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REVIEW

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Microbial reprogramming of immunogenic cell death: a new paradigm in tumor immunotherapy

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ABSTRACT Immunogenic cell death (ICD), a special form of cell death, transforms "cold" tumors into "hot" tumors by fulfilling the following three key conditions: antigenicity; adjuvanticity; and a suitable tumor microenvironment (TME). Tumor cells release damage-associated molecular patterns (DAMPs) during ICD, thereby activating the dendritic–cytotoxic T cell axis to elicit systemic antitumor immune responses. However, drug resistance and immune-related adverse effects often limit traditional ICD inducers, including chemotherapy and radiotherapy. Notably, microbiota and microbial metabolites can trigger ICD in tumor cells, leading to the release of DAMPs, modulation of immune cell functions, and TME remodeling. This study comprehensively reviews the mechanisms underlying ICD regulation *via* microbiota and microbial metabolites. In addition, this review examines emerging strategies, including engineered microbiota, microbial-based combination therapies (such as incorporating immune checkpoint inhibitors or chemotherapy), and dietary interventions. Despite challenges associated with individual microbiota variability and mechanistic complexity, this study highlights the potential of microbiota-mediated ICD modulation as a novel paradigm for personalized cancer therapy, thereby providing insights for future directions of scientific research.

KEYWORDS Immunogenic cell death; damage-associated molecular patterns; microbiota and microbial metabolites; tumor microenvironment; antitumor immune responses

Introduction

Immunogenic cell death (ICD) is among the 12 recognized modes of regulated cell death (RCD)[1]. "Cold" tumors are converted into "hot" tumors during ICD[2], resulting in the release or surface exposure of damage-associated molecular patterns (DAMPs). These DAMPs trigger pattern recognition receptors (PRRs) on antigen-presenting cells (APCs), thereby enhancing the ability of APCs to uptake, process, and present tumor antigens. This process activates antigen-specific $CD8^+$ T cell responses and establishes long-term immunologic memory[3,4]. Various therapeutic modalities, including chemotherapy, radiotherapy (RT), virotherapy, protease inhibitors, sonodynamic therapy (SDT), and photodynamic therapy (PDT), have been shown to induce ICD in tumor cells[5-8]. However, traditional ICD-inducing methods face limitations, such as drug resistance, off-target toxicity, tumor recurrence, and immune-related adverse events. Consequently, developing novel agents and strategies to induce ICD has become crucial for combination and personalized cancer therapies.

Recently, microbiota and microbial metabolites have garnered considerable attention. In 2020 Nejman et al.[9] used various detection methods to identify intratumor bacteria, which revealed distinct bacterial species associated with different cancer types. Studies identifying the microbiome as a biomarker and therapeutic target for cancer have notably increased with technologic advances. For example, Lin et al.[10] provided the first systematic analysis to uncover microbial gradient variations across different colorectal cancer (CRC) locations using multi-cohort metagenomic data. Specifically, Lin et al.[10] found significant enrichment of *Veillonella parvula* and *Alistipes onderdonkii* in right-sided CRC, whereas *Streptococcus anginosus* enrichment was associated with left-sided CRC, and *Peptostreptococcus anaerobius* showed a

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location-specific prevalence in rectal cancer (RC). Notably, *Fusobacterium nucleatum* (Fn) was consistently enriched across all CRC anatomic sites, showing promising therapeutic potential. The microbiota offers unique advantages, including inherent adjuvanticity[11] and tumor-targeting specificity[12]. Moreover, recent studies have suggested that microbiota and microbiota metabolites can modulate ICD, remodel the tumor microenvironment (TME), and enhance antitumor immune responses. This "microbiota-immunity" axis presents novel opportunities for developing microbiome-based adjuvant therapies. It may be possible to enhance the immunogenicity of conventional ICD-inducing treatments, such as chemotherapy and RT, by strategically modulating specific microbes or microbial metabolites and potentially overcome major limitations in current tumor immunotherapy.

Therefore, this review aims to systematically explore the molecular mechanisms through which bacteria, oncolytic viruses (OVs), fungi, and microbial metabolites regulate ICD. In addition, recent advances in engineered microbiota, microbial-based combination strategies integrating chemotherapy or immune checkpoint inhibitors (ICIs), and dietary interventions are summarized. This review may promote interdisciplinary collaboration among microbiologists, oncologists, and immunologists to advance personalized cancer therapies, enhance clinical outcomes, and provide novel insights for developing innovative cancer treatment strategies.

Microbiota regulate cancer pathogenesis and therapeutic response

Various factors influence cancer development and progression, including genetic alterations, environmental exposures, and lifestyle changes. Despite decades of clinical research, cancer remains a major global health challenge. By 2040 the global cancer incidence is projected to reach approximately 29.9 million cases with an estimated 15.3 million mortalities[13]. Consequently, scientists are actively investigating new strategies to overcome the limitations of conventional treatments and improve the overall therapeutic outcomes. For example, combining an anti-programmed death-ligand 1 (PD-L1) monoclonal antibody with *Faecalibacterium prausnitzii* has been shown to effectively inhibit tumor growth by reducing PD-L1 expression and increasing cytotoxic $CD8^+$ T cell infiltration within the TME[14]. Such a combined approach significantly enhances tumor-specific immune responses. The microbiota residing in the gut and other anatomic locations can influence cancer development and progression while modulating treatment-related adverse effects[15]. For example, gut microbiota dysbiosis has been shown to impair the recruitment of trastuzumab-induced $CD4^+$ T cells and granzyme B-positive cells. Furthermore, in human epidermal growth factor receptor 2-positive patients (HER2+) with breast cancer, non-responders were shown to exhibit a lower gut microbiota α-diversity compared to complete responders, along with a reduced abundance of *Bifidobacteriaceae*, *Turicibacteraceae*, *Lachnospiraceae*, and *Prevotellaceae*[16]. Fecal microbiota transplantation (FMT) is a therapeutic procedure that involves the transfer of intestinal microbiota from a healthy donor to a patient with the aim of reconstituting a functional gut microbial ecosystem[17]. Currently, FMT is an effective treatment for recurrent *Clostridioides difficile* infections[18]. Safety data from Routy et al.[19] demonstrated that combining FMT with anti-PD-1 therapy did not increase the incidence of immune-related adverse events. Moreover, studies indicate that levels of microbial metabolites, such as short-chain fatty acids (SCFAs), have a significant correlation with long-term clinical benefits in non-small cell lung cancer patients receiving nivolumab treatment[20], while indole-3-carboxaldehyde mitigates intestinal injury triggered by ICI therapy, thereby optimizing treatment safety[21]. **Table 1** summarizes clinical trials on the combination of gut microbiota modulation and immunotherapy conducted over the past 3 years. The tumor microbiome can form through multiple pathways, including direct mucosal barrier penetration, dissemination from adjacent tissues, metastatic seeding of cancer cells, and hematogenous or lymphatic spread[30]. The gut microbiota contributes to the pathogenesis of cancer and therapeutic modulation *via* the following three principal mechanisms: (1) some microorganisms (e.g., Fn and enterotoxigenic *Bacteroides fragilis*) promote tumorigenesis *via* chronic inflammation or direct DNA damage[31,32]; (2) microbial metabolites, such as SCFAs and secondary bile acids, directly influence tumor cell behavior through epigenetic modifications (e.g., histone deacetylase inhibition) and regulation of signaling pathways, including Wnt/β-catenin and nuclear factor-κB pathways[33,34], and regulate the TME and modulate immune cell activity[35]; and (3) dynamic shifts in intestinal microbiota composition can significantly affect the efficacy and toxicity of conventional therapies and immunotherapies[36]. These findings highlight new research directions for cancer prevention, such as through microbiota-targeted interventions, and establish a theoretical foundation for microbiome-based adjuvant therapies, such as combining probiotics with immunotherapy. Recent metagenomic and metabolomic studies further demonstrate that microbial communities and microbial community metabolites can independently or synergistically induce ICD, remodel the TME, and potentially address the limitations of traditional ICD-inducing therapies. Such microbiota-based strategies hold significant promise for reducing treatment-related adverse effects, enhancing therapeutic efficacy, and overcoming drug resistance to ultimately improve patient prognosis.

Table 1 Clinical research on gut microbiota intervention combined with tumor immunotherapy

Trial name/NCT No.	Population	Biomarker assay	Intervention	Primary endpoint	Unique design features	Ref.
NCT03772899	Untreated patients with advanced melanoma	16S rRNA-seq, metagenomics, flow cytometry, plasma metabolomics, tumor immune profiling	Single-dose healthy donor FMT + anti-PD-1 (nivolumab or pembrolizumab)	Safety	1. First-line setting; 2. healthy donor FMT *via* oral capsules; 3. multi-omics integration and animal validation.	[19]
ALICE NCT03164993	mTNBC	16S (V3–V4) rRNA-seq to characterize the diversity and taxonomic composition	Chemotherapy (pegylated liposomal DOX + cyclophosphamide) ± atezolizumab	Safety and PFS	1. Use of immunogenic chemotherapy (anthracycline + low-dose cyclophosphamide); 2. atezolizumab showed clinical benefit even in PD-L1-negative disease; 3. serial fecal sampling at baseline and 8 weeks; 4. first systematic evaluation of gut microbiota and immunotherapy response in mTNBC.	[22]
NCT03353402	Anti-PD-1-refractory metastatic melanoma patients	16S rRNA-seq, metagenomics, IHC, RNA-seq	FMT (from CR donor) + antibiotic pretreatment + nivolumab rechallenge	Safety, feasibility	1. First phase I clinical trial combining FMT with immunotherapy rechallenge in refractory melanoma; 2. use of CR donors; 3. antibiotic preconditioning + multi-route FMT (colonoscopy + oral capsules); 4. systematic multi-omics correlative studies.	[23]
NCT03341143	PD-1 advanced melanoma patients	Metagenomics, flow cytometry, single-cell RNA-seq, serum multi-omics	Single colonoscopy-delivered FMT from long-term responder donors + pembrolizumab rechallenge	Safety, feasibility, ORR	1. First phase II trial using responder-derived FMT + PD-1 rechallenge; 2. multi-omics integration and trans-kingdom network analysis; 3. investigation of engraftment efficiency and immune correlation.	[24]
NCT06218602	Relapsed/refractory lymphoma receiving anti-CD19 CAR-T therapy	Fecal/plasma metabolomics, 16S rRNA-seq, metagenomics	Antibiotic exposure; meropenem (mouse model); SCFAs (*in vitro*)	PFS, OS, relapse incidence	1. Multi-center cohort; 2. multi-omics integration; 3. modulate the microbiome to augment CAR-T immunotherapy.	[25]
NCT03174197	Newly diagnosed glioblastoma	WES/next generation sequencing, RNA-seq, multiplex immunofluorescence, fecal metagenomics	Concurrent phase: RT + TMZ + atezolizumab → adjuvant phase: TMZ + atezolizumab	OS	1. Phase I/II single-arm; 2. integrated multi-omics; 3. correlation of gut microbiome with immune infiltration.	[26]
NCT03654833	Relapsed malignant mesothelioma after first-line chemotherapy	WES, RNA-seq, 16S rRNA gut sequencing, multiplex immunofluorescence imaging	Atezolizumab + bevacizumab	12-week disease control rate	1. Integrates tumor genomics, transcriptomics, gut microbiome, spatial immunophenotyping; 2. first to define $\log(G_R/G_{NR})$ microbial ratio as predictive biomarker; 3. links microbiome to TME.	[27]

