靶向重编程肿瘤相关巨噬细胞的纳米递送系统在乳腺癌治疗中的研究进展

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摘要: 肿瘤相关巨噬细胞 (tumor-associated macrophages, TAMs) 在乳腺癌肿瘤微环境 (tumor microenvironment, TME) 中通常呈现促肿瘤的M2型。这些M2型TAMs通过多种机制显著加剧了乳腺癌的恶性进展: 它们分泌生长因子和细胞因子促进肿瘤细胞增殖、侵袭和迁移; 通过诱导血管新生和重塑细胞外基质为肿瘤转移铺路; 并通过提供生存信号等方式介导肿瘤细胞对化疗、靶向治疗及免疫治疗抵抗, 导致耐药。因此, TAMs是驱动乳腺癌发生发展、转移和耐药的关键因素。纳米递送系统凭借其优异的靶向性、载药多样性及微环境响应特性, 通过重塑炎症环境, 调控氧化应激与免疫信号网络, 调控糖、脂、氨基酸代谢重编程等途径为靶向调控TAMs表型极化提供了新策略, 成为逆转TME的关键研究方向, 具有重要的临床转化潜力。本文系统综述了TAMs的表型极化对乳腺癌发生发展、转移及耐药的关键影响, 以及基于纳米递送系统的TAMs重编程策略及其调控的分子网络机制, 以期为乳腺癌的精准治疗提供新思路。

关键词: 乳腺癌; 肿瘤微环境; 肿瘤相关巨噬细胞; 细胞重编程; 纳米递送系统

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Research progress of nano-delivery systems targeting reprogramming tumor-associated macrophages in the treatment of breast cancer

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Abstract: In the tumor microenvironment (TME) of breast cancer, tumor-associated macrophages (TAMs) predominantly exhibit a pro-tumor M2 phenotype. These M2 TAMs significantly exacerbate breast cancer malignant progression through multiple mechanisms: they secrete growth factors and cytokines to promote the proliferation, invasion and migration of tumor cells; they facilitate tumor metastasis by inducing angiogenesis and remodeling the extracellular matrix; and they mediate the resistance of tumor cells to chemotherapy, targeted therapy and immunotherapy by providing survival signals, *etc.*, leading to drug resistance. Consequently, TAMs are pivotal drivers of breast cancer initiation, progression, metastasis, and therapy resistance. With its excellent targeting, drug-carrying diversity and microenvironmental response properties, the nano-delivery system provides a new strategy for targeting and regulating the phenotypic polarization of TAMs by remodeling the inflammatory environment, modulating oxidative stress and immune signaling networks, and regulating the metabolic reprogramming of glucose, lipids, and amino acids, making it a key research direction for reversing TME, which has an important

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potential for clinical translation. This review systematically summarizes the critical impact of TAM phenotypic polarization on breast cancer pathogenesis, metastasis, and drug resistance, alongside nano delivery-based strategies for TAM reprogramming and the underlying molecular network mechanisms they regulate, aiming to provide new insights for the precision treatment of breast cancer.

Key words: breast cancer; tumor microenvironment; tumor-associated macrophage; cellular reprogramming; nano delivery system

乳腺癌是全球发病率位居第二的恶性肿瘤, 同时也是导致女性癌症相关死亡的主要原因[1]。据2025年癌症预测统计数据, 超过310万女性 (占所有女性癌症病例的32%) 被诊断为乳腺癌[2]。肿瘤相关巨噬细胞 (tumor-associated macrophages, TAMs) 作为肿瘤微环境 (tumor microenvironment, TME) 中最丰富的免疫浸润细胞群, 其在乳腺癌中的浸润比例 (最高可达50%) 显著高于胃癌、肺癌等多种实体肿瘤[3]。TAMs具有显著的功能可塑性, 在肿瘤发生发展中表现出双重调控特性: 在肿瘤早期阶段, 以M1型TAMs为主, 其固有的免疫监视功能可通过直接吞噬作用清除肿瘤细胞; 然而随着TME中细胞因子的刺激和外泌体等作用, 巨噬细胞会发生表型极化, 转化为具有促肿瘤特性的M2型TAMs。M2型TAMs可通过分泌血管内皮生长因子 (vascular endothelial growth factor, VEGF)、基质金属蛋白酶 (matrix metalloproteinases, MMPs) 等多种生物活性介质, 促进肿瘤血管生成、细胞外基质 (extracellular matrix, ECM) 重塑及免疫抑制微环境的形成, 并且乳腺癌中M2型TAMs的极化比例显著高于其他恶性肿瘤类型, 这种特征性表现与免疫抑制微环境的形成、高复发风险及治疗抵抗性密切相关[4]。因此, 靶向调控TME中TAMs极化状态, 重编程TAMs, 使M2型TAMs向M1型转化, 成为乳腺癌治疗的关键策略。

