumor growth within 1.5 h. Remarkably, 10 out of 15 mice survive beyond 40 days, with 5 achieving complete tumor regression by Day 60, whereas neutrophil + anti-CTLA4 alone extends survival only to 50 days.

5.1.2. *Cell-membrane-based pro-inflammatory therapy*

Cell membrane carriers are ideal for situations where it is necessary to retain the targeting capabilities of the source cell while avoiding the complexity and potential risks associated with living cells. Ke et al. [254] have engineered neutrophil-mimicking nanoparticles by coating doxorubicin (DOX)-loaded poly(lactic-*co*-glycolic acid)-polyethylene glycol (PLGA-PEG) cores (PD) with membranes from human promyelocytic leukemia cells HL60-derived neutrophil-like cells. Neutrophil-like cell membranes confer nanoparticles targeting ability and accumulate in inflamed residual GBM tissue, extending median survival from 19 days (DOX group) to 37 days in mice. Nanoengineering and genetic engineering synergistically engineer immune cell-membrane-based therapeutic agents platforms that are gaining significant attention. Zhai et al.[233] have constructed T cells highly expressing programmed death receptor 1 (PD1-CTLL2) using retroviruses and used the cell membranes of the PD1-CTLL2 to encapsulate albumin nanoparticles loaded with type I interferon (IFN) inducer ORY-1001 (OPEN) (Fig. 12B). This design has enabled active targeting of PDL1-expressing tumor cells, simultaneously blocking the PD1/PDL1 immunosuppressive axis and triggering OPEN internalization. Upon release, ORY-1001 upregulates IFN-α/β secretion in tumors, enhancing tumor cell expression of MHC-I and PDL1, which recruits additional $CD8^+$ T cells and OPEN. OPEN suppresses tumor growth by 89% in breast cancer models, outperforming control therapies: PD1-expressing nanovesicles (PEN) and CTLL-2 membrane-coated epigenetic nanoinducer (OEN) achieved only 38% and 47% inhibition, respectively. This study combines epigenetic drugs with ICTAs for the first time, enabling tumor-targeted epigenetic drug delivery alongside immune checkpoint blockade. It provides a new direction in leveraging nanoengineering to enhance the efficacy and safety of tumor immunotherapy.

5.1.3. *EVs-based pro-inflammatory therapy*

When treatment plans require simultaneous consideration of storage and transport stability, avoidance of risks associated with living cell therapies, penetration of complex physiological barriers (such as the BBB), and the implementation of synergistic multi-drug therapies, EVs demonstrate unique advantages. Furthermore, EVs naturally contain diverse immunologically active components that can target the immune system *via* the paracrine system or circulation, enabling them to exert immunomodulatory functions. Notably, EVs derived from different cell sources exhibit significant functional differences, which are closely linked to the characteristics of their parent cell[255]. For instance, CAR-T cell-derived exosomes (CAR-Exos) have been shown to express CARs and cytotoxic molecules on their surface. They are similarly applicable for tumor therapy and, compared to CAR-T cell therapy, demonstrate a lower risk of CRS and higher stability[190]. On the other hand, EVs derived from DCs, known as DC-EVs, inherit the

antigen presentation and co-stimulatory capabilities of DCs. This means they contain MHC-peptide complexes and immune co-stimulatory molecules. This enables DC-EVs to induce specific anti-tumor immune responses through both DC-dependent and DC-independent pathways. In the independent pathway, DC-EVs can directly activate T cells, presenting a potential strategy to overcome the tumor immunosuppressive microenvironment. To leverage this, Chen et al.[256] have conjugated interleukin-12 (IL-12) and an anti-CTLA-4 antibody (aCTLA-4) onto the surface of DC-EVs using DSPE-PEG-NHS. This engineered approach not only provides the cytokine signal (IL-12) necessary for T cell activation and blocks an immune checkpoint (CTLA-4), but also enhances T cell activation.

5.2. Treatment of diseases by anti-inflammatory

This section summarizes the inflammation-related diseases that are treated by anti-inflammatory strategies, mainly RA, DM, AS, AD, IBD, IRI, sepsis, and HLH.

5.2.1. RA

RA is a chronic autoimmune disease that primarily affects bilateral joints and is characterized by synovial inflammation. While the exact etiology of RA remains unclear, it is widely believed to involve both environmental and genetic factors[257]. Conventional therapies involve the administration of NSAIDs or glucocorticoids to control inflammation, but their therapeutic efficacy is limited[258]. Direct use of biologic agents such as infliximab and tocilizumab to inhibit pro-inflammatory cytokines (*e.g.*, TNF-α and IL-6) is associated with high cost, poor specificity, and multiple adverse effects. Therefore, there is an urgent need for more rational therapeutic approaches that can alleviate synovial inflammation and reverse bone erosion in RA[259]. The pathological microenvironment of RA is characterized by inflammatory cell infiltration, elevated ROS, and enrichment of pro-inflammatory cytokines, providing a molecular basis for designing specifically targeted therapies[260,261].

Whole-cell-based anti-inflammatory therapy: Whole cells themselves hold unique value as powerful, naturally occurring vehicles due to their innate inflammatory tropism and tissue penetration capabilities (*e.g.*, neutrophils, macrophages), or by acting directly as effector cells. Persistent immune responses driven by abnormal activation of $CD4^+$ T cells are central to joint swelling, accompanied by neutrophil migration to synovial regions, exacerbating inflammatory damage[260,262]. Neutrophils themselves are key effector cells in RA inflammation, directly contributing to joint damage (*e.g.*, by releasing proteases, reactive oxygen species, etc.). Drug-loaded neutrophils after targeting the lesion site, can simultaneously achieve a dual “carrier-effector” function. This makes them suitable for early intervention and acute inflammation control in RA. Building on this, Yu et al. [261] have developed a neutrophil-based drug delivery system (GAC@NEs) using gadolinium oxide (GAC)-loaded bovine serum albumin nanoparticles with an intracellular loading strategy. After intravenous injection, GAC@NEs are recruited to inflamed joints. On the one hand, GAC enables non-invasive dynamic monitoring of RA progression (*via* MRI/PAI/NIR multimodal imaging), on the other hand, GAC ablates inflammatory cells through its intrinsic photothermal effect under near-infrared light irradiation (808 nm, 0.75 W/cm^2, 5 min), precisely modulating local inflammation. Further studies reveal that synovial $CX3CR1^+$ resident macrophages maintain RA immune homeostasis by forming a physical barrier to limit inflammatory responses[263,264], this highlights the therapeutic potential of macrophages themselves. Leveraging the abundance of peritoneal macrophages. Zhang et al.[265] have injected nuclear localization peptide-IL-10 plasmid composite nanoparticles intraperitoneally, utilizing macrophage "hitchhiking" to deliver the therapeutic gene to the joints, promoting M2-like polarization in arthritic microenvironments. The sustained target gene expression induced by this approach offers novel strategies for managing RA and other chronic inflammatory conditions. However, the use of whole cells also presents challenges. For example, the adoptive transfer of Treg cells can prevent RA progression, but these cells are prone to Th17 cell transformation during *in vitro* expansion, leading to functional loss[266]. Meanwhile, existing CAR-T therapies are constrained by autologous cell sources and narrow therapeutic windows[267,268]. These limitations drive the development of novel therapeutic agents. At the pathological mechanism level, immunomics has revealed that precursor DCs (pre-DCs), the progenitors of immature DCs, are closely linked to RA treatment resistance. Their abundance changes in peripheral blood can serve as prognostic markers, and DCs’ immunometabolic reprogramming has been identified as a potential intervention target[269,270]. The central role of B cells in synovial lymphoid aggregates highlights the therapeutic value of targeted depletion or functional blockade[68]. Furthermore, the regulatory effect of mast cell dopamine D3 receptors (D3R) on TLR4 and the remodeling of activation phenotypes mediated by Mas-related G protein-coupled receptor-X2 (MRGPRX2) have opened new avenues for RA treatment[83,271]. These discoveries provide a theoretical foundation for overcoming traditional therapeutic bottlenecks in RA.