Table 1 Continued

Trial name/NCT No.	Population	Biomarker assay	Intervention	Primary endpoint	Unique design features	Ref.
NCT02853318	Recurrent ovarian cancer patients with resistance to platinum	Multi-omics: RNA-seq, digital spatial profiling, 16S rRNA-seq, metabolomics	Pembrolizumab + bevacizumab + oral cyclophosphamide	Median PFS (10.2 months)	1. Tumor-immune-gut axis integrated analysis; 2. longitudinal sampling; 3. definition of "durable clinical benefit" group for mechanistic study.	28
NCT03817125	ICB-naïve metastatic melanoma patients	Fecal metagenomics, metabolomics, qPCR, flow cytometry, serum proteomics, IHC	Vancomycin preconditioning + SER-401 (intervention) or placebo + nivolumab	Safety	1. Prospective biomarker stratification; 2. multi-omics integration; 3. antibiotic preconditioning window.	29

16S rRNA-seq, 16S ribosomal RNA gene sequencing; CAR-T, chimeric antigen receptor T-cell; CR, complete response; DOX, doxorubicin; FMT, fecal microbiota transplantation; ICB, immune checkpoint blockade; IHC, immunohistochemistry; mTNBC, metastatic triple-negative breast cancer; ORR, objective response rate; OS, overall survival; PD-1, programmed cell death protein 1; PD-L1, programmed death ligand 1; PFS, progression-free survival; qPCR, quantitative polymerase chain reaction; RT, radiotherapy; SCFAs, short-chain fatty acids; TMZ, temozolomide; TME, tumor microenvironment; WES, whole exome sequencing.

ICD: an emerging strategy to activate antitumor immunity

In recent years immunotherapy has offered new hope to patients with cancer, whether tumor cell death is immunogenic or non-immunogenic. In 2018 the Nomenclature Committee on Cell Death classified RCD according to morphology, biochemistry, and function, clearly defining RCD into 12 types[1]. Among these RCD types, ICD is a form of programmed cell death that can activate the host adaptive immune response. Unlike other RCDs, ICD is triggered by cellular stress and requires the following three key conditions: antigenicity; adjuvanticity; and an appropriate TME[37]. Tumor cells undergo ICD and release or expose various danger signals, namely DAMPs, including calreticulin (CRT), heat shock proteins (HSPs), high-mobility group box 1 (HMGB1), adenosine triphosphate (ATP), and type I interferon (IFN-I). CRT undergoes endoplasmic reticulum (ER)-to-cell surface translocation during ICD, in which CRT functions as an "eat-me" signal to facilitate phagocytosis by dendritic cells (DCs)[38]. Concurrently, large amounts of ATP are released into the extracellular milieu, serving as a "find-me" signal that binds to ionotropic purinergic receptor 7 on DCs, thereby activating the inflammasome and promoting interleukin (IL)-1β secretion[39]. HMGB1 is released from the nucleus into the extracellular space, where HMGB1 interacts with Toll-like receptor 4 (TLR4) on DCs to enhance antigen-presenting capacity[37]. HSPs, including HSP70 and HSP90, further assist in antigen presentation[40]. These events collectively counteract the immunosuppressive tumor microenvironment (ITME) and enhance responsiveness to immunotherapy[41]. Not all DAMPs are universally produced by different ICD inducers[42]. For example, triptolide has been shown to activate ER stress and modulate oxidative stress-induced ICD in cervical cancer cell lines (HT-3, U14, and HeLa), promoting the release of DAMPs, including CRT, ATP, and HMGB1[43]. Similarly, isoquercitrin induces ICD in gastric cancer (GC) cells by provoking ER stress and disrupting mitochondrial membrane potential, leading to the secretion of CRT, HMGB1, ATP, HSP70, and HSP90[44]. ICD represents a pivotal mechanism in the development of innovative anticancer therapies. However, the translation of ICD-based strategies into clinical application remains limited by several challenges. Therefore, identifying novel agents and strategies to modulate ICD constitutes an important direction for future cancer research.

Microbial regulation of ICD

Bacteria, fungi, and viruses are major components of the human microbiota that influence immune responses, tumorigenesis, cancer progression, metastasis, and therapeutic outcomes[45]. These microorganisms possess unique advantages,

including inherent adjuvanticity and tumor-targeting capabilities. Building on these properties, the ICD-regulating mechanisms of bacteria, viruses, and fungi have been discussed here. Various bacteria, OVs, and fungi known to induce ICD are summarized in **Table 2**, emphasizing the roles in remodeling the TME and enhancing antitumor immunotherapy.

Bacteria

Bacteria-based approaches have gained notable prominence as promising therapeutic strategies for cancer treatment[61,62]. Reportedly, some bacteria can directly or indirectly induce ICD in cancer cells, thereby activating long-term systemic antitumor immunity. Rustetska et al.[63] analyzed the microbial community in vulvar squamous cell carcinoma using next-generation 16S ribosomal RNA gene sequencing (16S rRNA-seq) and a quantitative polymerase chain reaction (qPCR), revealing significantly elevated abundances of Fn and *Pseudomonas aeruginosa* and identifying Fn and *P. aeruginosa* as potential tumorigenic pathogens. Interestingly, another study indicated that even a single, ultra-low dose of *P. aeruginosa* could markedly inhibit tumor growth[46]. Mechanistically, *P. aeruginosa* infection induces tumor cell necroptosis *via* phosphorylation of receptor-interacting protein kinase 3 (RIP3) and mixed lineage kinase domain-like protein (MLKL), coupled with HMGB1 release, indicating an ability to trigger ICD. Furthermore, infected tumor cells exhibit increased ATP secretion compared to uninfected controls with enhanced infiltration of IFN-γ- and IL-2-secreting lymphocytes in the TME. The released DAMPs effectively activate DC maturation, boosting antigen presentation and eliciting durable antitumor immunity. Similarly, infection of melanoma cells with *Salmonella typhimurium* has been shown to cause phenotypic changes consistent with ICD. Attenuated *S. typhimurium* expressing tdTomato induced cytoplasmic vacuolization and characteristic ICD markers, such as elevated extracellular ATP release, in a murine B16F10 model. These treated cells were efficiently phagocytosed, which activated APCs and enhanced adjuvanticity and immunogenicity. Vaccination with *Salmonella*-treated B16F10 cells in Pmel-1 mice stimulated gp100-specific T cell proliferation and inhibited tumor growth[47]. Probiotics also exhibit antioxidant, antimicrobial, anti-inflammatory, and immunomodulatory capabilities. For example, treatment with *Lacticaseibacillus casei* ATCC 393 upregulated death receptors (FS7-associated cell surface antigen/Death Receptor 4/5) and the pro-apoptotic B-cell lymphoma 2 (Bcl2)-associated X protein (Bax) in CT26 and HT29 cells, while reducing anti-apoptotic Bcl-2 in CT26 cells, suggesting apoptosis induction *via* the extrinsic pathway. *L. casei*-treated colon cancer cells have shown ICD markers, including CRT surface exposure, HMGB1 nuclear translocation, and intracellular ATP depletion. Upregulation of IFN-I and IL-1β in CT26 cells confirmed that *L. casei* induced apoptosis and activated adaptive immunity through DAMP release, converting immunologically silent ("cold") tumors into immunoreactive ("hot") lesions[48].

In addition to whole bacteria, bacterial components can contribute to immune regulation, which influences tumor progression. For example, extracellular vesicles (EVs) are natural nanoparticle-carrying bioactive molecules that mediate intercellular communication[64]. *Lactobacillus reuteri*, a Gram-positive gut probiotic[65], produces EVs called REVs, which have demonstrated significant anticancer effects when administered orally. REVs demonstrated stability in the gastrointestinal tract and modulated apoptotic pathways by downregulating Bcl-2, upregulating Bax, and promoting the cleavage of caspase-3 and poly (ADP-ribose) polymerase. Oral administration of indocyanine green (ICG)-loaded REVs followed by photothermal therapy (PTT) resulted in complete tumor regression within 32 d in a mouse model. REV-ICG treatment suppressed cell proliferation and angiogenesis upon near-infrared (NIR) irradiation, as validated by IHC for Ki67 and CD31, and induced markers of ICD, including enhanced CRT exposure and HMGB1 release[49]. In addition, Fu et al.[66] constructed bacterial flagellum–drug nanoconjugates for carrier-free immunochemotherapy. By leveraging the long-lasting retention capacity of the flagella, efficient intracellular uptake, and antitumor immune properties, these conjugates enable sustained intratumoral drug exposure, thereby enhancing ICD induction by chemotherapeutic drugs and antitumor efficacy.