纳米递送系统具有独特的靶向递送能力、载药多样性及微环境响应特性, 基于纳米技术的TAMs重编程策略通过调控巨噬细胞的代谢重编程等实现表型极化, 在克服乳腺癌治疗局限性方面展现出重要潜力。本文系统阐述了TAMs在乳腺癌发生发展、转移及治疗耐药过程中的关键调控机制, 并总结了利用近年来基于纳米技术的TAMs重编程研究进展, 为开发潜在的乳腺癌治疗策略奠定了基础 (图1)。

1 TAMs对乳腺癌发生发展的影响

TAMs作为TME中占比最高的免疫细胞群体 (约占30%～50%), 在乳腺癌恶性进展中发挥关键调控作用。研究表明, 在肿瘤演进过程中, TAMs受TME中细胞因子、缺氧信号及代谢产物的持续调控, 从具有抗肿瘤活性的M1型逐渐极化成促肿瘤的M2型, 从而形成有利于肿瘤发生发展的免疫抑制微环境[5]。

M1型极化主要依赖于Toll样受体 (toll-like receptors, TLR) 信号通路、辅助性T细胞1 (T helper 1 cell, Th1) 型细胞因子及病原相关分子模式的激活, 其特征性标志物诱导型一氧化氮合酶 (inducible nitric oxide synthase, iNOS) 可催化产生高浓度一氧化氮, 通过诱导肿瘤细胞周期阻滞和线粒体凋亡途径发挥直接杀伤作用[6]。此外, M1型TAMs通过分泌白细胞介素-12 (interleukin-12, IL-12) 和白细胞介素-23 (interleukin-23, IL-23) 异源二聚体驱动$CD8^+$ T细胞活化和Th1型免疫应答, 其产生的肿瘤坏死因子-α (tumor necrosis factor-α, TNF-α) 与白细胞介素1β (interleukin-1β, IL-1β) 可协同上调肿瘤细胞主要组织相容性复合体I分子表达, 增强肿瘤细胞免疫原性, 引诱肿瘤细胞坏死, 并抑制肿瘤免疫逃逸, 从而抑制乳腺癌的发生发展。而M2型极化主要受白细胞介素-4 (interleukin-4, IL-4)、白细胞介素-13 (interleukin-13, IL-13) 等辅助性T细胞2 (T helper 2 cell, Th2) 型细胞因子和白细胞介素-10 (interleukin-10, IL-10)、转化生长因子-β (transforming growth factor-β, TGF-β) 等免疫抑制因子共同调控。该表型高表达精氨酸酶1 (arginase-1, Arg1) 和甘露糖受体CD206分子, 并且通过分泌VEGF促进肿瘤血管形成, 其释放的TGF-β不仅抑制$CD8^+$ T细胞浸润, 还诱导上皮−间质转化 (epithelial-mesenchymal transition, EMT)[7]。此外, M2型TAMs还通过程序性死亡配体1 (programmed death ligand 1, PD-L1)/程序性死亡受体1 (programmed death 1, PD-1) 轴介导T细胞耗竭, 同时通过IL-10诱导调节性T细胞 (regulatory T cells, Tregs) 扩增, 共同构建免疫抑制微环境[8,9]。

上述证据表明, TAMs表型动态平衡对维持乳腺癌免疫微环境稳态具有决定性作用, M1型TAMs通过iNOS介导的直接杀伤、抗原呈递及Th1免疫激活等发挥显著的肿瘤抑制作用; 而M2型则通过促血管生成、EMT诱导及免疫检查点调控等多通路协同促进肿瘤发生发展。