Cell-membrane-based anti-inflammatory therapy: The cell membrane coating strategy provides nanocarriers with biomimetic camouflage. This approach bypasses the complexities associated with utilizing live cells while simultaneously conferring favorable biocompatibility, prolonged systemic circulation time, and inherent inflammatory tropism. It is particularly well-suited for encapsulating nanomedicines featuring a microenvironment-responsive core. For example, Ma et al.[272] have developed a multifunctional probe termed mZPMG NPs. They loaded methotrexate (MTX) and glucose oxidase (GOx) into a zinc imidazolate framework-8 (ZIF-8) core, combined it with platinum nanoparticles (Pt NPs), and subsequently coated it with a macrophage cell membrane. The macrophage membrane coating significantly enhanced the accumulation of MM-ZIF-8-Pt NPs-MTX-GOx (mZPMG NPs) within inflamed joints. In a collagen-induced arthritis (CIA) mouse model, administration of mZPMG NPs resulted in a 72.92% reduction in clinical arthritis scores compared to treatment with PBS.

EV-based anti-inflammatory therapy: Engineered EVs demonstrate prominent potential in achieving smart responses to RA inflammatory cues (such as specific enzymes and chemokines), multifunctional integration, superior nano-sized advantages, and enhanced safety profiles. Wang et al.[273] have modified the membrane surface of M2-like macrophage exosomes by maleimide-mercapto reaction and carboxyl-amino reactions with 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride and *N*-hydroxysuccinimide to modify with oligo-lysine and MMP-responsive PEG, respectively, to obtain MEX. After intravenous administration, PEG prolongs circulation, while CCR2 on MEX responds to CCL2 in inflamed joints, enabling enrichment at lesions. MMP cleavage of PEG exposes oligolysine to clear cfDNA. In CIA mouse models, the M2/M1 ratio in the treatment group

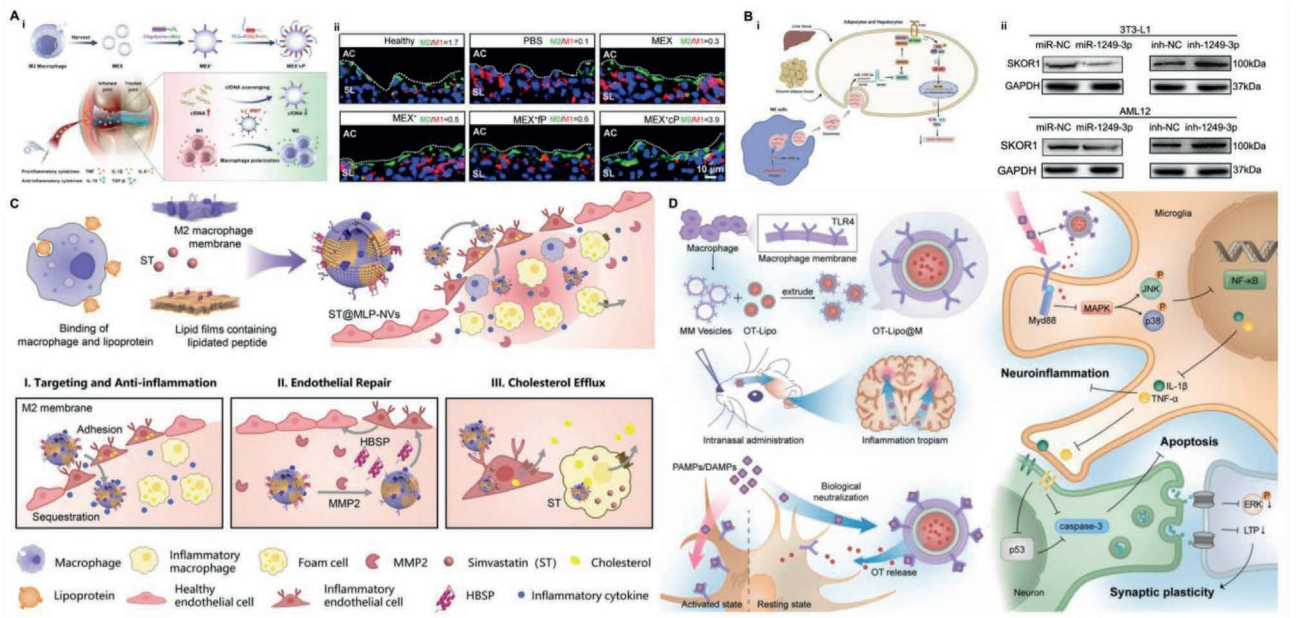

Figure 13 Examples of ICTAs treating a disease by suppressing inflammation in RA, DM, AS and AD. (A) MEX + cP ameliorate CIA. (i) Design and preparation of MEX + cP. (ii) The spatial distribution of M1-like macrophages. Reprinted with the permission from Ref. 273. Copyright©2023, John Wiley and Sons. (B) MiR-1249-3p relieves insulin resistance and inflammation. (i) NK-derived exosomal miR-1249-3p regulates insulin resistance in type 2 diabetes mice. (ii) The expression of SKOR1 protein in 3T3-L1 adipocytes. Reprinted with the permission from Ref. 274. Copyright©2021, Springer Nature. (C) Schematic diagram of the MLP-NVs preparation process. Reprinted with the permission from Ref. 235. Copyright©2022, John Wiley and Sons. (D) OT-Lipo@M and its anti-AD mechanisms. Reprinted with the permission from Ref. 275. Copyright©2023, Elsevier.

surged to 3.9 (*vs.* 0.1 in PBS controls), effectively reversing the inflammatory microenvironment. Furthermore, the abundance of peritoneal macrophages is exploited, too (Fig. 13A).

5.2.2. *DM*

DM is a chronic inflammatory disease characterized by persistent hyperglycemia, primarily classified into T1D and T2D, with T2D being more prevalent.

T1D is an autoimmune disorder in which T cells attack and destroy insulin-producing β cells in pancreatic islets[276]. Conventional treatments rely mainly on exogenous insulin supplementation, which fails to cure the disease and leaves patients vulnerable to multiple complications. Teplizumab, currently the most advanced immunotherapy for T1D, is used in Phase II and III patients, but its efficacy diminishes over time. As with RA, B cell depletion to inhibit antigen presentation has been explored for T1D treatment, yet the effects are neither universal nor sustained[277]. T2D is a prevalent metabolic disorder characterized by persistent hyperglycemia and insulin resistance, with disease progression often accompanied by severe long-term complications, including retinopathy, nephropathy, neuropathy, stroke, myocardial infarction, heart failure, and non-alcoholic fatty liver disease. In addition to lifestyle interventions and pharmacological treatments such as metformin, glucagon-like peptide-1 (GLP-1) analogs, and sodium-glucose cotransporter-2 (SGLT-2) inhibitors, help control blood glucose while preventing complications[34,278]. Although the glucose-lowering effects of high-dose salicylates implicate inflammation as a key driver in T2D pathogenesis[279], their utility remains limited and transient. Therefore, an urgency to develop more targeted therapeutic strategies.

Whole-cell-based anti-inflammatory therapy: Given the autoimmune core pathology of T1D, cell-based strategies, particularly CAR-engineered T cells or Tregs, represent a prioritized approach. The selection criteria for such strategies emphasize precise targeting specificity for self-antigens and the sustained functional stability of therapeutic cells *in vivo*. Neutrophils, DCs, T cells, and mast cells all play critical roles in the onset and progression of T1D[280]. Neutrophils may contribute to T1D pathogenesis by infiltrating islets and interacting with other immune cells, and individuals with lower circulating neutrophil levels exhibit a higher risk of developing T1D[281,282]. DCs promote T1D by presenting β cell antigens to T cells, triggering destructive insulitis[283]. Mast cells are increased in the pancreas of T1D patients and are linked to diabetic complications (*e.g.*, nephropathy) and impaired wound healing in diabetic foot ulcers[284]. CAR-based immunotherapy represents a promising strategy to modulate immune dysregulation in T1D. Analogous to CAR-T cell therapy in oncology, identifying T1D-specific antigens is fundamental to enhancing therapeutic efficacy[285]. Fishman et al.[286] have reprogrammed $CD8^+$ T cells *via* electroporation with mRNA encoding insulin B-chain peptide (InsB15-23)/β2-microglobulin (β2m)/CD3ζ, generating engineered T cells capable of recognizing insulin B/β2-microglobulin complexes, which functions as an activation receptor for T cells, thereby the reprogrammed $CD8^+$ T cells were able to kill insulin-reactive T cells, alleviating insulitis and preventing autoimmune diabetes in NOD mice. Tenspolde et al.[229] and Adabi et al.[287] have utilized phage display technology to develop insulin-specific scFv and generate CAR-Tregs for T1D treatment by retrovirally transducing $CD4^+$ T cells with Foxp3 plasmids, marking the first creation of CAR-Tregs for this purpose.