Throughout the long history of cancer immunotherapy, bacteria have demonstrated antitumor immunity. Given the capacity to elicit ICD, engineered or attenuated bacterial strains may ultimately synergize with standard treatments, such as surgery, chemotherapy, or RT, to advance novel anticancer immunotherapeutic approaches.

OVs

OVs capable of inducing ICD have garnered significant attention[67]. To date, four OV therapies have received global approval for oncologic applications with talimogene laherparepvec (T-VEC) the only widely used agent[68]. As a novel antitumor therapy, oncolytic virotherapy selectively infects, replicates within, and destroys tumor cells while sparing normal cells[68,69]. Upon tumor cell lysis, viral pathogen-associated molecular patterns alongside ICD-related DAMPs are released[70], including HSPs, HMGB1, CRT, ATP, and cytokines [such as IFN-I, tumor necrosis factor (TNF)-α, IFN-γ, and IL-12]. These signals promote APC activation and maturation[71], thereby activating adaptive immune responses to indirectly target uninfected tumor cells. Reportedly, multiple OVs can trigger tumor ICD, including oncolytic adenovirus[72], herpes simplex virus (HSV)[50], vaccinia virus (VACV)[70], and Newcastle disease virus (NDV)[51]. For example, T-VEC, an HSV-1-derived vector,

Table 2 Microbiota associated with ICD induction

Microbes	Cancer type	DAMPs	Mechanisms	Ref.
Bacteria				
Pseudomonas aeruginosa	TC-1 tumor cells	ATP, HMGB1	Induces necroptosis along with HMGB1 and ATP releases to facilitate DCs maturation and remodel the TME.	46
Salmonella typhimurium	Melanoma cells	ATP	Induces cellular vacuolization and ICD and releases ATP to activate APC.	47
Lacticaseibacillus casei ATCC393	Colon cancer cells	ATP, HMGB1, CRT	Induces apoptosis in CRC through exogenous death receptor signaling and induces adaptive immune responses by releasing ICD-related DAMPs.	48
Lactobacillus reuteri	A549 cells	HMGB1, CRT	Induces apoptosis through the MAPK pathway and induces ICD in combination with drugs.	49
Oncolytic virus				
Talimogene laherparepvec	Melanoma cells	ATP, CRT	Induces ICD *via* CRT exposure and ATP secretion.	50
Newcastle disease virus	Lung cancer	HMGB1, HSP70, HSP90, CRT	NDV-modified vaccine-triggered ICD stimulates DCs maturation and T-cell activation.	51
Influenza virus	Melanoma cells	ATP, HMGB1, CRT	Induces ICD *via* the secretion of HMGB1 and ATP, as well as the surface exposure of CRT. Modification of hemagglutinin enhances the antitumor efficacy of induced ICD.	52
Immune-oncolytic VACV Ankara	MA104, HeLa, MCF-7, Renca, LLC1, B16, and CT26 cells	ATP, HMGB1, CRT	IOVA infection promoted CRT exposure and universal HMGB1 release, with ATP elevation in 1/3rd cell lines.	53
Zika virus	Human glioblastoma multiforme cells		ZIKV-LAV mediated GBM cell death *via* apoptosis and pyroptosis and induced ICD.	54
Engineered oncolytic extracellular vesicles (bRSVF-EVs) loaded with MPs	Human embryonic kidney 293T, Lewis lung carcinoma cells	CRT, HMGB1, HSP70	Induces ICD *via* ER stress and subsequent triggering of the PERK/eIF2α/ATF4/CHOP pathway	55
Coxsackievirus B3	4T1 cell	ATP, HMGB1, CRT	Exerts antitumor effects by increasing DAMPs and immune cell infiltration in the TME	56
Fungi				
Aspergillus ustus	TNBC cells	ATP, HMGB1, CRT	MHO7 derived from *Aspergillus ustus* activates the PERK/eIF2α/ATF4/CHOP pathway.	57
Amphotericin B	K562, MCF-7, HT29	ATP, HMGB1, CRT	Induces ICD and promotes phagocyte conversion to "M1-like"	58
Trametes robiniophila Murr	TNBC cells	ATP, HMGB1, CRT	Huaier induces ICD *via* CircCLASP1/PKR/eIF2α pathway	59
Didymella sp. CYSK-4	Lung cancer and melanoma cells	ATP, CRT	Ascomylactam C derived from *Didymella* spp. CYSK-4 induces ICD *via* PERK/eIF2α/ATF4/CHOP pathway	60

ATP, adenosine triphosphate; ATF4, activating transcription factor 4; CHOP, C/EBP homologous protein; CRC, colorectal cancer; CRT, calreticulin; DAMPs, damage-associated molecular patterns; DCs, dendritic cells; eIF2α, eukaryotic initiation factor 2 alpha; ER, endoplasmic reticulum; HMGB1, high mobility group box 1; ICD, immunogenic cell death; IOVA, Immune-Oncolytic VACV Ankara; MAPK, mitogen-activated protein kinase; MPs, misfolded proteins; NDV, Newcastle disease virus; PERK, PKR-like endoplasmic reticulum kinase; TNBC, triple-negative breast cancer; TME, tumor microenvironment; ZIKV-LAV, Zika virus live-attenuated vaccine.

induces ICD with efficacy comparable to DOX and superior to cisplatin. T-VEC directly kills tumor cells and releases ICD markers (such as CRT translocation and ATP release) and enhances maturation of blood DC antigen-1$^+$ myeloid DCs, as indicated by elevated CD80, CD83, and PD-L1 levels, producing dual antitumor effects[50]. Similarly, influenza A virus (IAV)-infected B16-F10 melanoma cells have been shown to exhibit classic ICD features with exposure to IAV hemagglutinin and tyrosinase-related protein 2 and other tumor antigens. IAV-infected B16-F10 melanoma cells promote the migration, antigen uptake, cross-presentation, and *in vitro* maturation of bone marrow-derived DCs. Notably, *in vivo* studies on IAV-induced ICD cell vaccines have shown effective suppression of melanoma cell growth[52]. Unlike T-VEC and IAV, VACV serves as a versatile therapeutic vector. Notably, a novel VACV strain [Immune-Oncolytic VACV Ankara (IOVA)], exhibited combined high tumor-selective replication and strong ICD induction, inducing > 75% CRT surface expression and increasing HMGB1 and ATP release to activate immature DCs and exert tumor cytotoxicity[53]. The live-attenuated Zika virus vaccine strain (ZIKV-LAV) exhibited notable oncolytic effects against human glioblastoma (GBM) cells *in vitro* through Axl and integrin αvβ5 receptors, thereby mediating efficient infection and lysis of GBM cells and concomitantly inducing ICD[54]. Among innovative approaches, NDV-modified lung cancer vaccines can induce ICD, enhance DC maturation and T cell activation to significantly suppress tumor growth, potentiate T helper cell 1 responses, and recruit inflammatory cells, demonstrating robust immunotherapeutic efficacy[51]. Engineered oncolytic EVs (bRSVF-EVs) loaded with misfolded proteins (MPs) have been reported for immunotherapeutic efficacy. MPs were efficiently packed in bRSVF-EVs by inhibiting lysosomal function *via* bafilomycin A1 treatment and expressing the respiratory syncytial virus fusion (RSVF) protein. Consequently, these bRSVF-EVs exhibited the following dual mechanisms: activation of innate immunity *via* ribosome-dependent heterologous antigen presentation; and direct cytosolic delivery of MPs to induce ER stress and ICD[55]. In addition, combined treatment with engineered oncolytic coxsackievirus B3 modified with microRNA (miR-CVB3) and CpG-melittin (CpGMel) complexes (miR-CVB3 + CpGMel) has demonstrated superior efficacy compared to individual treatments in triggering tumor cell death and stimulating release of DAMPs. Notably, this regimen significantly suppressed primary and metastatic growth in 4T1 tumor-bearing mice, while extending survival[56]. These findings highlight the diverse potential of various OVs in inducing ICD and novel perspectives and directions for future antitumor therapies. The concurrent blockade of PD-1 and its ligand (PD-L1), combined with oncolytic virotherapy, represents an area of active preclinical and clinical investigation. Despite demonstrating innovative antitumor potential, the safety profile of oncolytic viruses remains a subject of concern. In a clinical trial involving 19 patients with drug-resistant high-grade glioma treated with the oncolytic HSV-1 teserpaturev (G47Δ), three patients developed fever and the study reported a small number of serious adverse events, including death, cerebral infarction, and hemiplegia[73]. Similarly, research on T-VEC indicates that the adverse reactions are primarily influenza-like symptoms and local injection site reactions[74]. These findings suggested that future research on oncolytic virotherapy should systematically evaluate risks and benefits in broader clinical trials. This research effort will facilitate the advancement of such therapies toward more effective and controllable tumor treatments, while ensuring patient safety. Leveraging ICD-mediated immunostimulation with viral and nanoscale delivery innovations may yield more effective personalized cancer vaccines. Overall, these findings establish OVs as potent ICD inducers.