2 TAMs对乳腺癌转移的影响

研究证实, TAMs表型极化在乳腺癌转移进程中

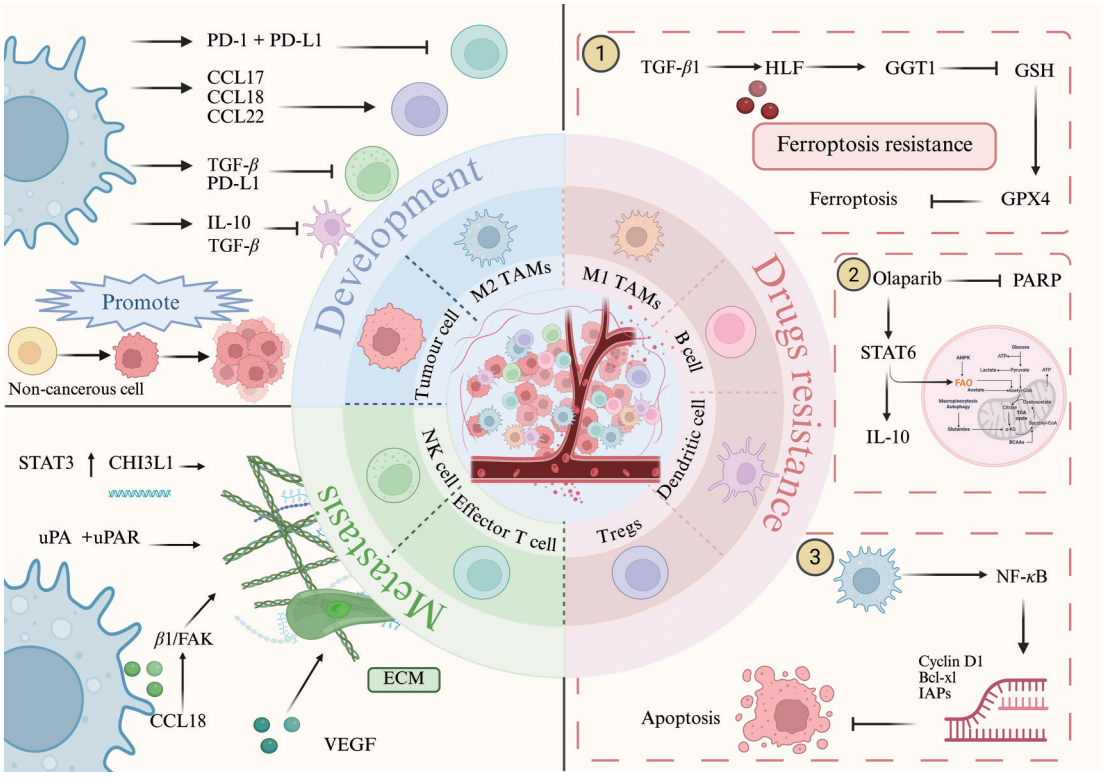


Figure 1 The multi-factor regulatory networks of M2 TAMs driving tumorigenesis, metastasis and drug resistance. TAMs: Tumor-associated macrophages; NK cell: Natural killer cell; Tregs: Regulatory T cells; PD-L1: Programmed death-ligand 1; PD-1: Programmed death 1; TGF-β: Transforming growth factor-beta; STAT3: Signal transducer and activator of transcription 3; HLF: Hepatic leukemia factor; GGT1: Gamma-glutamyl transferase 1; GSH: Glutathione; GPX4: Glutathione peroxidase 4; NF-κB: Nuclear factor-kappa B

发挥关键调控作用。研究表明, M2 型 TAMs 通过分泌多种细胞因子形成复杂的调控网络, 协同促进肿瘤细胞侵袭转移[10]。例如, M2 型 TAMs 高表达壳多糖酶 3 样蛋白 1 (chitinase-3-like protein 1, CHI3L1), CHI3L1 通过与肿瘤细胞表面白细胞介素 13 受体 α2 特异性结合, 激活丝裂原活化蛋白激酶信号通路, 显著上调 MMPs 基因的表达, 与此同时, M2 型 TAMs 分泌的尿激酶型纤溶酶原激活物与其受体结合后, 可激活纤溶酶原–纤溶酶转化级联反应, 协同促进 ECM 降解[11,12]。这种协同作用进一步增强了 ECM 的重塑, 促进乳腺癌细胞从原发肿瘤部位脱离然后向周围组织及器官转移[13]。除直接降解 ECM 外, M2 型 TAMs 分泌的 C-C 基序趋化因子配体 18 (C-C motif chemokine ligand 18, CCL18) 可通过激活肿瘤细胞整合素 β1/FAK 信号轴, 增强肿瘤细胞与 ECM 的黏附力并诱导侵袭伪足形成, 这一机制在乳腺癌肝转移模型中显示出特异性促进作用[14,15]。更值得关注的是, 碱性螺旋–环–螺旋 2 (spermatogenesis and oogenesis specific basic helix-loop-helix 2, Sohlh2) 作为 M2 型 TAMs 极化的关键调控枢纽, 可通过结合肝脏 X 受体 α (liver X receptor alpha, LXRα) 启动子区域增强其转录活性, 形成 Sohlh2/LXRα 调控轴。该调控轴激活 ATP 结合盒转运蛋白 A1 (adenosine triphosphate-binding cassette transporter A1, ABCA1) 介导的胆固醇外排通路, 破坏巨噬细胞膜脂质稳态, 促进 M2 型极化表型的稳定。同时, Sohlh2 过表达可诱导 EMT, 进一步促进肿瘤转移[16-18]。因此, 巨噬细胞中的 Sohlh2 可能是乳腺癌转移治疗的新治疗靶点[17]。