Cell-membrane-based anti-inflammatory therapy: For the targeted delivery of anti-inflammatory or hypoglycemic drugs to chronic inflammatory sites in T2D treatment, biomimetic carriers utilizing cell membrane coatings are the preferred approach. The critical selection criteria focus on the carrier's highly efficient inflammatory tissue homing capability imparted by the membrane and the nanomedicine delivery system's stimuli-responsive drug release characteristics specific to the inflammatory microenvironment. Macrophages, the primary immune cells driving inflammation in pancreatic islets and insulin-targeted organs in T2D, contribute to diabetic neuropathy and the development of complications such as nephropathy[288,289]. Taking advantage of this mechanism, Wu et al.[219] have developed polycationic polylysine-modified anionic bovine serum albumin nanoparticles (BSA NPs) coated with peritoneal macrophage membranes (BSA@MM), which evade immune clearance, neutralize inflammatory cytokines, block inflammatory cascades, and reduce cytokine release. BSA@MM demonstrates glucose-lowering effects comparable to the antidiabetic drug glibenclamide, offering a novel strategy for T2D treatment.

EV-based anti-inflammatory therapy: When precise modulation of key insulin sensitivity signaling pathways is required in T2D, engineered EVs are prioritized. This preference arises from their ability to deliver functional molecular cargo (*e.g.*, microRNAs (miRNAs)) capable of effectively regulating specific metabolic-inflammatory pathways. The core selection criterion here centers on the cargo molecules' capacity to specifically target and repair dysfunctional disease-relevant signaling nodes. NK cells are central to obesity-induced inflammation and insulin resistance. Adipocytes in obese patients upregulate ligands for NK cell-activating receptors, promoting NK cell proliferation. Thus, NK cell-based therapeutic agents hold promise for obesity-related DM intervention. Wang et al.[274] have revealed that NK-derived exosomes from lean mice transfer functional miRNA (miR-12349-3p) to adipocytes and hepatocytes *via* intercellular communication, miR-12349-3p directly targets the SKOR1 gene, regulating the formation of the SMAD6/MYD88/SMURF1 ternary complex and mediating glucose homeostasis by suppressing the TLR4/NF-κB signaling pathway (Fig. 13B). This significantly alleviates insulin resistance and chronic inflammation in mice with obesity-induced T2D.

5.2.3. AS

AS is a chronic inflammatory disease of arterial walls characterized by the formation of plaques containing lipids, connective tissue, and immune cells in the intima of medium-to-large arteries[290]. Despite current interventions targeting hypertension, hyperlipidemia, and anticoagulation therapy, overall therapeutic efficacy remains suboptimal, and the high risk of recurrent events underscores the central role of inflammatory mechanisms in disease progression[235,291]. In early atherosclerotic lesions, chronic inflammation arises from persistent activation of arterial immune cells due to ongoing inflammatory stimuli or failed resolution of inflammation[292]. These immune cells are predominantly monocytes/macrophages[293,294].

Whole-cell-based anti-inflammatory therapy: When the therapeutic goal requires direct execution of complex biological functions, such as targeted lysis of pathogenic cells or modulation of efferocytosis, engineered whole cells represent the preferred strategy due to their inherent functional activity and phenotypic stability. Senescent cells are critical drivers in the formation and progression of atherosclerosis. Amor et al. [295] identified urokinase-type plasminogen activator receptor (uPAR), a target specifically expressed on senescent cell surfaces, through screening in three senescence models. Subsequently, they constructed uPAR-targeted CAR-T cells. By virtue of the living cells' capacity to actively infiltrate diseased tissue and execute precise cytolytic activity, these CAR-T cells demonstrated highly efficient senescent cell clearance across multiple models, thereby mitigating chronic tissue damage. Yao et al. [296] employed a freeze-thaw/lyophilization approach to generate deceased macrophages. These cellular structures not only retained the "homing" capability intrinsic to macrophages but also effectively delivered efferocytosis-promoting therapeutics (*e.g.*, atorvastatin) to inflammatory plaques, facilitating high drug accumulation at the lesion site. This targeted delivery modulated macrophage immunology within the plaque, suppressing AS progression. Crucially, the deceased macrophages maintained their original phenotypic profile within the inflammatory plaque microenvironment.

Cell-membrane-based anti-inflammatory therapy: For scenarios necessitating penetration of barrier-rich lesion microenvironments (*e.g.*, endothelial physical barriers, immune phagocytic effects), cell membrane-based carriers offer superior advantages by leveraging the natural targeting and immune evasion properties conferred by their membrane proteins. Given that monocyte influx into the arterial wall is a hallmark of all stages of AS, Huang et al.[297] have developed monocyte membrane-coated PLGA nanoparticles (MoNPs) that enhance VCAM1-dependent interactions with inflamed endothelium, reduce phagocytic uptake, and promote MoNP accumulation at atherosclerotic sites. This effectively suppresses yes-associated protein (YAP) and transcriptional coactivator with PDZ-binding domain (TAZ) expression, thereby inhibiting arterial inflammation in AS. Macrophages also take up oxidized low-density lipoprotein (oxLDL) to form foam cells, which worsens the progression of AS[298,299]. To address this pathological feature, Guo et al. [235] have designed biomimetic hybrid nanovesicles (MLP-NVs) fused from M2-like macrophage membranes and lipidated peptides (Fig. 13C). MLP-NVs inherit scavenger receptors from M2-like macrophage membranes, sequester proinflammatory cytokines, efficiently bind and clear oxLDL, and release helix B surface peptide (HBSP) *via* matrix metalloproteinase-2 (MMP2)-responsive lipidated peptides to restore plaque endothelial function, synergistically inhibiting AS progression in mice. Neutrophils, as rapid responders in the innate immune system, contribute to AS pathogenesis by releasing granule contents such as myeloperoxidase (MPO) and neutrophil elastase through degranulation and NETs formation, directly damaging vascular endothelium and driving plaque development[300]. Liu et al. [301] have constructed a neutrophil membrane-coated zeolitic imidazolate framework-8 (ZIF-8) nanodelivery platform (AM@ZIF@NM) to transport anti-microRNA-155 antisense oligonucleotides (ASOs) to endothelial cells in atherosclerotic lesions. The neutrophil membrane enhances targeting *via* CD18/ICAM-1 interactions between neutrophil membrane proteins and endothelial cells, while the ZIF-8 "core" enables high ASO loading and efficient endolysosomal escape. AM@ZIF@NM significantly suppresses arterial inflammation and delays plaque progression by modulating the miR-155/Bcl6 axis.

EV-based anti-inflammatory therapy: For therapeutic scenarios requiring precise intervention in intracellular signaling pathways or clearance of pathogenic proteins, the core value of engineered EVs lies in their intrinsic intercellular communication capabilities and high-efficiency drug delivery properties. Beyond genetically engineered exosomes derived from SNHG12-overexpressing

macrophages (Ce-Exo), which target atherosclerotic plaques to repair DNA damage[185], Wang et al.[302] further developed engineered exosomal "nanosponges" (EVTx). These were fabricated by employing Lipofectamine 2000 Transfection Reagent to engineer the expression of a mutated EGF-A domain (H306Y) onto the surface of HEK293T-derived exosomes. This modification conferred ultra-high affinity for proprotein convertase subtilisin/kexin type 9 (PCSK9), with each EV surface accommodating approximately 400 EGF-A domains. This density enables the EVTx nanosponges to efficiently adsorb circulating PCSK9, facilitating its degradation *via* the lysosomal pathway. This mechanism achieves a fundamental "clearance" of PCSK9 at its source. Consequently, this strategy restores the cyclic expression of low-density lipoprotein receptors (LDLRs) on the hepatocyte surface membrane, effectively lowering cholesterol levels and reducing AS plaque burden.