Fungi

Growing evidence indicates that fungi, as highly immunogenic components of the human microbiome, directly or indirectly participate in cancer initiation and progression, eliciting a therapeutic response by modulating host immune homeostasis and inflammatory reactions[75,76] in colorectal[77], pancreatic[78], and head and neck cancers[79]. Reportedly, fungal metabolites are key effectors of ICD induction. For example, MHO7, a small molecule extracted from *Aspergillus ustus*, exhibited cytostatic and cytotoxic effects on triple-negative breast cancer (TNBC) cells with a half-maximal inhibitory concentration (IC_{50}) of 0.96–1.75 μM. Mechanistically, MHO7 induced reactive oxygen species (ROS) production, depleted glutathione levels, and activated the protein kinase R-like ER kinase (PERK)/eukaryotic initiation factor 2 alpha (eIF2α)/activating transcription factor 4 (ATF4)/C/EBP homologous protein (CHOP) pathway, causing oxidative and ER stress that triggered release of DAMPs (CRT, HMGB1, and ATP) from TNBC cells. MHO7 also promoted the release of antitumor cytokines, such as IL-6, IL-1β, IFN-γ, and TNF-α, increasing CD86$^+$ and major histocompatibility complex (MHC)-II$^+$ DCs and the population of CD4$^+$ and CD8$^+$ T cells, while decreasing regulatory T (Treg) cells[57]. The antifungal drug, amphotericin B (AmB), has been shown to induce ICD in tumor cell lines by increasing CRT expression and HMGB1 and ATP release. At subtoxic doses, AmB enhanced CRT exposure on leukemia cells (particularly phagocytic monocytic THP-1 cells), promoting "M1-like" polarization and stimulating dose-dependent antitumor immunity[58]. Huaier (*Trametes robiniophila* Murr), a fungal species used in traditional Chinese medicine[80], has been reported to induce ICD in breast cancer cells, as evidenced by elevated CRT exposure, ATP secretion, and HMGB1 release. Notably, co-culture with Huaier-treated TNBC cells markedly promoted DC maturation. Oral Huaier administration recruited tumor-infiltrating lymphocytes in

xenograft models to suppress tumor growth. Mechanistically, Huaier induces ICD in TNBC cells *via* the circCLASP1/protein kinase R (PKR)/eIF2α signaling pathway[59]. Another fungal metabolite, ascomylactam C, is a 13-membered cyclic alkaloid derived from the mangrove endophytic fungal strain of *Didymella* spp. CYSK-4 has been reported to increase ROS levels *in vitro* and *in vivo* to damage mitochondria-associated ER structures, thereby activating the PERK/eIF2α/ATF4/CHOP pathway and inducing DAMP release in lung cancer and melanoma cells to activate T cell-mediated antitumor immunity[60].

Together, fungal communities and fungal community metabolites activate antitumor immunity through ICD, offering novel therapeutic avenues for cancer treatment. Future directions include elucidating molecular mechanisms underlying fungal–host immune interactions and optimizing fungal drug delivery and dosages of fungal-derived drugs for specific cancer types to facilitate clinical translation.

In conclusion, these studies indicated that microbiota can potentiate ICD effects through multiple mechanisms, including activating ER stress to promote DAMP release, stimulating DC maturation, and altering the TME to improve T-cell infiltration.

Microbial metabolite regulation of ICD

Microbiota-derived metabolites are vital natural compounds that directly link the microbiome to cancer. These bioactive molecules can diffuse from intestinal origins to modulate antitumor immune responses locally and systemically. Microbiota-derived metabolites significantly influence cancer progression and therapeutic outcomes, including chemotherapy, RT, and immunotherapy, by remodeling the TME and regulating immune functions.

SCFAs

SCFAs are predominantly produced by anaerobic bacteria with acetate, propionate, and butyrate the most abundant[81,82]. SCFAs primarily affect tumor development through two main mechanisms: direct action on cancer cells; and indirect modulation of immune responses. Most studies indicate that both pathways contribute to the inhibitory effects of SCFAs on tumor growth and progression[82]. For example, an analysis of fecal and blood samples from 20 healthy individuals and patients with GC revealed significant gut microbiota dysbiosis with patients exhibiting decreased abundance of SCFA-producing beneficial bacteria (such as *Faecalibacterium* and *Ruminococcus*) and increased abundance of *Akkermansia muciniphila* with decreased systemic SCFA levels. Mechanistically, butyrate enhanced $CD8^+$ T cell cytotoxicity *via* the G protein-coupled receptor 109A/homeodomain only protein homeobox signaling pathway, suppressing gastric carcinogenesis[83]. Similarly, Wang et al.[84] identified three critical ICD-related genes (*LY96*, *BCL2*, and *IFNGR1*) in severe acute pancreatitis (SAP) that were significantly associated with SCFA metabolism. *LY96* and *IFNGR1* had a positive correlation with SCFA receptor genes (*FFAR2* and *FFAR3*) but had a negative correlation with the epigenetic regulator, histone deacetylase 9, whereas *BCL2* exhibited an inverse correlation pattern. Notably, butyrate exhibited strong binding affinity with these genes (especially *BCL2*), suggesting that SCFAs (particularly butyrate) modulate immune responses in SAP by regulating ICD-related genes. In addition, animal studies with dietary mannose administration showed suppressed ovarian tumor growth in immunocompetent murine models owing to enrichment of *Faecalibaculum rodentium* with metabolomic profiling identifying propionate and butyrate as key mediators of mannose-induced antitumor activity[85]. Conversely, methylmalonic acid, a propionate metabolite byproduct, was shown to induce exhaustion of activated $CD8^+$ T cells and facilitate tumor immune evasion in cell culture and animal models[86]. Future research should focus on enhancing probiotic therapies targeting beneficial SCFA production while minimizing harmful metabolites to maximize the potential of microbial metabolism in cancer immunotherapy.

Overall, microbial metabolites significantly impact various stages of oncogenesis and tumor progression. The development of microbial metabolites as novel cancer therapeutics promises substantial clinical benefits for patients. However, some microbial metabolites display dual functionality, exhibiting tumor-promoting and antitumor activities. This complex characteristic underscores the need for further mechanistic studies to elucidate the underlying molecular mechanisms.

Cholesterol and vitamins

Cholesterol and vitamin-derived microbial metabolites have been implicated in antitumor immune responses. Reportedly, cholesterol and vitamin-derived microbial metabolites contribute to ICD by modulating cytokine production and immune cell activities, particularly T cells. Cholesterol metabolism has a key regulatory role in ICD. Notably, antidepressants (sertraline and indatraline) induce the nuclear translocation of transcription factor EB (TFEB), causing lysosomal cholesterol accumulation in an autophagy-independent manner. This mechanism involves inhibiting cholesterol binding to Niemann-Pick disease, type C1/2 transport proteins, and upregulating phospholipase A2 group XV to increase cholesterol levels. Accumulated lysosomal cholesterol disrupts membrane permeability and autophagy, thereby triggering ICD[87]. Zhao et al.[88] developed a tetraphenylporphyrin cholesterol conjugate nanosystem to mediate PDT to selectively induce ICD in lung cancer, enhancing antitumor

immunity by promoting DC maturation and T cell activation, thereby sensitizing tumors to ICIs. Thus, the system significantly suppressed primary tumors and eradicated metastatic lesions. Vitamin-derived metabolites from gut microbiota also participate in ICD regulation. These vitamins have essential physiologic roles in the host and help maintain gut microbial homeostasis by supporting the growth of commensal bacteria and suppressing competing pathogenic strains. Among the vitamins, vitamin C induces ROS accumulation in tumor cells and synergizes with oncolytic adenoviruses to exhibit antitumor effects by significantly enhancing ICD and reshaping the TME[89]. Shi et al.[90] designed a multifunctional folate-targeted conjugate combining DOX and ICG. This conjugate integrates SDT, chemodynamic therapy, and chemotherapy to simultaneously induce ferroptosis and ICD. This combined approach effectively overcomes immunotherapy resistance in bladder cancer and enhances ICB efficacy. These findings establish a theoretical foundation for developing novel tumor immunotherapy strategies based on metabolic regulation.

Other microbial community metabolites

Reportedly, specific gut microbial metabolites can significantly influence tumor treatment sensitivity. In a study involving 26 patients with locally advanced RC, *Lactobacillus* was significantly enriched in the gut microbiota of RT-sensitive patients, accompanied by elevated serum methylglyoxal (MG) levels. Mechanistically, MG has been shown to enhance radiosensitivity in RC models *in vitro* and *in vivo* with modifying the TIME *via* ICD induction through the PERK/eIF2α/ATF4 and cyclic GMP-AMP synthase (cGAS)-stimulator of interferon genes signaling pathways[91]. Another study reported a microbial resource library derived from 56 peritoneal pseudomyxoma samples, revealing *Aspergillus* spp. LJ2020F001 exhibits potent antitumor activity through high-throughput screening with mass spectrometry identifying a novel compound to be the active component (aspercyclicins). *In vitro* experiments further demonstrated that aspercyclicins specifically induced ICD, which was characterized by increased release of DAMPs and enhanced phagocytic clearance efficiency with low toxicity to normal cells, demonstrating promising clinical translation potential[92]. These studies revealed the critical involvement of specific gut microbial metabolites in enhancing tumor therapeutic sensitivity, offering novel insights and directions for future cancer treatment strategies. Tartrolon D (TRL), biosynthesized by *Teredinibacter turnerae*, shows broad-spectrum antitumor activity with reported antiproliferative activities (IC_{50}: 0.03–13 μM) against multiple tumor cell lines (L929, HCT116, B16-F10, WM293A, SK-MEL-28, PC-3M, and MCF-7) and non-tumor cells (HEK293A) with particular sensitivity observed in metastatic melanoma cells (SK-MEL-28, B16-F10, and WM293A; IC_{50}: 0.07–1.2 μM). TRL induces ICD through apoptosis, autophagy, and ER stress, as evidenced by membrane exposure of CRT, endoplasmic reticulum protein 57, and HSP70, with HMGB1 release. TRL-treated B16-F10 cells exhibited increased MHC II and CD1d expression, thereby triggering immune cell activation of splenocytes derived from C57BL/6 mice[93]. In addition, four dextrorotatory chromomycin A (CA) compounds were isolated from the actinobacterial strain *Streptomyces* spp. BRA-384 and have been reported to show potent cytotoxicity in advanced metastatic melanoma models. Notably, CA_{5-8} and DOX-treated B16-F10 cells underwent ICD, which was characterized by CRT exposure and HMGB1 release. Among CA_{5-8} and DOX-treated B16-F10 cells, CA_5 exhibited the most potent effects, effectively activating APCs and T cells to enhance antitumor activity. Immunization of C57BL/6 mice with CA_5-treated cells further confirmed ICD induction[94]. Overall, microbial metabolites are significantly implicated in cancer pathogenesis and targeting microbial metabolites represents a promising starting point for novel therapeutic development, potentially benefiting cancer patients. However, the immunomodulatory functions of microbial metabolites exhibit intrinsic duality. As a representative example, lipopolysaccharide-induced sepsis initiates early-phase inflammatory cascades *via* activation of the TLR4 signaling pathway[95]. In addition, mycotoxins present multidimensional hazards, compromising not only agricultural yield and post-harvest preservation but also posing documented risks of carcinogenicity, teratogenicity, and mutagenicity to human health[96]. Thus, any translational development or clinical application of such metabolites necessitates rigorous risk assessment frameworks and systematic safety management protocols.