综上所述, M2 型 TAMs 通过多途径协同驱动乳腺癌转移: M2 型 TAMs 通过分泌 CHI3L1 和 uPA 等因子降解 ECM; 通过分泌 CCL18 增强肿瘤细胞黏附及侵袭伪足形成, 此外, 还通过 Sohlh2 激活 LXRα/ABCA1 轴扰乱巨噬细胞脂质稳态以稳定 M2 表型, 并诱导 EMT, 促进乳腺癌转移。因此, 靶向干预 TAMs 相关信号通路 (如 Sohlh2、CHI3L1) 或可为抑制乳腺癌转移提供新的治疗策略。

3 TAMs 对乳腺癌治疗耐药的影响

TAMs 通过构建复杂的代谢与信号网络及免疫抑制微环境, 在乳腺癌治疗耐药中发挥关键调控作用。在化疗及靶向治疗方面, M2 型 TAMs 分泌的 TGF-β1 可激活肝白血病因子, 上调 γ-谷氨酰转移酶 1 (γ-glutamyl-transferase1, γ-GGT1) 以增强谷胱甘肽 (glutathione,

GSH) 代谢通路, 显著提高肿瘤细胞对铁死亡的抵抗能力, 提升肿瘤细胞对顺铂的耐受性[19]; 同时 M2 型 TAMs 通过糖基化修饰介导的代谢重编程, 促进溶酶体组织蛋白酶 B 的分泌, 加剧化疗耐药; 在聚腺苷二磷酸核糖聚合酶抑制剂奥拉帕尼治疗中, 虽然短期内可激活抗肿瘤免疫应答, 但通过转录激活蛋白 6 信号轴可诱导 TAMs 发生脂代谢依赖性重编程, 上调脂肪酸氧化 (fatty acid oxidation, FAO) 相关基因, 并增加 IL-10 分泌, 加速药物疗效衰减[20]。此外, TAMs 还可以激活 NF-κB 通路, NF-κB 的激活增强了细胞周期蛋白 D1、B 细胞超大淋巴瘤 (B-cell lymphoma-extra large, Bcl-xl) 和细胞凋亡蛋白抑制剂 (inhibitor of apoptosis proteins, IAPs) 等因子的转录, 从而促进抗凋亡信号传导, 导致对放疗、化疗和内分泌治疗的广泛耐药[21,22]。尤其在肿瘤免疫治疗中, 作为免疫抑制微环境的核心组分, M2 型 TAMs 通过多重机制削弱疗效, 导致乳腺癌对免疫治疗敏感性显著降低: 在免疫检查点抑制剂治疗中, M2 型 TAMs 通过高表达 PD-L1 和 B7-H4 并分泌 TGF-β、IL-10 及 Arg1、吲哚胺 2,3-双加氧酶, 导致 T 细胞功能衰减[23-25]; 在癌症疫苗治疗中, M2 型 TAMs 分泌携带非编码 RNA 的外泌体, 抑制树突状细胞 (dendritic cells, DCs) 成熟或清除溶酶病毒颗粒, 限制病毒在肿瘤内的复制和扩散[26], 导致相关疫苗疗效削弱; 在嵌合抗原受体 T 细胞免疫疗法 (chimeric antigen receptor T-Cell immunotherapy, CAR-T) 中, M2 型 TAMs 激活癌症相关成纤维细胞分泌胶原蛋白, 形成致密基质屏障, 阻碍 CAR-T 细胞浸润, 上调 CD47, 与 CAR-T 细胞竞争性结合, 从而保护肿瘤细胞免受吞噬[27,28]。