5.2.4. AD

AD is a complex neurodegenerative disorder of the central nervous system involving multiple cascading pathological mechanisms, including abnormal deposition of β-amyloid (Aβ), hyperphosphorylation of Tau protein, and neuroinflammation. A major bottleneck in current clinical treatment lies in the BBB, which severely limits drug delivery efficiency, rendering existing therapies such as anticholinesterase agents, NMDA receptor antagonists, and monoclonal antibodies ineffective in halting disease progression[303,304]. Chronic neuroinflammation has been implicated throughout AD development, though its causal role remains debated[305]. Immunotherapy is emerging as a novel intervention strategy, with monoclonal antibodies targeting aggregated Aβ demonstrating the ability to reduce amyloid plaques and slow cognitive decline in some early-stage AD patients[306]. Engineered ICTA offers a novel pathway for addressing therapeutic impasses.

Whole-cell-based anti-inflammatory therapy: For scenarios requiring direct modulation of neuroimmune responses, engineered whole cells emerge as the ideal carrier due to their advantages in active migration capacity and sustained regulatory effects. Saetzler et al.[307] have developed Aβ-specific CAR-Tregs displaying a normal Treg phenotype, which could be activated *in vitro*, and could suppress activated $CD8^+$ T cells in a non-MHC-restricted manner, clearing pathological proteins while reshaping an immune-tolerant microenvironment, offering novel preclinical therapeutic possibilities for AD.

Cell-membrane-based anti-inflammatory therapy: When the therapeutic objective shifts to efficient clearance of neurotoxins, cell membrane-coated nanocarriers demonstrate unique efficacy through surface receptor-mediated "capture-depletion" mechanisms. Microglia and monocyte-derived macrophages hold high therapeutic potential for AD[308]. Microglia, resident macrophages in the central nervous system, become aberrantly activated and drive neurodegenerative processes in AD. Excessive neurotoxins such as LPS and Aβ aggregates bind to PRRs on microglial membranes, triggering sustained activation and cascading release of inflammatory mediators, leading to synaptic damage and neuronal dysfunction. Cheng et al.[275] have developed oxytocin-loaded macrophage membrane-coated nanocarriers derived from RAW 264.7 cells. These membrane-coated carriers evade immune clearance *via* surface membrane proteins and specifically "capture" neurotoxins through TLR4 receptors, achieving dual intervention by suppressing microglial hyperactivation and modulating inflammatory chemotaxis, offering a strategy for early AD prevention (Fig. 13D).

EV-based anti-inflammatory therapy: For therapeutic strategies necessitating delivery across the BBB to specific brain regions, engineered EVs prove indispensable, leveraging their intrinsic membrane penetrative capacity and cargo delivery advantages. Hou et al.[225] have utilized RAW 264.7 macrophage-derived exosomes loaded with silibinin (Slb). By exploiting ligand-receptor interactions between macrophage-derived exosome membranes and BBB endothelial cells, Slb is precisely delivered to affected brain regions. Slb selectively binds to $A\beta_{1-42}$ monomers to reduce deposition and internalizes into astrocytes to inhibit NF-κB pathway activation, ultimately improving synaptic integrity and cognitive function in AD model mice. These studies, through innovations in nanoengineering or genetic engineering, address AD treatment barriers across multiple dimensions, clearing toxic proteins, suppressing neuroinflammation, and restoring immune homeostasis, laying the foundation for developing AD-specific therapeutic strategies.

5.2.5. IBD

IBD is a category of digestive system disorders characterized by chronic, relapsing inflammation of the gastrointestinal mucosa. It primarily includes Crohn's disease (CD) and ulcerative colitis (UC). The core pathological features involve intestinal dysbiosis (imbalanced gut microbiota), disruption of the intestinal epithelial barrier integrity, and dysregulated host immune responses. Current treatments often employ topical anti-inflammatory agents (such as 5-aminosalicylic acid), immunosuppressants (like azathioprine and methotrexate), or biologics (such as infliximab and vedolizumab)[3,313]. However, these therapies are frequently associated with significant adverse effects and have limited efficacy. Therefore, there is an urgent need to develop novel therapeutic strategies that are more effective and safer.

Whole-cell-based anti-inflammatory therapy: When the therapeutic focus centers on rebuilding immune tolerance and achieving dynamic regulation of gut immune homeostasis, the selection of intact cells is often prioritized. This is due to their capacity for active, sustained, and dynamic regulatory functions. For example, immune cell infusion therapy represents an emerging approach for IBD. Tregs are crucial for maintaining immune tolerance, functioning by suppressing the overactivation of effector T cells (Th1/Th17) and reducing the release of pro-inflammatory cytokines (such as TNF-α and IL-17). Building upon the observation of IL-23 receptor (IL23R) overexpression in intestinal tissue samples from CD patients, Cui et al.[314] have developed an IL23R-targeting CAR and generated IL23R-CAR Tregs. Notably, these IL23R-CAR Tregs retain their regulatory phenotype even within pro-inflammatory environments and elicit a specific activation against colon biopsy-derived cells from active CD, representing a promising therapy for active CD.

Furthermore, specific functionalized dead cells, such as macrophages, can provide an active adhesion and protective platform. While the gut microbiota is a critical therapeutic target in IBD, oral probiotics suffer from low colonization efficiency and limited therapeutic efficacy within the intestine. To address this, Wang et al.[315] have constructed a gelated peritoneal macrophage (GPM) system. Peritoneal macrophages are dispersed in a solution containing 10% PEG-DA and 0.1% I2959, then processed using a combination of low-temperature treatment and UV curing technology. This approach induces internal gelation of the macrophages while preserving their surface receptors. The resulting GPMs demonstrate an ability to neutralize multiple pro-inflammatory cytokines. Critically, *E. coli* Nissle 1917 (EcN) bound to the preserved TLRs on the GPM surface through ligand-receptor interactions, forming GPM-EcN complexes. Compared to adhesion