In summary, microorganism-derived metabolites that induce ICD constitute an effective antitumor strategy. Chen and Mellman defined three tumor phenotypes based on T-cell infiltration that strongly correlate with the ICI response[97]. Among the three tumor phenotypes, immune desert and immune-excluded phenotypes (collectively termed "cold" tumors) are non-inflamed and generally refractory to ICIs. Conversely, the immune-inflamed phenotype ("hot" tumor) is densely infiltrated by T cells and shows favorable ICI responsiveness. Microbiota and microbial metabolites critically modulate ICI efficacy by reshaping host immunity and the TME[98]. For example, Preet et al.[99] demonstrated that extracellular vesicles derived from commensal *Bifidobacterium* enhance anti-PD-1 therapy in syngeneic mouse models by up-regulating key cytokines, such as TNF-α and IL-2, modulating immune and oncogenic signaling pathways, and increasing intratumoral $CD8^+$ T-cell infiltration. Likewise, Jia et al.[100] reported that indole-3-propionic acid co-produced by *Lactobacillus johnsonii* and *Clostridium sporogenes* reinvigorates $CD8^+$ T-cell function, thereby potentiating antitumor immunity against melanoma, breast cancer, and CRC. Collectively, microbiota and microbiota metabolites convert "cold" into "hot" tumors by reversing peripheral immune exhaustion, heightening tumor immunogenicity, promoting immune-cell infiltration, and suppressing immunosuppressive cell populations.

Figure 1 demonstrates the process by which DAMPs released after microbiota- and metabolite-induced ICD activate antitumor immune responses. This process involves multiple mechanisms and **Figure 2** illustrates the molecular mechanisms underlying ICD-regulation by microbes and microbe metabolites. Future studies should focus on clarifying the complexity and dynamics of microbes and microbe metabolites with continued exploration of the ICD-inducing mechanisms and therapeutic effects to harness the therapeutic potential and develop more potent cancer treatment approaches.

Emerging therapeutic approaches in oncology leveraging the properties of gut microbiota and microbiota metabolites

Engineered microbiota regulates ICD

Immunotherapy has become a pillar in modern oncotherapeutic regimens owing to a modulation effect on innate and adaptive immunity. However, the clinical efficacy is considerably limited by inefficient delivery of immunotherapeutic agents, off-target adverse effects, and the non-immunogenic nature of the TME. Recently, advances in synthetic biology have enabled engineered microbial therapies leveraging tumor-targeting capability and immunomodulatory properties of bacteria[12]. When combined with ICD-inducing methods, these engineered bacteria markedly enhance antitumor immune responses. Commensal strains, such as *Escherichia coli* Nissle 1917 and *Bifidobacterium* spp., have been reported to serve as highly efficient drug delivery vectors owing to innate tumor-targeting properties[101,102]. For example, attenuated *Salmonella* VNP20009 can specifically accumulate in hypoxic tumors. *Salmonella*-coated zirconium-based metal-organic frameworks [MOFs] (UiO-66-NH_2) were loaded with ICG and luteolin (LUT) with LUT enhancing tumor cell sensitivity to therapy *via* autophagic cell death and ICG mediating photothermal effects (42–45°C) to directly kill tumor cells and promote release of DAMPs, thereby synergistically enhancing ICD[103]. To overcome immunosuppression and resistance due to the ITME, engineered microbes have been combined with nanomaterials to demonstrate unique advantages. For example, DOX-induced T cell-dependent antitumor immune response is typically very weak. Therefore, He et al.[101] designed DOX-loaded *Bifidobacteria* (DNPs@Bi) to enhance ICD, tumor-associated antigen (TAA) presentation, DC maturation, and cytotoxic T cell infiltration to significantly inhibit tumor progression and metastasis. Similarly, Zhao et al.[104] developed a hybrid bacterial system (B. b@QDs) integrating *Bifidobacterium bifidum* (B. b) with silver sulfide quantum dots, which combined hypoxia targeting, tumor-associated macrophage polarization, and PTT. B. b@QDs facilitates direct interaction between B. b and tumor-associated macrophages, leading to reversal of the ITME. Some tumor-associated bacteria, such as Fn, bind CRC cells *via* lectin Fap2[105], inducing chemotherapy resistance and suppressing the immune microenvironment[106,107]. Li et al.[108] developed a multifunctional nanodrug (MPLO@HA) combining metformin, oxaliplatin (OXA), and lauric acid with coating and hyaluronic acid to effectively reverse Fn-mediated chemoresistance, induce ICD, promote M1-phenotype macrophage polarization, and reduce the number of Tregs and myeloid-derived suppressor cells, thereby improving CRC therapy outcomes. The poor efficacy of chemotherapy for pancreatic cancer is primarily attributed to two factors: the dense extracellular matrix (ECM) that impedes drug penetration[109]; and drug degradation mediated by tumor-associated bacteria[110]. Consequently, Yao et al.[111] designed a probiotic nanomedicine system using matrix metalloproteinase-2-responsive peptides to conjugate *Clostridium butyricum* (CB) with drug-loaded liposomes to deliver a transforming growth factor-β1 receptor inhibitor (vactosertib), which suppresses ECM production. In addition, CB competitively inhibited γ-proteobacteria, enhancing gemcitabine-induced pancreatic tumor ICD and immune responses. Notably, RT induces ICD and ATP release but CD39/CD73-mediated immunosuppressive adenosine (ADO) inhibits immune responses. To address this finding, Wu et al.[11] synthesized a radiation-sensitizing bismuth–ellagic acid MOF (Bi-EA MOF) *in situ* on *E.* coli Nissle 1917 for targeted delivery of the CD39 inhibitor, sodium polyoxotungstate. This system enhanced RT sensitivity, promoted ICD-associated ATP release, and blocked ATP-to-ADO conversion. Similarly, ADO produced under hypoxic conditions inhibited ICD by binding to the A2A receptor (A2AR), whereas MnO_2-modified photosynthetic bacteria (MnO_2@PSB) reduced ADO production and downregulated A2AR under 808-nm laser irradiation, inducing ICD and boosting antitumor immunity[112]. Traditional strategies overlook the increase in ADO, an immunosuppressive metabolite, during ICD, which leads to suboptimal treatment outcomes. Reportedly, elevated A2AR expression in breast cancer correlates with Treg cell infiltration. Xiang et al.[113] proposed combined Fe/Mo-based lipid peroxidation nanoamplifiers and A2AR blockade to maximize an ICD-associated antitumor immune response. These strategies effectively reversed the ITME by inhibiting ADO production, providing novel insights for optimizing ICD-mediated immunotherapy. In addition, 3-(2-nitrophenyl) propionic acid-paclitaxel nanoparticles have been shown to induce ICD in MDA-MB-231 and 4T1 cells, promote T cell infiltration, and enhance IFN-γ and TNF-α secretion. When administered in combination with an anti-PD-L1 antibody *in vivo*, these nanoparticles significantly improved antitumor immune responses[114]. While combination immunotherapy intensified efficacy, immune-related adverse events often arise. Tumor-specific delivery using bacterial vectors provides an effective solution. Notably, attenuated *S. typhimurium* presents