综上, TAMs 通过多种机制驱动乳腺癌治疗耐药, 主要包括通过铁死亡抵抗、FAO 代谢重编程、NF-κB 信号激活及免疫抑制微环境构建驱动乳腺癌多重耐药, 靶向其代谢−信号−免疫抑制网络的协同策略是治疗耐药的关键方向。

4 重编程 TAMs 的纳米递送系统

纳米递送技术凭借其高效穿透 TME 屏障、多模态协同治疗及精准调控 TAMs 功能的独特优势, 为肿瘤治疗提供了新的策略。近年来, 研究者们在纳米递送系统通过重塑炎症微环境、调控氧化应激与免疫信号网络、调控代谢重编程等策略调控 TAMs 极化进行了大量的研究 (图 2 和表 1[29-39])。

4.1 靶向 TAMs 重塑炎症环境的纳米递送系统

乳腺癌免疫微环境的显著特征表现为 T 淋巴细胞和 TAMs 等免疫细胞的高度浸润, 这种慢性炎症环境通过持续分泌促瘤因子驱动肿瘤进展[40]。针对这一特性, 近年来研究者开发了多种基于纳米技术的创新策略, 通过调节炎症环境, 重塑 TAMs 极化平衡, 有效逆

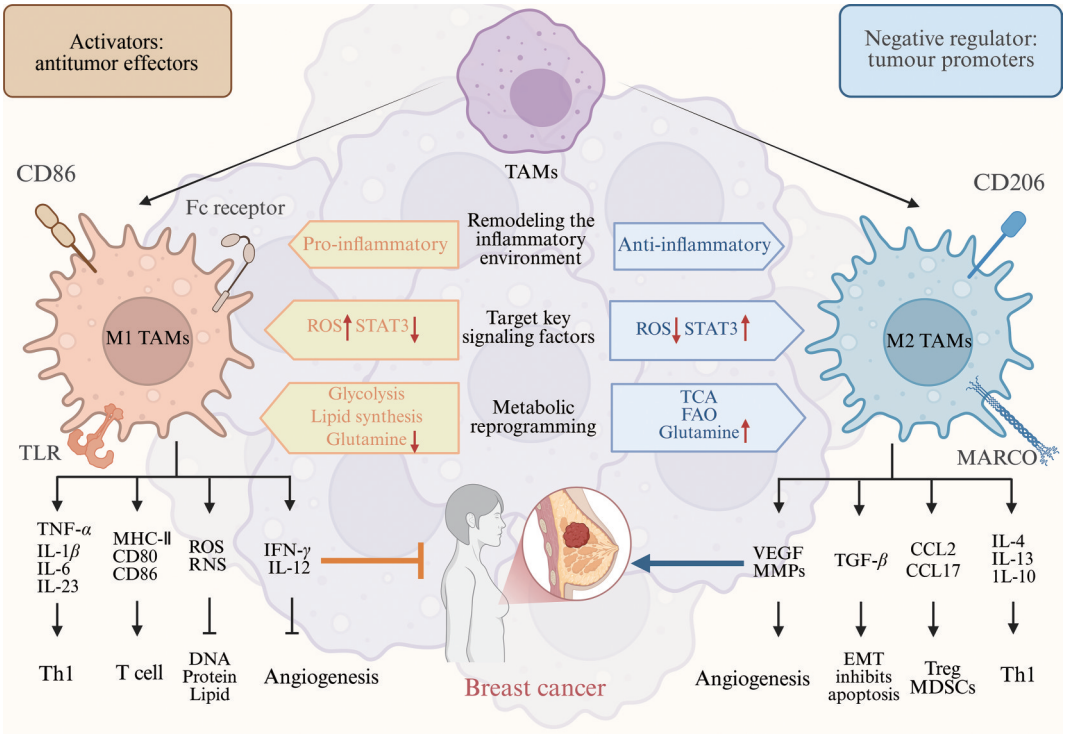


Figure 2 The M1/M2 polarization and functional regulation of TAMs. TLR: Toll-like receptor; Th1: T helper 1 cell; MHC-II: Major histocompatibility complex class II; ROS: Reactive oxygen species; RNS: Reactive nitrogen species; IFN-γ: Interferon-gamma; TCA: Tricarboxylic acid cycle; MDSCs: Myeloid-derived suppressor cells; MARCO: Macrophage receptor with collagenous structure