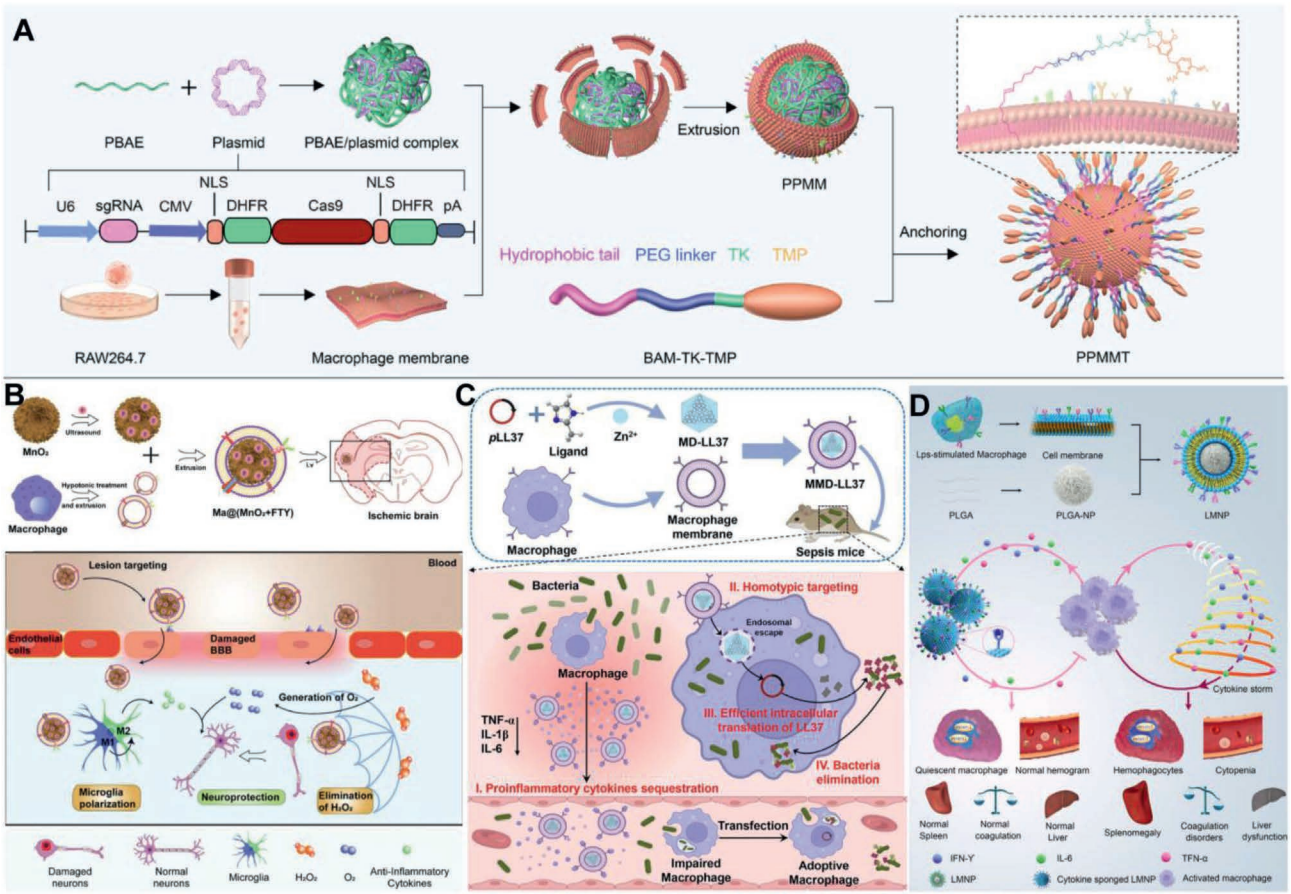

Figure 14 Examples of ICTAs treating a disease by suppressing inflammation in IBD, IRI, sepsis, and HLH. (A) Schematic illustration of the NanoProCas9 system. Reprinted with the permission from Ref. 309. Copyright©2021, John Wiley and Sons. (B) The formation and accumulation of Ma@(MnO2+FTY) in ischemic brain. Reprinted with the permission from Ref. 310. Copyright©2021, The American Association for the Advancement of Science. (C) MMD-LL37 for the treatment of sepsis. Reprinted with the permission from Ref. 311. Copyright©2022, American Chemical Society. (D) Schematic illustration of LMNP for the treatment of HLH. Reprinted with the permission from Ref. 312. Copyright©2023, Elsevier.

rates on normal Caco-2 cells (58.7%), GPM adhesion significantly increases to 78.3% on inflamed Caco-2 cells. This enhanced adhesion markedly improves EcN retention in inflamed intestinal regions, thereby offering a novel strategy for targeted probiotic delivery.

Cell-membrane-based anti-inflammatory therapy: Cell membrane coating technology proves particularly advantageous when precise targeting of colonic lesions, penetration of the mucus barrier, and localized execution of intelligent responsive therapy are required. Recognizing the pivotal role of macrophages in regulating intestinal inflammation in IBD patients, Yan et al.[309] have engineered a targeted biomimetic nanocomplex called NanoProCas9. This platform utilizes a three-pronged approach for precision therapy: initially, the cationic polymer PBAE condenses a trimethoprim-regulated dsCas9 plasmid to form the nanoparticle core; subsequently, encapsulation with a macrophage membrane enables inflammatory chemokine-mediated targeted delivery; finally, hydrophobic modification with a ROS-responsive trimethoprim prodrug molecule establishes a microenvironment-triggered activation mechanism. Following intravenous administration, inflammatory homing driven by receptors on the macrophage membrane directs NanoProCas9 accumulation to colonic lesions. The locally elevated ROS microenvironment then activates the prodrug, initiating the CRISPR-Cas9 system to perform gene editing on *PHD2*, a key pro-inflammatory mediator. This strategy effectively preserves colonic epithelial barrier integrity while significantly suppressing TNF-α expression in diseased tissues (Fig. 14A).

Similarly, leveraging the observation that inflammatory cytokine receptors (including TNFR1 and IL-6R) exhibit higher expression on M2-like macrophages compared to M1-like or M0-like subtypes, Luo et al.[316] have coated M2-like macrophage membranes (M2M) onto self-propelling "nanomotors" (Motor@M2M), which deplete H_2O_2 to generate O_2 and incorporate them into sodium alginate microspheres (SAMs). The Motor@M2M complex employs membrane receptors (such as LFA-1 and VLA-4) to anchor onto inflamed colonic epithelium, neutralizing cytokines directly at the site. Its autonomous propulsion facilitates penetration through the mucus barrier for deeper tissue access, thereby mitigating oxidative stress and inflammation through hydrogen peroxide depletion, hypoxia alleviation (*via* HIF-1α expression inhibition), and induced macrophage reprogramming.

EV-based anti-inflammatory therapy: For developing efficient oral biologics to synergistically repair IBD damage, EVs are the preferred engineering platform due to their natural biomembrane

structure, which effectively protects protein payloads from enzymatic and acidic degradation. Molinaro et al. [317] have extracted immune cell membrane proteins and reassembled them onto lipid nanoparticles, extruding the mixture to yield composite vesicles called "Leukosomes". These Leukosomes combine the physical stability of liposomes with the functional properties of biological membranes. After successful encapsulation of the glucocorticoid dexamethasone, they demonstrate specific inflammation-targeting capabilities.

In a similar way, Liu et al.[318] have developed an orally deliverable, genetically engineered EV system (Gal-IL10-EVs). They first used Lipofectamine 3000 transfection to enable stable expression of the immunomodulatory factor IL-10 in HEK 293T cells. Differential centrifugation is employed to isolate IL-10-loaded EVs. Subsequently, a galactose-targeting peptide is incorporated *via* hydrophobic insertion to enhance specific recognition by macrophages. Finally, the EVs are encapsulated within a pH-responsive chitosan-alginate hydrogel. This coating facilitates drug release triggered by the colonic inflammatory microenvironment, enabling targeted IL-10 delivery. This approach reshapes macrophage phenotype, scavenges excess ROS, and reduces the secretion of pro-inflammatory cytokines, significantly ameliorating experimental colitis pathology. Collectively, this work provides a novel approach for oral biologic delivery in IBD treatment.

5.2.6. *IRI*

IRI is a distinct form of irreversible tissue damage that occurs in blood-rich vital organs, such as the heart, brain, liver, and kidneys, following the restoration of blood supply after a period of ischemia. Its hallmark features include exacerbated oxidative stress and inflammatory responses at the injury site, leading to increased cellular apoptosis and worsened tissue damage. The pathogenesis of IRI is complex, with its core mechanisms centered on free radical damage and calcium overload. Current clinical management primarily focuses on minimizing ischemic duration or administering anti-inflammatory agents and antioxidants[319,320]. However, these strategies offer limited effectiveness and carry risks of off-target toxicity. There is a pressing need to develop organ-selective drug delivery strategies to overcome these fundamental treatment limitations.

Whole-cell-based anti-inflammatory therapy: In the context of cerebral IRI, whole living cells emerge as the optimal delivery strategy when therapeutic interventions require rapid transit through inflammation-induced, transiently permeable physiological barriers (*e.g.*, the BBB) within the critical early reperfusion window (hours post-ischemia), while simultaneously leveraging immune cells for active molecule protection. Macrophages, neutrophils, and T cells inherently migrate toward inflammatory lesions. Illustrating this approach, Zhang et al.[321] have engineered a neutrophil-targeting delivery system termed *c*/PGP-PEG-DGL/CAT-Aco. This system consists of *cis*-palmitic anhydride-modified catalase encapsulated within crosslinked dendrigraft poly-L-lysine (DGL) nanoparticles, surface-functionalized with the neutrophil-targeting peptide PGP. *c*/PGP-PEG-DGL/CAT-Aco exhibits high-affinity binding to the neutrophil CXCR2 receptor ($K_D = 1.576 \times 10^{-7}$ mol/L, comparable to free PGP). The nanoparticles successfully evade lysosomal degradation within neutrophils *via* the proton sponge effect. Under this protective cellular transport, catalase enzymatic activity remains preserved. Subsequently, exosome-mediated shuttling facilitates neuronal delivery of the therapeutic cargo, resulting in significant attenuation of H_2O_2-induced neuroinflammation.