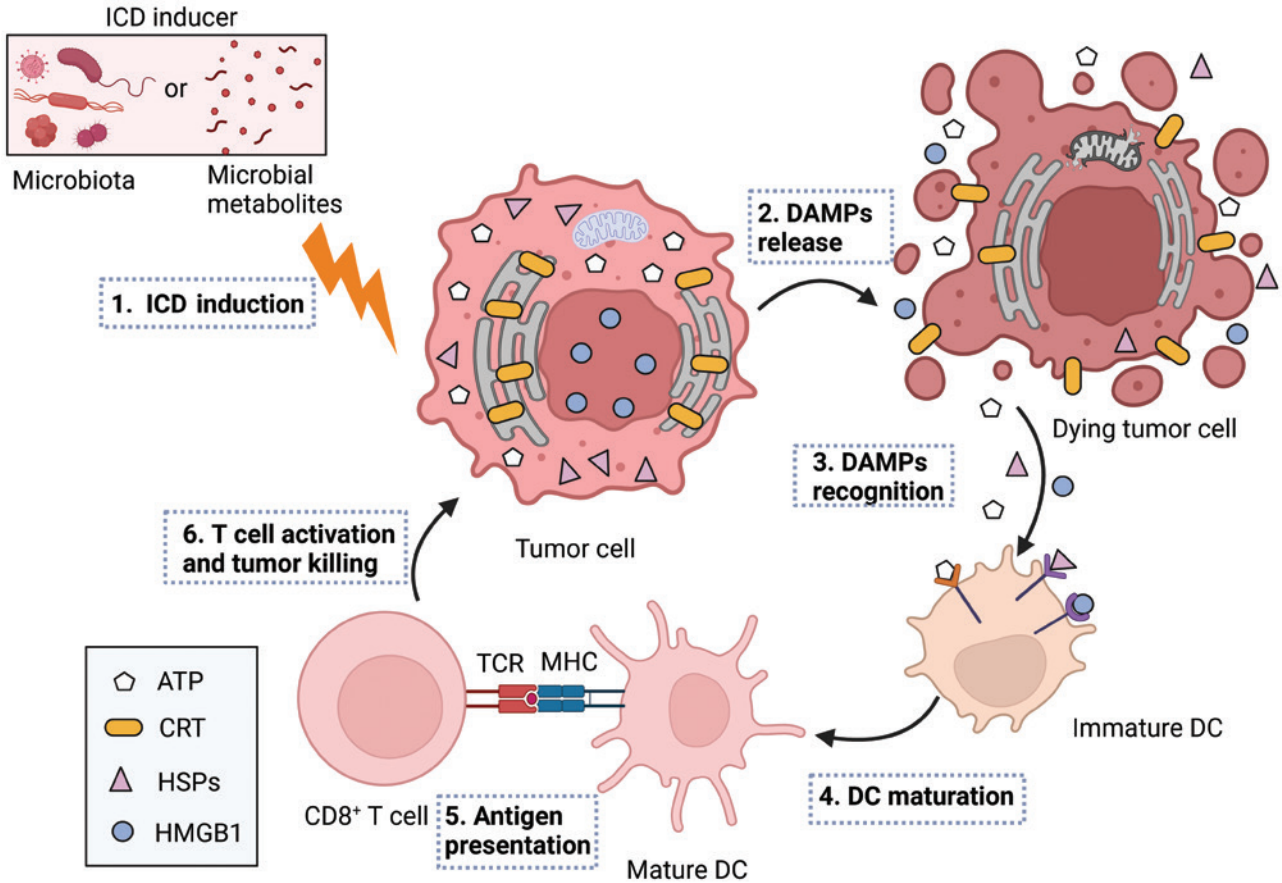


Figure 1 Microbiota and microbial metabolites initiate antitumor immune responses by inducing ICD. This schematic systematically illustrates the complete process by which microbiota and microbial metabolites, serving as inducers of ICD, ultimately initiate specific antitumor immune responses through a cascade of "ICD induction–DAMPs release–DAMPs recognition–DC maturation–antigen presentation–T cell activation and tumor killing." **1. ICD induction**: Microbiota and microbial metabolites act on tumor cells as inducers of ICD, triggering ICD in tumor cells. **2. DAMPs release**: Dying tumor cells undergoing ICD release or expose various DAMPs, including ATP, HMGB1, and HSPs, as well as the translocation of CRT from the ER to the cell surface. **3. DAMPs recognition**: The released DAMPs are recognized and taken up by immature DCs and these DAMPs initiate the activation program of the DCs. **4. DC maturation**: Stimulated by DAMPs, immature DCs differentiate into mature DCs. This transition equips DCs with a highly efficient antigen-presenting capacity. **5. Antigen presentation**: Mature DCs present tumor antigens *via* MHC molecules on the surface to the TCRs on $CD8^+$ T cells, thereby establishing a bridge for antigen-specific recognition. **6. T cell activation and tumor killing**: $CD8^+$ T cells that recognize the antigen–MHC complex are activated, initiating a specific antitumor immune response. These activated $CD8^+$ T cells (effector T cells) can precisely recognize and kill tumor cells. ATP, adenosine triphosphate; CRT, calreticulin; DAMPs, damage-associated molecular patterns; DC, dendritic cell; ER, endoplasmic reticulum; HMGB1, high mobility group box 1; HSPs, heat shock proteins; ICD, immunogenic cell death; MHC, major histocompatibility complex; TCR, T cell receptor (figure created with BioRender.com).

unique advantages as a delivery vector, owing to dual payloads for carrying cytotoxin A (ClyA) and *Vibrio vulnificus* flagellin B (FlaB), which synergistically activate antitumor immunity. ClyA facilitates the release of TAAs and DAMPs by inducing ICD, whereas FlaB repolarizes M2-like macrophages toward an M1 phenotype *via* TLR4 signaling. This combination strategy showed significant anti-metastatic effects in mouse models by reprogramming the TIME and stimulating innate and adaptive immunity[115,116]. Synthetic biology has enabled the development of engineered bacteria as novel living therapeutics with great preclinical potential. While developing and utilizing engineered bacteria, safety considerations must be addressed, particularly in immunocompromised patients or those undergoing other cancer treatments because even attenuated pathogenic strains and probiotics may pose risks of infection or adverse reactions. For example, the attenuated strain, *Clostridium novyi*-NT, was administered *via* intratumoral injection at varying doses to patients with treatment-refractory solid tumors in a phase I

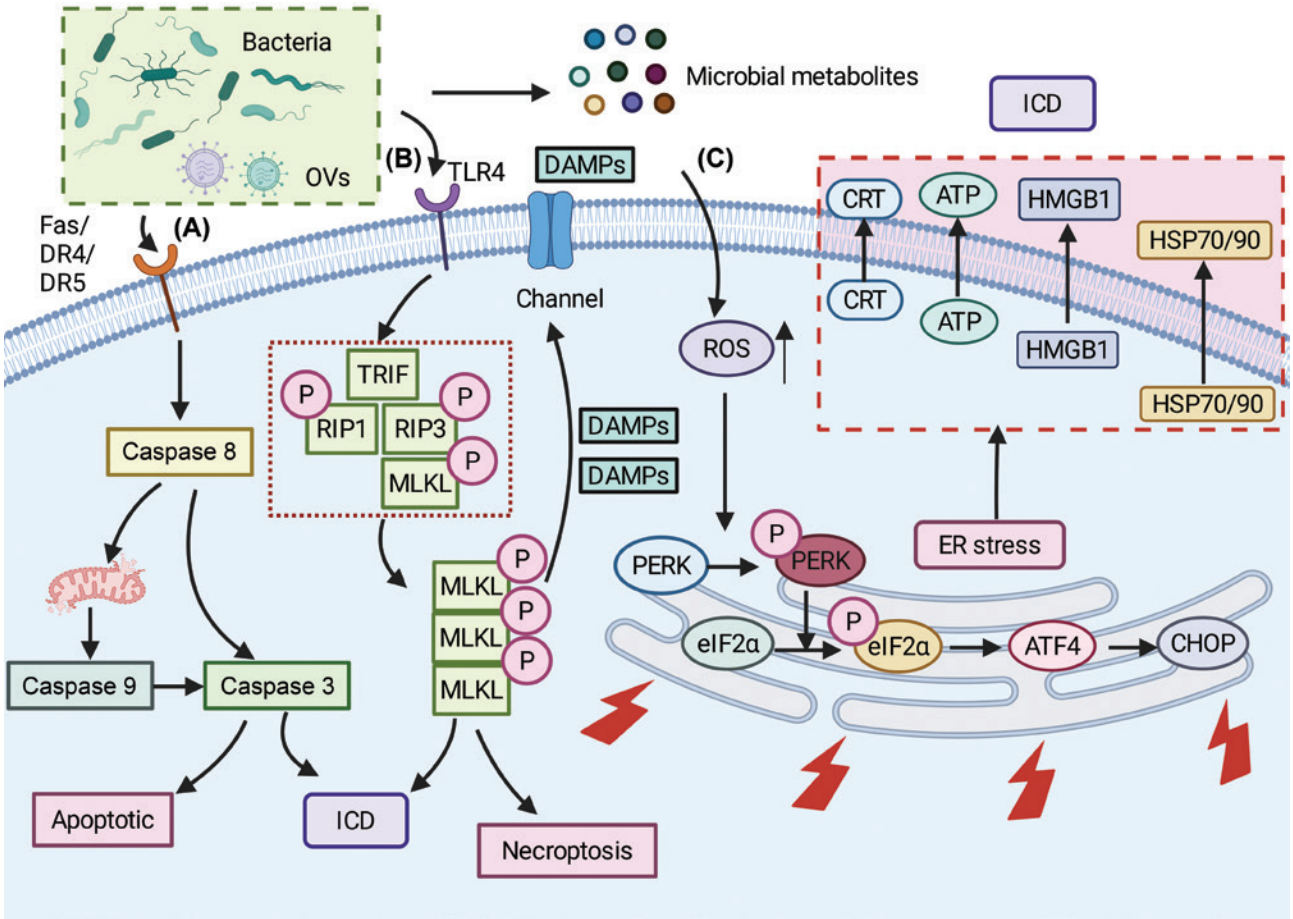


Figure 2 Schematic diagram of key signaling pathways through which microbes and microbial metabolites induce ICD in tumor cells. This schematic systematically summarizes the molecular mechanisms by which microbiota (bacteria and oncolytic viruses) and the metabolites trigger ICD in tumor cells through key signaling pathways. **(A) Apoptosis pathway**: Microbial components or oncolytic viruses activate death receptors (e.g., Fas, DR4, and DR5) on the tumor cell surface, initiating the caspase-8-mediated extrinsic apoptosis pathway. Mitochondrial damage further activates the caspase-9-mediated intrinsic apoptosis pathway. Under specific conditions, these apoptotic processes ultimately induce ICD in tumor cells. **(B) Necroptosis pathway**: Bacterial infection (e.g., *Pseudomonas aeruginosa*) recruits TRIF *via* TLR4, triggering the assembly of the RIP1-RIP3 necrosome. Activated RIP3 phosphorylates MLKL. Phosphorylated MLKL oligomerizes and inserts into the plasma membrane to form pores, leading to the release of DAMPs, and ultimately inducing ICD in tumor cells. **(C) ER stress pathway**: Microbial metabolites trigger ROS accumulation, inducing ER stress. ER stress activates PERK and activated PERK phosphorylates eIF2α. Phosphorylated eIF2α selectively promotes ATF4 translation and ATF4 upregulates CHOP expression. CHOP synergistically facilitates DAMP release, including CRT exposure, HMGB1 and HSP70/90 release, and ATP secretion, ultimately inducing ICD in tumor cells. ATP, adenosine triphosphate; ATF4, activating transcription factor 4; CHOP, C/EBP homologous protein; CRT, calreticulin; DAMP, damage-associated molecular pattern; DR4, death receptor 4; DR5, death receptor 5; eIF2α, eukaryotic initiation factor 2α; ER, endoplasmic reticulum; Fas, FS7-associated cell surface antigen; HMGB1, high mobility group box 1; HSP70/90, heat shock protein 70/90; ICD, immunogenic cell death; MLKL, mixed lineage kinase domain-like protein; PERK, PKR-like endoplasmic reticulum kinase; RIP1, receptor-interacting protein kinase 1; RIP3, receptor-interacting protein kinase 3; ROS, reactive oxygen species; TLR4, Toll-like receptor 4; TRIF, TIR-domain-containing adapter-inducing interferon-β (figure created with BioRender.com).

clinical trial. The optimal dose of 1×10^6 spores resulted in tumor regression in 42% of the patients with disease stabilization achieved in 86% of evaluable patients. However, the treatment was associated with serious adverse events, including sepsis and gas gangrene[117]. Bacteria not only proliferated at the tumor sites but also invaded normal tissues in some cases, leading to side effects, such as fever, vomiting, diarrhea, and nausea[118,119]. Consequently, real-time monitoring of bacterial colonization in patients during therapy is essential to ensure the safety and efficacy of bacterial-based therapeutics.