Table 1 Nano-delivery systems for reprogramming TAMs in the last five years. GDNP: Ginseng-derived nanoparticles; HMMDN: Hollow manganese dioxide nanoparticle; IL-10: Interleukin 10; VEGF: Vascular endothelial growth factor; CQ: Chloroquine; PFH: Perfluorohexane; DPPA: Anti-PD-L1 peptide; UCNPs: Upconverting nanoparticles; PFC: Perfluorocarbon; DOX: Doxorubicin; TEV: Tumor-derived extracellular vesicles; CS: Chondroitin sulfate; CTS: Cryptotanshinone; FNA: Framework nucleic acid, PPS: Polyporus polysaccharide, SPIONs: Superparamagnetic iron-based nanocomposites; IFN-γ: Interferon-gamma; SMPs: Succinate-loaded microparticles; LDHA: Lactate dehydrogenase A; MSNPs: Metabolic supramolecular nanoparticles; FAO: Fatty acid oxidation; MI3-PD: MYC inhibitor prodrug

Strategy		Name	Type	Mechanism	Ref.
Inflammatory modulation		GDNP	Nanoparticles	Increase CCL5 and CXCL9; promote the infiltration of $CD8^+$ T cells	[29]
		HMMDN-Met	Nanoparticles	Down-regulate the expression of IL-10 and VEGF	[30]
Signaling pathway targeting	ROS	Pt(IV)/CQ/PFHNPs-DPPA-1	Nanoparticles	The reduction of platinum to cisplatin; increases ROS	[31]
		UCNPs@mSiO$_2$-PFC/Ce6@RAW-Man/PTX	Nanoparticles	PFC oxygen-carrying and activate Ce6 to produce reactive oxygen species	[32]
	STAT3	siSTAT3-DOX@TEV	Nanocarrier system	siSTAT3 silenced STAT3 gene expression and down-regulated STAT3	[33]
		CS/LyP-1-PC Lip	Liposomes	CTS inhibits STAT3 phosphorylation and reduces Tregs, MDSCs	[34]
	NF-κB	CpG-siRNA-tFNA	Nucleic acid self-assembled delivery system	Activate TLR9/NF-κB pathway; silence PI3Kγ	[35]
		Man/PPS-SPIONs	Nanoparticles	Stimulate IFN-γ and activate NF-κB pathway	[36]
Metabolic reprogramming	Glucose metabolism	SMPs	Microparticles	Inhibit IDH2 and stabilize HIF1α; enhancement LDHA expression	[37]
	Lipid metabolism	MSNPs	Nanoparticles	TLR7/8 agonist synergizes with FAO inhibition	[38]
	Amino acid metabolism	$\alpha v\beta$3-MI3-PD NP	Nanoparticles	Block glycolysis-glutamine axis	[39]

转免疫抑制并增强抗肿瘤应答。例如Han等[29]开发了一种从人参中分离的细胞外囊泡样人参衍生的纳米颗粒, 可特异性上调促炎C-C趋化因子配体5 (C-C motif chemokine ligand 5, CCL5) 和CXC趋化因子配体9的表达, 将M2型TAMs极化为M1型TAMs, 显著促进$CD8^+$ T细胞浸润, 与PD-1单抗联合治疗可协同激活抗肿瘤免疫应答, 且无肝肾等毒副作用。Chong等[30]设计的仿生纳米递送系统 (HMMDN-Met) 通过酸性响应性释放二甲双胍, 同时表面修饰M2pep靶向肽特异性识别M2型TAMs表面标志物, 显著增强纳米颗粒在肿瘤组织的靶向蓄积能力, 该系统通过抑制线粒体复合物I活性阻断氧化磷酸化 (oxidative phosphorylation, OXPHOS) 代谢, 同时下调VEGF与IL-10表达, 实现代谢与免疫的双调控。

以上这些纳米制剂通过精准调控M2/M1表型比例、增强效应免疫细胞浸润及抑制促瘤因子分泌, 有效打破了乳腺癌免疫抑制屏障, 通过整合递送系统智能化 (如采用靶向肽修饰、环境响应释放) 与多种机制协同 (代谢抑制、免疫通路激活), 为乳腺癌提供了低毒高效的联合治疗策略。