Cell-membrane-based anti-inflammatory therapy: When therapeutic development requires multifunctional integration, including lesion targeting, ROS scavenging, anti-inflammatory polarization, and physical barrier repair within a single carrier, while leveraging microenvironmental cues (*e.g.*, elevated ROS, chemokine gradients) to trigger responsive behaviors, cell membrane-based technologies represent the optimal solution. Within the evolution of brain-targeted delivery systems, macrophage membrane-derived therapeutics demonstrate dual value: crossing the BBB and modulating diseased microenvironments. Li et al. [310] have engineered macrophage membrane-coated MnO_2 nanoparticles loaded with fingolimod, that is Ma@(MnO_2+FTY). The macrophage membrane confers targeted chemotaxis toward inflammatory lesions. The high-surface-area MnO_2 nanoparticles efficiently scavenge excess ROS while generating O_2 to mitigate neuronal death. Simultaneously, fingolimod polarizes microglia toward the protective M2-like phenotype in ischemic brains, reversing pro-inflammatory microenvironments and reducing reperfusion injury (Fig. 14B).

EV-based anti-inflammatory therapy: For therapeutic interventions requiring persistent penetration of reconstructed physiological barriers during later IRI stages (hours post-event), while protecting nucleic acid/protein therapeutics against oxidative/proteolytic microenvironments, engineered EVs are emerging as a primary breakthrough strategy in targeted delivery. Given that NETs amplify inflammatory tissue damage while impairing revascularization and vascular remodeling post-stroke, Wang et al.[322] have developed M2-like macrophage-derived exosomes (M2exo) encapsulating DNase 1 (M2exo@DNase 1). These exosomes cross the BBB and accumulate in peri-ischemic areas. As M2exo secretes anti-inflammatory cytokines, resident microglia polarize to the M2-like phenotype, exerting neuroprotection. Furthermore, DNase 1 released from exosomes degrades pathological NETs, dampening inflammation and promoting vascular remodeling, thereby establishing a viable therapeutic strategy for cerebral IRI. Cheng et al.[323] have generated RVG-modified EVs through Lamp2b-RVG plasmid transfection of HEK293T cells. This approach leverages lysosome-associated membrane protein 2b (LAMP2b) as an exosomal surface anchor fused to the rabies virus glycoprotein (RVG) peptide, conferring BBB penetration and specific neuronal acetylcholine receptor targeting. Post-transfection, differential centrifugation yields RVG-functionalized EVs (RVG-EVs). Subsequently, electroporation is used to load miR-100-5p antagonists into RVG-EVs, creating the engineered construct RVG-EVs-Antagomir. Following intranasal administration in hypoxic-ischemic (HI) mouse models, RVG-EVs-Antagomir selectively accumulated in ipsilateral brain lesions, effectively reducing miR-100-5p levels. Critically, treatment administered within a 24-h window preceding or following HI injury significantly counteracts brain damage, demonstrating an expanded therapeutic time frame for HI intervention.

5.2.7. *Sepsis*

Sepsis is a systemic inflammatory clinical syndrome triggered by pathogenic infections, frequently leading to organ dysfunction with unfavorable prognoses and high mortality rates. Confronted with the dual challenges of pathogen clearance and cytokine storm modulation, conventional therapies often fall short[324,325]. Engineering strategies that endow immune cells or their derivatives

with targeted anti-inflammatory and bactericidal functions are forging innovative paths for immunomodulatory sepsis treatment.

Whole-cell-based anti-inflammatory therapy: To reactivate the innate phagocytic/killing functions of immune cells while counteracting pathogens' intracellular evasion tactics, engineered whole cells can reverse immunoparalysis. Although macrophages, as central effectors of innate immunity, possess dual phagocytic/bactericidal and immunomodulatory capabilities, they become functionally impaired during sepsis. Addressing this, Liu et al.[326] have engineered macrophages by direct co-incubation with the novel antimicrobial luminescent small molecule TPA2PyPh. This luminophore specifically binds to intracellular lipid droplets. The engineered macrophages leverage natural lipid uptake mechanisms to deliver the luminescent cargo to intracellular pathogens post-phagocytosis, enabling highly efficient clearance of multidrug-resistant bacteria in sepsis through dual disruption of bacterial membranes and DNA.

Concurrently targeting *Staphylococcus aureus* immune evasion, Tang et al.[327] have designed CAR mRNA directed against *S. aureus* surface protein A (SasA), co-encapsulated with siRNA against caspase-11 (siCASP11), which enhances mitochondrial reactive oxygen species (mtROS) killing in LNPs. Surface modification of LNPs with macrophage-targeting peptide CRV enabled *in vivo* generation of CAR MΦ upon intravenous administration, significantly boosting extracellular MRSA phagocytosis while blocking intracellular survival. Developing an alternative approach, Zhou et al.[328] have employed neutrophils as carriers. Using click chemistry, they conjugate the CXCR2-targeting peptide Ac-PGP to DNA tetrahedrons, creating the APT delivery system. Circulating neutrophils internalize APT and transport it to inflammatory sites, where tetrahedron-encapsulated anti-inflammatory agent baicalin is released.

Cell-membrane-based anti-inflammatory therapy: A critical unmet need exists for single-vehicle platforms integrating pathogen targeting, antimicrobial gene delivery, cytokine neutralization, and antioxidant functions, while leveraging sepsis microenvironmental cues (*e.g.*, elevated ROS, dysregulated pH) to engineer intelligently responsive therapeutics. Sepsis-associated encephalopathy (SAE), a severe complication frequently observed in ICU patients with sepsis, is pathophysiologically rooted in dysregulated oxidative stress-inflammatory cascades. Addressing this, Qu et al.[329] have developed macrophage membrane-cloaked metal-coordinated polyphenol (tannic acid) and flavonoid (quercetin) nanoparticles (mAOI NPs). Exploiting the homotypic targeting properties of macrophage membranes, mAOI NPs selectively accumulate at inflammatory loci, synergistically modulating oxidative stress and inflammatory responses to mitigate sepsis progression. In a cognate strategy, Cao et al.[311] have engineered pH-responsive metal-organic frameworks (MOFs) encapsulated with plasmid DNA encoding the antimicrobial peptide LL-37, subsequently cloaked with macrophage membranes (MMD-LL37). This design achieves dual functionality: the membrane coating facilitates targeted macrophage-specific delivery, enabling sustained *in vivo* antimicrobial peptide production, while membrane-bound receptors adsorb proinflammatory cytokines, suppressing sepsis amplification pathways (Fig. 14C).

EV-based anti-inflammatory therapy: Engineered apoptotic EVs offer unique advantages when simultaneous requirements exist for capturing diffusible pathogen toxins, blocking nutrient scavenging mechanisms such as siderophore-mediated iron acquisition, and precisely modulating immune cell phenotypes. During infection, pathogens can induce pyroptosis or necrosis to disrupt tissue niches, thereby activating innate immune clearance through mechanisms like pore-induced intracellular traps (PITs) or NETs. Capitalizing on this biological principle, Li et al.[330] have developed macrophage-derived engineered apoEVs loaded with anti-inflammatory mesoporous silica nanoparticles carrying microRNA-146a. These multifunctional vesicles serve as molecular decoys that capture iron-binding proteins to neutralize bacterial toxins while concurrently delivering microRNA-146a payloads to phagocytes for inflammation resolution. Notably, apoEVs derived from alternative cellular sources, including erythrocytes and mesenchymal stem cells, demonstrate comparable potential for targeted delivery to inflammatory sites, suppression of inflammatory cell infiltration, and attenuation of pro-inflammatory cytokine secretion[330,331].

5.2.8. HLH

HLH represents a multifactorial, life-threatening hyperinflammatory syndrome characterized by dysregulated activation and proliferation of lymphocytes, monocytes, and macrophages. This cascade, triggered by intrinsic or extrinsic pathogenic factors, drives uncontrolled release of inflammatory cytokines culminating in cytokine storms that frequently progress to multiorgan failure and mortality. While core pathophysiological mechanisms are increasingly understood, targeted therapeutic options remain limited. Currently, only emapalumab (an interferon-γ-directed monoclonal antibody) is approved for primary HLH[332,333]. To address these therapeutic bottlenecks, innovative strategies continue to emerge.