Engineered bacteria have become a novel living therapeutic modality with great preclinical potential based on

synthetic biology. **Figure 3** highlights the therapeutic procedures and immune effects of engineered microbial therapy in tumor-bearing mice. However, these the therapeutic procedures and immune effects remain largely preclinical, warranting optimization of safety and targeting of bacterial carriers with validation of the efficacy through clinical trials. Integrating synthetic biology and nanotechnology may drive next-generation precision anticancer therapies.

Microbiota regulates ICD through synergistic effects

Probiotics can influence disease progression by regulating the gut microbiota and immune system. Notably, DOX, a typical ICD inducer, exerts therapeutic effects by stimulating immune responses against tumors. Reportedly, short *Bifidobacteria* BBr60, pentose-producing bacteria PP06, and long *Bifidobacteria* BL21 individually exhibit no direct antitumor activity. However, combined administration of PP06/BL21 with DOX has been shown to significantly enhance the inhibitory effects on tumors[120]. In addition, ICIs are widely used in cancer immunotherapy, yet the clinical benefits are found in only a subset of patients. Growing evidence suggests that the gut microbiota has a crucial role in modulating the TIME and influencing ICI efficacy. Species, such as *Coprobacillus cateniformis*[121], *Erysipelatoclostridium ramosum*[121], *Lactobacillus gallinarum*[122], *Lactobacillus rhamnosus* GG[123], and *Roseburia intestinalis*[124], have been shown to enhance antitumor immunity in response to PD-1/PD-L1 inhibition in murine models. For example, Rv3628 derived from *Mycobacterium tuberculosis* exhibits potent tumor immunoadjuvant activity. Intravenous Rv3628 activated DCs in the spleen and lymph nodes in mice, thereby enhancing antigen presentation, particularly in tumor-bearing hosts. As an adjuvant, Rv3628 can significantly improve antitumor immunity in three distinct models (OVA-expressing B16 melanoma, CT26 carcinoma, and parental B16 melanoma). Notably, Rv3628 synergizes with anti-PD-1 therapy to promote tumor regression[125]. Similarly, cells infected with the oncolytic adenovirus, AdV5/3-D24-ICOSL-CD40L, have been shown to display hallmark ICD characteristics, including CRT exposure, ATP release, and HMGB1 secretion. When combined with pembrolizumab, this treatment could further enhance antitumor efficacy in a mesothelioma mouse model by promoting intratumoral T-cell infiltration and modulating the TME[126]. Pancreatic ductal adenocarcinoma (PDAC) is a highly aggressive malignancy and attenuated *Listeria* monocytogenes was used to deliver tetanus toxoid protein ($TT_{856-1313}$) to PDAC cells to improve therapeutic outcomes. This activated pre-existing TT-specific memory T cells to eliminate infected tumor cells in murine models. Combining this approach with low-dose gemcitabine can present a synergistic immune effect, converting immunologically "cold" tumors into "hot" tumors[127].

Currently, cancer treatment approaches include surgical intervention, RT, chemotherapeutic agents, molecularly targeted drugs, and immunotherapeutic strategies. Despite the transformative impact of immunotherapy in oncology, treatment resistance remains a major barrier to widespread clinical success. Microorganisms, particularly probiotics, can act as adjuvants in cancer therapy by modulating antitumor immunity, reducing drug toxicity and side effects, and enhancing the efficacy of both chemotherapy and immunotherapy, thereby providing a supportive role in improving overall anticancer outcomes.

Regulating the microbiota through dietary intervention

Emerging evidence indicates that dietary components have a crucial role in modulating and maintaining the symbiotic microbial communities inhabiting the digestive tract, collectively known as the gut microbiota[128]. Consumption of pomegranate has been shown to enrich beneficial gut microbes, such as *Lactobacillus* spp. and *Bifidobacterium* spp., while suppressing pathogenic bacteria, such as the *Bacteroides fragilis* group and *Clostridia*[129]. Dietary fiber, including guar gum, can alter gut microbial metabolism by enriching *Actinobacteriota*, particularly *Bifidobacterium*, along with modifying multiple genera within the phyla Bacteroidota and Firmicutes, which may in turn increase susceptibility to colonic inflammation[130]. Therefore, it is essential to investigate how dietary interventions influence the gut microbiota. Various gut bacteria ferment dietary fibers to produce SCFAs, which act as key endogenous signaling molecules involved in lipid regulation and inflammation mitigation[131]. For example, probiotics, including *Lactobacillus*, *Bifidobacterium*, and *Roseburia*, generate SCFAs, such as butyric acid, acetic acid, and lactic acid, through dietary fiber fermentation, which can reduce neuroinflammation and improve cognitive function, thereby exerting beneficial effects in disorders, such as Alzheimer's disease[132]. In addition, clinical trials in patients with metabolic syndrome have shown that butyrate supplementation produces significant antihypertensive effects[133]. Increasing evidence reveals that specific dietary components, such as high-salt diets, can alter gut microbiota-derived metabolites, thereby regulating ICD. Specific phytochemical constituents have been shown to display notable ICD-inducing properties in antitumor immunity. **Table 3** summarizes dietary components capable of inducing ICD, highlighting the DAMPs that are released and the combined effects with ICIs.

Although dietary interventions can regulate the gut microbiota and influence disease progression, dietary interventions may also present potential risks. Animal studies involving female ARE-Del mice showed that long-term consumption of a diet containing hydroxypropyl-modified high-amylose resistant starch (HAMSP), administered before and after the

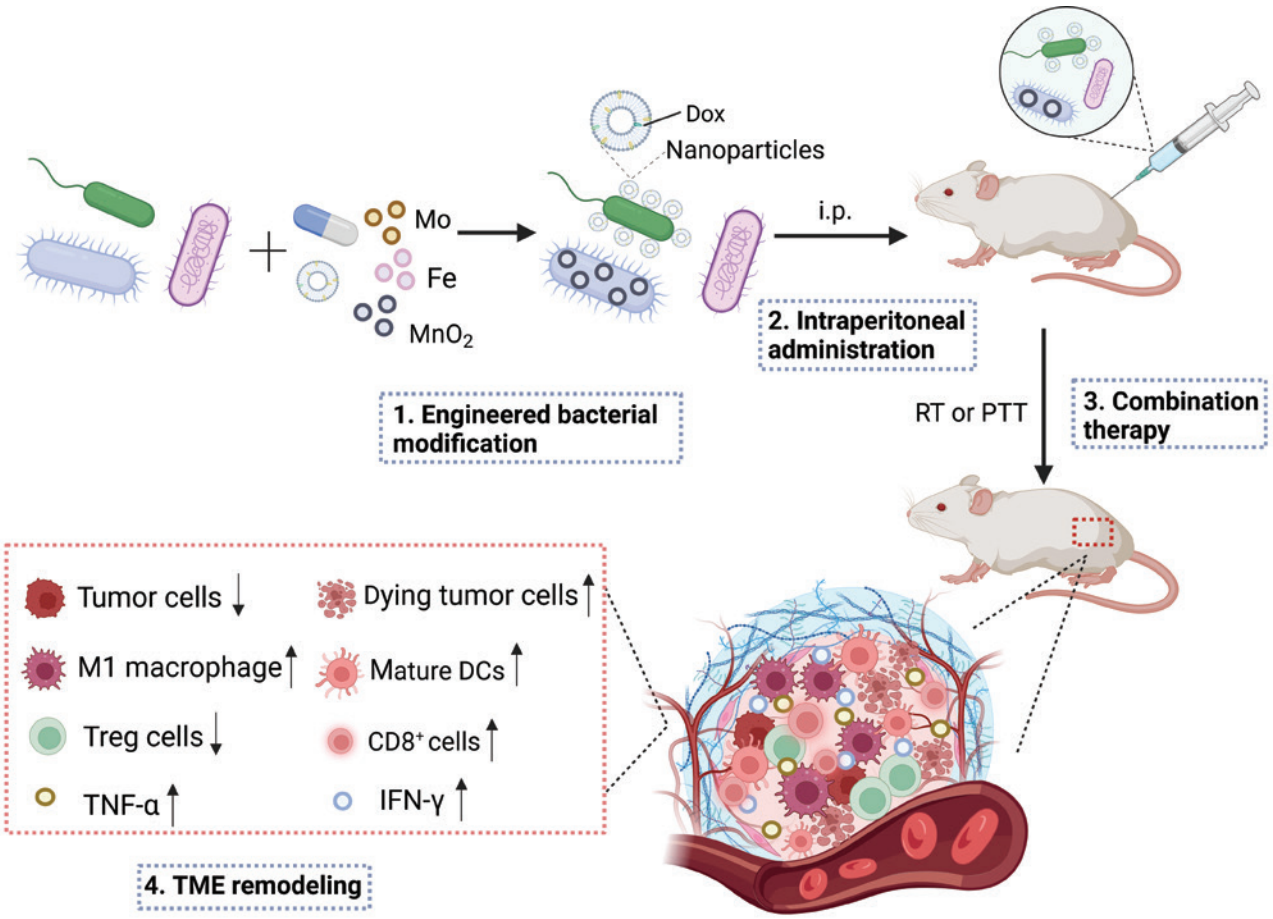


Figure 3 Synthetic biology-engineered microbial therapy reprograms the TME. This schematic illustrates a therapeutic strategy using synthetically modified microbiota administered *via* intraperitoneal injection, combined with radiotherapy or photothermal therapy, to effectively remodel the TME. **1. Engineered bacterial modification**: Bacteria are chemically modified (e.g., with Mn, Fe, and MnO_2) and integrated with nanomaterials to construct an engineered bacterial delivery system capable of loading therapeutic agents, such as DOX. **2. Intraperitoneal administration**: Drug-loaded engineered bacteria are administered *via* intraperitoneal injection into tumor-bearing mice. **3. Combination therapy**: Treated tumor-bearing mice are subsequently subjected to RT or PTT. **4. TME remodeling**: Following combination therapy, the TME undergoes significant remodeling, characterized by the following: increased numbers of dying tumor cells; enhanced infiltration of mature DCs and $CD8^+$ T cells; polarization of macrophages toward the M1 phenotype; reduced proportion of Tregs; and significantly elevated expression of pro-inflammatory cytokines (TNF-α and IFN-γ). DC, dendritic cell; DOX, doxorubicin; IFN-γ, interferon-gamma; PTT, photothermal therapy; RT, radiotherapy; TME, tumor microenvironment; TNF-α, tumor necrosis factor-alpha; Treg, regulatory T cell (figure created with BioRender.com).