4.2 靶向氧化应激与免疫信号网络调控TAMs的纳米递送系统

4.2.1 调控氧化应激 活性氧 (reactive oxygen species, ROS) 是与氧代谢有关的、含氧自由基和易形成自由基的过氧化物的总称, 在生理浓度下参与细胞信号转导, 但过度积累则导致脱氧核糖核酸 (deoxyribonucleic acid, DNA) 损伤等氧化应激效应, 最终导致程序性细胞死亡[41,42]。TME的缺氧特征不仅促进肿瘤进展[42], 还上调VEGF、TGF-β等免疫抑制因子并激活髓源性抑制细胞 (myeloid-derived suppressor cells, MDSCs) 和Tregs等, 削弱治疗效果[43]。针对这一特征, Yang等[31]开发了响应性纳米超声造影剂 [Pt (IV)/CQ/PFHNPs-DPPA-1], 通过释放铂和氯喹 (chloroquine, CQ), 将铂(IV) 还原为顺铂, 提升胞内ROS水平, 诱导肿瘤细胞免疫原性死亡 (immunogenic cell death, ICD) 并促进TAMs向M1型转化; Yoon等[32]制备的多功能复合纳米颗粒 (UCNPs@mSiO$_2$-PFC/Ce6@RAW-Man/PTX) 通过PFC携氧和激活Ce6产生活性氧, 在缺氧肿瘤中释放氧气, 促进TAMs向M1表型极化。

4.2.2 抑制STAT3信号 除ROS外, 信号传导及转录激

活蛋白3 (signal transducer and activator of transcription 3, STAT3) 是驱动乳腺癌生存、转移及免疫抑制的又一核心因子[44], 可被白细胞介素-6 (interleukin-6, IL-6)、IL-10等细胞因子及多种生长因子激活[45]。在乳腺癌中, STAT3呈现持续性激活并通过调控抗凋亡蛋白B淋巴细胞瘤-2、VEGF、MMP9等靶基因促进肿瘤进展、转移及免疫抑制基因的转录表达[46,47]。针对STAT3的调控, Peng等[33]构建多功能纳米载体系统 (siSTAT3-DOX@TEV) (tumor-derived extracellular vesicles, TEV), 通过递送siSTAT3沉默STAT3基因表达, 驱动TAMs向M1表型转化, 有效抑制肿瘤进展; Luo等[34]开发双靶向脂质体 (CS/LyP-1-PC Lip) 通过抑制STAT3磷酸化, 重编程TAMs, 减少Tregs、M2型TAMs及MDSCs等免疫抑制细胞浸润, 协同抑制肿瘤生长和肺转移。

4.2.3 激活NF-*κ*B信号 TME中的分子信号网络存在高度交互性。以转录因子NF-*κ*B为例, 激活经典NF-*κ*B通路, 通常抑制M2型TAMs极化, 促进M1表型极化。Qian等[35]开发的CpG-siRNA-tFNA自组装纳米递送系统, 通过TLR9激活经典NF-*κ*B通路及沉默磷脂酰肌醇3-激酶-*γ* (phosphatidylin-ositol-3-kinase, PI3K*γ*) 基因, 解除其对NF-*κ*B的负调控, 两者协同诱导TAMs向M1表型极化。Liu等[36]开发甘露糖修饰的猪苓多糖负载超顺磁性氧化铁纳米复合物 (Man/PPS-SPIONs), 刺激干扰素-*γ* (interferon-*γ*, IFN-*γ*) 分泌, 激活下游NF-*κ*B通路, 诱导M2型TAMs向M1型极化。

4.3 调控TAMs代谢重编程的纳米递送系统

TAMs的代谢重编程通过糖、脂、氨基酸代谢途径驱动其功能极化, M1型TAMs依赖糖酵解, M2型TAMs则利用三羧酸 (tricarboxylic acid, TCA) 循环、FAO及谷氨酰胺代谢维持免疫抑制。针对这一特性, 纳米递送系统可通过代谢重编程TAMs, 重塑TAMs表型。