Whole-cell-based anti-inflammatory therapy: Whole-cell therapeutic approaches aim to directly reprogram key immune cells like lymphocytes to correct intrinsic defects. CAR-T cell-associated HLH constitutes a distinct pathological entity independent of CRS, typically emerging during or after CRS resolution. Ye et al.[334] have documented sustained complete remission (CR) in patients treated with a novel bispecific loop-structured CD19/CD22 CAR-T therapy (CD19/CD22 BS LoopCAR-T). Notably, patients exhibit only grade 1 CRS while achieving durable therapeutic responses.

Cell-membrane-based anti-inflammatory therapy: Cellular membrane strategies prioritize efficient neutralization and clearance of circulating inflammatory mediators to rapidly quell cytokine storms. Given the pivotal role of activated macrophages, which phagocytose blood cells and secrete excessive IFN-γ, TNF-α, and IL-6 in HLH pathogenesis, Wang et al.[312] have engineered cytokine nanosponges (LMNPs) by coating PLGA nanoparticles with membranes from lipopolysaccharide-activated macrophages (Fig. 14D). Compared to particles derived from unstimulated macrophages (MNPs), LMNPs retain membrane-bound cytokine receptors (*e.g.*, IFN-γR, IL-6R), enhancing adsorption of recombinant murine IFN-γ and IL-6 (76.3% and 63.1%, respectively). Remarkably, LMNP administration (4 doses) achieves 100% survival at 96 h post-induction in murine models, where untreated controls succumbed within 12 h.

EV-based anti-inflammatory therapy: To date, no clinical evidence exists for EV-based therapies directly applied to HLH. Nevertheless, EVs emerge as a promising innovative strategy to address HLH challenges, leveraging their inherent biological properties and significant immunomodulatory potential. HLH subtypes demonstrate markedly heterogeneous cytokine profiles, exemplified by extreme elevations of IFN-γ and IL-18 in primary

HLH, along with rapid disease progression and compelling needs for personalized therapy. Beyond allogeneic hematopoietic stem cell transplantation (allo-HSCT), which can potentially cure select primary HLH cases but carries substantial risks including graft-versus-host disease and infections, current therapies lack the combined efficacy, precision, and safety required for optimal management. The therapeutic promise of engineered EVs resides in several key attributes: Their innate tropism and biological barrier-penetrating capabilities enable precision delivery to cellular "storm epicenters" when engineered with surface ligands targeting receptors on hyperactivated macrophages or T lymphocytes. Simultaneously, EVs serve as versatile multi-cargo platforms capable of transporting combinatorial therapeutic payloads. Crucially, engineered EVs exhibit superior safety profiles compared to whole-cell approaches due to their inherent lack of replicative capacity, thereby mitigating risks of oncogenesis and uncontrolled proliferation. Future research delineating stage-specific immune microenvironmental dynamics and molecular drivers across HLH subtypes will establish the foundation for highly tailored, precision-engineered EV therapeutics, potentially inaugurating a transformative treatment paradigm for this complex syndrome.

6. Clinical applications and challenges

As previously mentioned, ICTAs have demonstrated significant potential in the immunotherapy of inflammatory diseases due to their ability to utilize patients' own cells for personalized treatment, garnering widespread attention from both academia and industry. Currently, numerous clinical trials involving ICTAs are being conducted for a variety of diseases, with engineered cell products such as CAR-T and CAR-M emerging as prominent directions in the field (Table 4). In terms of ICTAs types, current clinical trials for ICTAs primarily focus on whole cells, particularly T cells. The core of this strategy involves using genetic engineering techniques, such as CARs, to equip immune cells with specific targeting and cytotoxic capabilities, thereby directly eliminating abnormal cells. Among engineering strategies, genetic engineered ICTAs are the most widely used, and their development has been propelled by several key milestones: for instance, the FDA's approval of the first personalized immunotherapy product, Sipuleucel-T, for prostate cancer in 2011, and the successful cure of pediatric leukemia patients using CAR-T cell therapy in 2012 (Fig. 3). These breakthroughs have significantly accelerated the rapid advancement of the field, and multiple CAR-based products have now been approved for treating various hematologic malignancies. In the treatment of solid tumors, such as glioblastoma, gastric cancer, and prostate cancer, CAR therapy has long faced major challenges due to the highly heterogeneous and strongly immunosuppressive nature of the TME. In recent years, technological innovations, including localized delivery strategies and dual-target CAR designs, have led to critical advancements in solid tumor applications. New-generation CAR technologies are now systematically addressing core issues such as antigen heterogeneity, immune evasion, and immunosuppressive microenvironments. For example, studies have shown that using Ad5F35 adenoviral vectors to deliver CAR-CD3ζ to primary human macrophages promotes their polarization toward a pro-inflammatory M1-like phenotype (upregulating CD80/CD86), suppresses anti-inflammatory M2-like markers (such as CD163), and induces the expression of pro-inflammatory cytokines and chemokines. This, in turn, reverses neighboring M2-like macrophages to an M1-like phenotype, effectively countering the immunosuppressive state[169]. Additionally, the world's first non-viral, membrane-bound IL-7 engineered TIL therapy (NCT05468307) achieved an 83.3% disease control rate and a 68.8% one-year overall survival rate in patients with recurrent ovarian cancer, demonstrating promising clinical prospects. Notably, the success of genetically engineered ICTAs is not limited to oncology. In recent years, such therapeutic strategies have been extended to non-oncologic inflammatory diseases, including autoimmune conditions such as RA, DM, and SLE. Georg Schett's team pioneered the successful use of CD19 CAR-T cells to treat SLE patients, achieving rapid clearance of pathogenic B cells and inducing disease remission. Subsequent clinical studies have continued to validate its therapeutic potential. This cross-disciplinary application fully demonstrates the broad potential of ICTAs in immune regulation.

However, the clinical translation of ICTAs still faces numerous challenges. For example, a "cell backpack" therapy using IL-15Fc nanogels loaded into peripheral blood T cells for solid tumor treatment (NCT03815682) was terminated early due to a lack of clinical efficacy. The failure may be attributed to technical bottlenecks such as the complex manufacturing process of nano-engineered ICTAs, poor carrier stability, and gradual loss of function *in vivo* over time. Furthermore, safety and durability issues, including CRS triggered by CAR-T therapy (NCT02435849)

Table 5 Summary of the three types of ICTAs.

Characteristic	Whole cell	Cell membrane	EVs
Delivery capability	Low	High	High
Targeting specificity	High	Moderate	Moderate
Scalability	Low	High	Moderate
Immunogenicity	High	Low	Moderate
Half-life	Long (several days to several weeks)	Short to medium (a few hours to several days)	Short to medium (a few hours to several days)
Advantages	Complete biological functions	Multi-functional bionic camouflage	Natural nanoscale dimensions
Defects	Difficult & costly cell culture	Membrane protein instability	Low yield & high heterogeneity in purification
Applicability	Require active, sustained, and dynamic biological functions of cells (such as direct killing or local immune modulation)	Circumvent the complexity of living cells while retain membrane proteins (such as local immune modulation)	Transport functional molecules and precise intercellular communication (such as direct killing or local immune modulation)

and the limited persistence of CAR-M cells *in vivo* (NCT04660929), remain critical considerations in the clinical translation process. To overcome current limitations and further optimize the efficacy and safety of ICTAs, multiple strategies are being explored. For instance, the introduction of controllable gene expression switches, optimization of nanomaterial delivery efficiency, development of novel membrane fusion technologies, and incorporation of microenvironment-modulating factors are expected to enhance the targeting, persistence, and safety of ICTAs, thereby broadening their clinical application prospects.