onset of primary biliary cholangitis, reshaped the T-cell pool. This finding resulted in a reduction of naïve and central memory T-cell populations, an increase in effector memory T cells, and a decrease in $CD4^+CD8^+$ double-positive T cells within intestinal intraepithelial lymphocytes and the lamina propria. Moreover, HAMSP intake has been associated with hepatic steatosis[138]. Dietary choices play a critical role in shaping the composition and function of the gut microbiota, ultimately influencing host health. When developing diet-based ICD modulation strategies, it is essential to consider both safety and inter-individual variability in response to diet. Future research should further explore how dietary composition affects cancer-related processes by investigating the mechanisms of specific nutrients and whole foods in modifying the microbiome, as well as how meal timing influences microbial activity relevant to cancer regulation and therapeutic outcomes.

In summary, microbial-based strategies for inducing ICD should focus on exploiting the unique advantages of microorganisms through three primary research avenues: engineered bacteria; combination therapies; and dietary interventions. These approaches establish novel connections between the microbiota and ICD, activating antitumor immune responses through multiple immunologic pathways. Together, these interventions modulate microbial communities from three complementary perspectives to enhance ICD-mediated tumor eradication (**Figure 4**).

Table 3 Dietary components and formulations inducing ICD

Component/formulation	Source/nature	Mechanism	Application/combination Strategy	Ref.
γ-Mangostin	Phytochemical Constituents	1. Upregulates HSP90, annexin A1, and IL-1β 2. Activates cGAS signaling *via* DNA damage response 3. Promotes histone H3 acetylation through HDAC4 degradation	Leukemia cells	134
Piceatannol	Dietary phenolic compound (e.g., grapes, blueberries, and mushrooms)	1. Enhances OXA-induced DAMPs release (ATP, CRT, HMGB1) 2. Promotes autophagy *via* TFEB/TFE3 activation 3. Induces ER stress	Combined with OXA	135
Epigallocatechin-3-gallate	Tea polyphenol (green tea)	1. Promotes HMGB1 secretion and the surface expression of CRT and HSP70 2. Enhances DC maturation and $CD8^+$ T-cell activation	CT26 tumors/combined with anti-cytotoxic T-lymphocyte-associated protein 4 antibodies	136
VC@cLAV	Dietary antioxidants (lipoic acid and vitamin C)	1. Generates high ROS in cancer cells to induce ICD, while protecting normal cells 2. Increases antigen release and DC maturation (up to 56.5% *in vitro*) 3. Synergizes with anti-PD-1 to suppress primary and metastatic tumors	Combined with anti-PD-1 therapy	137

ATP, adenosine triphosphate; cGAS, cyclic GMP-AMP synthase; CRT, calreticulin; DC, dendritic cell; ER, endoplasmic reticulum; HDAC4, histone deacetylase 4; HMGB1, high mobility group box 1; HSP70, heat shock protein 70; HSP90, heat shock protein 90; ICD, immunogenic cell death; OXA, oxaliplatin; PD-1, programmed cell death protein 1; ROS, reactive oxygen species; TFE3, transcription factor binding to IGHM enhancer 3; TFEB, transcription factor EB; VC@cLAV, composition comprising alpha-lipoic acid and vitamin C.

Challenges and future trajectories of microbiota and microbial metabolites in ICD

Although advances in understanding how microorganisms and metabolites regulate ICD have accelerated progress in tumor immunotherapy, many critical challenges persist. Microbial activity and metabolite production are influenced by both internal factors, such as host genetics, and external factors, including diet, antibiotics, and chemotherapeutic drugs, making it difficult to develop universally effective therapeutic approaches across different patient populations. In addition, most current studies focus on animal models that cannot fully replicate the complexity of the human gut microbial ecosystem. As a result, both the safety and efficacy of microbial-targeted treatments require rigorous validation before clinical application. Future research should focus on elucidating the interactions between microorganisms and host-related factors to enhance the effectiveness of microbial-based immunotherapies. Key areas for further exploration include optimizing high-throughput screening methods for microbial metabolites to balance ICD induction efficiency with minimal toxicity, reducing harmful effects on normal tissues and cells, and investigating the therapeutic potential of microbial transplantation, such as FMT, in patients unresponsive to immunotherapy.

Microbial- and metabolite-induced ICD represents a highly promising frontier in cancer immunotherapy, though the precise mechanisms and dynamic regulation require further investigation. Future research directions should include systematically elucidating the molecular pathways through which microbial metabolites induce ICD and interact with the TME, designing combination regimens incorporating microbial metabolites and ICIs to improve treatment outcomes and patient survival, rigorously evaluating adverse effects, and developing personalized therapeutic strategies. Through collaborative, multidisciplinary efforts and precision medicine approaches, microbial regulation of ICD has the potential to deliver transformative clinical benefits to cancer patients. By addressing these challenges and deepening our understanding of the molecular mechanisms by which microorganisms and the metabolites induce ICD, the application could be extended to a broader range of tumors, offering patients with cancer more effective treatment options and improved quality of life.

Conclusions

ICD can activate adaptive immune responses, converting "cold" tumors into "hot" tumors. However, traditional methods for inducing ICD are often limited by drug resistance, ITME, and adverse side effects. Notably, microbiota and microbial metabolites have shown potential to regulate ICD and remodel the TME, thereby promoting T-cell infiltration

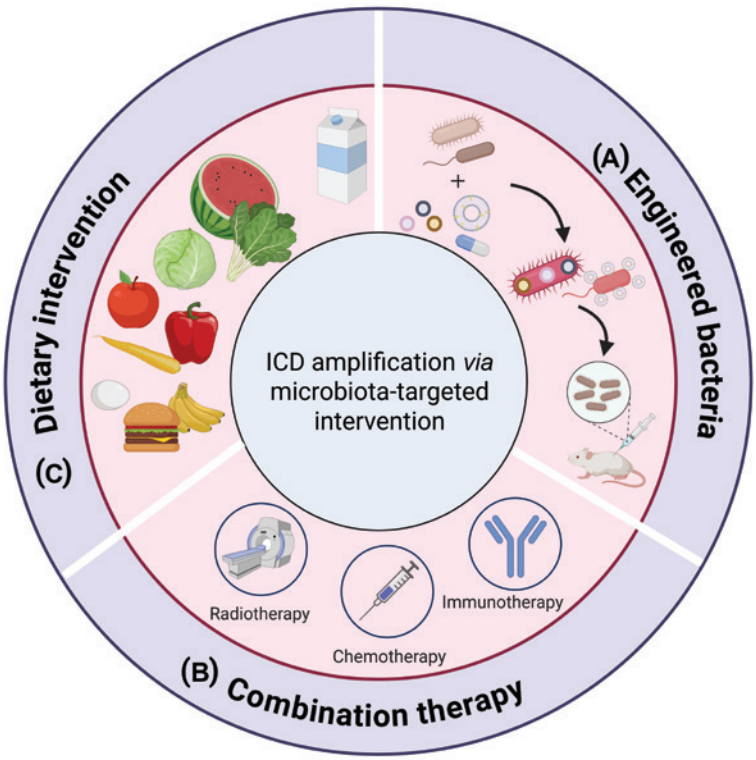


Figure 4 Strategies for targeted microbiota intervention to enhance ICD. This schematic summarizes the main strategies for enhancing ICD through microbiota modulation. **(A) Engineered bacterial modification**: Leveraging the tumor-targeting and immunomodulatory properties of bacteria, engineering approaches, such as chemical modification, genetic engineering, or nanocomposite integration, are used to construct engineered microbial delivery systems, thereby precisely boosting the ability to induce ICD at tumor sites. **(B) Combination therapy**: Microbiota-based therapies are combined with conventional antitumor treatments, such as immunotherapy, chemotherapy, and RT, to enhance overall antitumor efficacy and ICD induction through synergistic mechanisms. **(C) Dietary intervention**: By modifying dietary patterns or supplementing specific nutrients, the composition and function of the gut microbiota can be optimized, thereby strengthening the capacity to induce ICD in tumor cells. ICD, immunogenic cell death; RT, radiotherapy (figure created with BioRender.com).

and suppressing immunosuppressive cell activity. Future research is expected to identify more microorganisms and metabolites with ICD-inducing potential, offering more effective therapeutic approaches for cancer. The findings of this study highlight that immunotherapy based on microbial and microbial metabolite-induced ICD is poised to become a key strategy in future cancer treatment. Beyond offering new avenues for enhancing antitumor efficacy, this approach holds far-reaching potential across diverse scientific disciplines, including microbiology, immunology, and clinical medicine.

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Conflict of interest statement

No potential conflicts of interest are disclosed.

Author contributions

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