4.3.1 调控TAMs糖代谢的纳米递送系统 葡萄糖作为免疫细胞活动的主要能量来源, 其代谢的改变与TAMs的代谢和功能极化密切相关。研究表明, M1型TAMs依赖糖酵解和磷酸戊糖途径维持其促炎活性; M2型TAMs则通过TCA、FAO及OXPHOS维持免疫抑制与促进肿瘤转移[48]。研究表明, 靶向糖酵解限速酶可作为调控TAMs功能的新策略, Lu等[37]制备的琥珀酸负载的肿瘤细胞衍生微粒 (succinate-loaded microparticles, SMPs) 通过释放琥珀酸进入线粒体, 通过琥珀酰化抑制异柠檬酸脱氢酶2 (isocitrate dehydrogenase 2, IDH2) 活性, 抑制TCA循环, 同时促进L-2-羟基戊二酸积累, 稳定缺氧诱导因子1*α*, 增强糖酵解; 琥珀酸在核内诱导组蛋白H3K122琥珀酰化, 上调乳酸脱氢酶A (lactate dehydrogenase A, LDHA) 表达, 促进糖酵解, 诱导TAMs向M1型极化。

4.3.2 调控TAMs脂代谢的纳米递送系统 在缺氧、酸性和营养缺乏的TME中, TAMs通过增强FAO和脂质存储等代谢重编程适应高增殖活性的肿瘤细胞。这些肿瘤细胞相较于正常组织细胞, 常发生脂质代谢失调, 如脂肪酸合成和外排增加, 导致TME中脂肪酸显著富集。TAMs摄取这些脂肪酸, 将其以脂滴形式储存, 并依赖FAO主导的能量代谢模式, 以此驱动TAMs向促肿瘤M2表型极化[49,50]。靶向干预FAO可调控TAMs极化表型, Ramesh等[38]构建了代谢超分子纳米治疗剂 (metabolic supramolecular nanoparticles, MSNs), 通过TLR7/8信号通路激活与FAO抑制的双重作用, 迫使TAMs的代谢模式从氧化代谢向糖酵解转换, 下调免疫抑制分子表达并增加促炎因子分泌, 驱动TAMs转化成抗肿瘤表型, 显著抑制乳腺癌进展及转移。

4.3.3 调控TAMs氨基酸代谢的纳米递送系统 尽管氨基酸代谢并非细胞主要能量来源, 但其代谢产物通过调控炎症信号参与免疫应答。氨基酸缺乏可导致免疫细胞在迁移、分裂、成熟和效应功能方面出现缺陷, 谷氨酰胺作为机体内最丰富、用途最广泛的氨基酸, 不仅为巨噬细胞提供碳源和氮源支撑吞噬功能, 更是M2型TAMs极化的关键驱动因子[51]。因此, 靶向干预谷氨酰胺代谢可选择性调控TAMs表型。Esser等[39]开发的整合素*α*v*β*3靶向纳米颗粒 (*α*v*β*3-MI3-PD NPs) 通过精准递送MYC抑制剂, 靶向阻断C-MYC介导的糖酵解−谷氨酰胺分解代谢轴, 下调谷氨酰胺酶的表达, 选择性抑制M2型TAMs的代谢重塑而不影响M1型TAMs的抗肿瘤功能[52,53]。

5 结语与展望

靶向重编程TAMs的纳米递送系统为乳腺癌治疗开辟了新途径, 通过直接调控TAMs表型或通过间接干预免疫微环境, 可有效逆转肿瘤免疫抑制微环境并增强抗肿瘤免疫应答。与传统疗法相比, 现有纳米递送系统的优势在于独特的靶向性、载药多样性及微环境响应特性。纳米递送系统通过清除或极化M2型TAMs重塑肿瘤免疫抑制微环境, 提高肿瘤治疗的效果。但是由于肿瘤的高度异质性及致密ECM物理屏障, 常会削弱主动靶向策略的效果, 其次TAMs本身的动态异质性、表型可塑性及其复杂调控网络, 使得精准作用特定细胞亚群并维持稳定M1表型存在显著困难, 因此如何实现M2型TAMs的特异性靶向治疗一直是研究的瓶颈难题; 此外, 纳米制剂的规模化生产困难及临床前模型转化的局限性, 共同导致了临床转化的实质性障碍。基于以上瓶颈, 未来研究应更关注于开

发精准靶向且可以维持稳定表型的纳米制剂, 聚焦于促进临床转化、技术落地等方面。加强TAMs生物学认知及纳米技术创新, 有望推动更有效精准治疗乳腺癌的的策略进展。

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