7. Outlooks

ICTAs have emerged as a highly promising strategy for intervening in inflammation-related diseases by effectively integrating the diverse innate physiological functions of immune cells in inflammatory microenvironments, including inflammation regulation, intrinsic targeting, drug delivery, and deep tissue penetration. The three major types of ICTAs, including whole cells, cell membranes, and EVs, each possess distinct advantages and limitations in preparation, functionality, and clinical applicability (Table 5). From a preparation standpoint, ICTAs constructed from immune cell membranes are the simplest and most technically mature to fabricate. However, the integrity of functional membrane proteins may be compromised during extraction due to mechanical or chemical stresses. EVs retain the therapeutic activity of parental cell components, yet they suffer from low isolation yield, significant heterogeneity, and difficulties in purification and standardization. In contrast, whole cells entail the highest complexity in acquisition, preparation, and storage, as they require careful balance among drug loading, controlled release, targeting accuracy, and preservation of cell viability. Regarding drug-loading capacity, whole cells are constrained by their limited intracellular space and metabolic tolerance, which restricts payload capacity and necessitates careful evaluation of cargo cytotoxicity. Conversely, both cell membranes and EVs support higher drug loading through surface modification or internal encapsulation, accommodating a wider variety of therapeutic molecules. In terms of functional performance, whole cells exhibit exceptional targeting specificity and sustained efficacy owing to their autonomous biological activity and intact signaling machinery. However, they also provoke strong immune responses and are difficult to produce at scale due to stringent viability and culture requirements. Cell membranes strike a balance by retaining targeting proteins while reducing immunogenicity, supporting efficient drug loading and scalable production. Nonetheless, without endogenous support, their membrane proteins may gradually lose function, resulting in moderate *in vivo* persistence. EVs, as natural nanovesicles, demonstrate favorable biocompatibility and efficient cellular uptake but face challenges related to heterogeneity in size, composition, and cargo, which impede batch-to-batch consistency and large-scale manufacturing. Additionally, their inherent biological cargo (*e.g.*, DNA, mRNA, microRNA and no-coding RNA) may carry risks of unintended immune activation. Notably, recent technological innovations, such as controlled exosome release systems, prodrug strategies, microneedles, scaffolds, and stimuli-responsive biomaterials, have enabled more precise regulation of therapeutic delivery and efficacy. These advances help overcome inherent challenges in maintaining viability and achieving spatiotemporal control of drug release, thereby accelerating the clinical translation of ICTAs. In practical applications, the choice of ICTAs platform should be guided by specific disease contexts, therapeutic windows, and pharmacokinetic requirements. When necessary, a multi-platform combination strategy can be adopted to leverage synergistic effects.

In the engineering of ICTAs, nanoengineering, genetic engineering, and membrane-fused engineering each has unique advantages and limitations. The core advantage of nanoengineered ICTAs lies in their precise and controllable drug delivery and release capabilities. These technologies leverage endogenous microenvironmental cues (*e.g.*, weak acidity, high enzyme concentrations, or glutathione) and exogenous stimuli (*e.g.*, light, magnetic fields, ultrasound) to achieve spatiotemporally controlled drug release and theranostic integration, with minimal impact on cellular functions. Nevertheless, their targeting efficiency remains limited by the complex physical barriers and heterogeneity of the TME, such as abnormal vascular structures and interstitial hypertension, which hinder nanoparticle penetration and uniform distribution. However, nanoengineered ICTAs still face challenges such as complex manufacturing processes, potential immunogenicity of nanomaterials, and unclear long-term biosafety. Additionally, nanomaterials may affect cell viability by inducing apoptosis or metabolic disorders, and their functions may degrade over time *in vivo*. The scalability of production, quality control, and unpredictability of *in vivo* behavior severely limit clinical translation, necessitating a balance between efficacy and risk. In contrast, genetic engineered ICTAs have developed more rapidly and extensively. This technology fundamentally endows immune cells with novel and durable functions, such as enhanced targeted killing through the expression of CARs or microenvironment modulation *via* secretion of specific cytokines. However, safety concerns remain, such as insertional mutagenesis from viral vectors, off-target effects of gene editing, and severe adverse events like cytokine release syndrome. Biological barriers, including host immune rejection of engineered cells and low homing efficiency, also limit long-term efficacy. The complex manufacturing process, high costs, and challenges in regulating *in vivo* activity further hinder progress, particularly in highly heterogeneous TMEs where targeting efficiency and cellular persistence remain unstable. Membrane-fused engineered ICTAs offer an alternative technological approach. This strategy mimics natural membrane fusion mechanisms (*e.g.*, SNARE, gp41, hemagglutinin) to achieve cell−to−cell or cell−liposome fusion, enabling rapid introduction of exogenous membrane components or intracellular materials into immune cells. This method is efficient and rapid, avoids complex genetic manipulations, significantly shortens preparation time, and may reduce costs. However, the overall maturity of this technology remains low, with challenges in fusion efficiency and specificity. Non-specific fusion may lead to off-target toxicity and impair normal cell function; post-fusion cell viability may decline due to membrane disruption or content leakage; and the introduced functions often lack durability, struggling to maintain stable performance in dynamic *in vivo* environments. Moreover, in highly complex TMEs, fusion efficiency may be inhibited by factors such as proteolytic enzyme activity or differences in membrane fluidity, further limiting targeting efficiency and therapeutic outcomes. Thus, while fusion engineering strategies are attractive for their simplified preparation, their stability, reliability, and safety require further systematic validation. These engineering strategies are equally applicable to the modification of non-immune cell types, including bacteria and mesenchymal stem cells. For instance, nanoengineering can

be employed to enhance the targeted drug delivery capabilities of bacteria, while genetic engineering can be used to modify mesenchymal stem cells to express specific therapeutic factors, thereby expanding their potential applications in areas such as tumor treatment, tissue repair, and regenerative medicine. Clinical applications require tailored optimization based on disease microenvironment characteristics, therapeutic window demands, and safety thresholds.

Despite their immense potential, the clinical translation and industrialization of ICTAs still face significant challenges. First, the immunogenicity of allogeneic cell sources and personalized manufacturing models hinders large-scale production. Future efforts must establish standardized drug-loading processes to ensure batch-to-batch consistency. Therapeutic standards vary depending on the delivery vehicle. For whole-cell-based therapies, the ultimate goal is to achieve stable *in vivo* survival, proliferation, and sustained functionality, while rigorously monitoring biodistribution, immunogenicity, and long-term safety. For cell-membrane-based therapies, the emphasis lies in the integrity of membrane protein function, batch-to-batch uniformity in scaled production, and *in vivo* targeting efficiency. In contrast, the criteria for EV therapies are the most complex, centering on rigorous identification (such as specific transmembrane protein markers like CD9/CD63/CD81), precise control of drug loading, assurance of sterility and absence of exogenous viral contamination, as well as potency assays that reflect their immunomodulatory or tissue-repair functions. Through this mechanism-based precision selection and engineering, therapeutic benefits can be maximized while potential risks are minimized in complex inflammatory environments. Second, dynamic interactions between ICTAs and host microenvironments during *in vivo* delivery, such as cellular phagocytosis, metabolic clearance, and paracrine effects, lack quantitative evaluation tools. Advanced analytical methods (*e.g.*, single-cell sequencing, proteomics, metabolomics) and mathematical models are urgently needed to elucidate the spatiotemporal distribution of ICTAs *in vivo*. Third, inflammatory diseases involve shifts in immune cell quantity, type, phenotype, and activation states across pathological stages, necessitating deeper mechanistic studies to identify universal ICTAs candidates. Fourth, given the complexity of the inflammatory microenvironment, single-type engineered immune cell therapies often struggle to achieve a complete cure for diseases. Therefore, combining them with other immunotherapy approaches (such as PD-1 monoclonal antibodies, CAR-T cell therapy), chemotherapy, radiation therapy, or phototherapy has become an important strategy. To achieve synergistic effects and avoid severe adverse reactions, it is essential to rationally design combination treatment plans based on the characteristics of each therapy and the specific conditions of the microenvironment. This approach aims to maximize therapeutic synergy while preventing serious side effects. Overall, through the integration of multidisciplinary technologies (*e.g.*, synthetic biology, smart materials, systems medicine) and standardized processes, ICTAs hold promise for groundbreaking advances in the precision treatment of inflammation-related diseases.

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Author contributions

Yuxin Yang: Writing — original draft, Methodology, Investigation. Jinhu Liu: Writing — original draft, Investigation. Jie Liu: Writing — review & editing, Conceptualization. Suyun Wei: Writing — review & editing, Supervision. Xiaohui Kong: Writing — review & editing, Supervision. Weiwei Mu: Writing — review & editing, Supervision, Resources, Conceptualization. Yongjun Liu: Writing — review & editing, Supervision, Resources, Conceptualization. Na Zhang— review & editing, Supervision, Resources, Conceptualization.

Conflicts of interest

The authors declare no competing interests.

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