线粒体靶向纳米制剂在癌症免疫治疗中的研究进展

蔡 嘉, 黄红武, 彭丙枞, 唐嘉锶, 谢培康, 陈湘钰, 贺冬秀*

(南华大学衡阳医学院药学院, 湖南 衡阳 421001)

摘要: 线粒体通过直接参与免疫细胞的活化、增殖和分化, 调控多条免疫相关信号通路, 并借助其动力学和代谢变化影响肿瘤浸润免疫细胞的功能, 从而在抗癌免疫反应中发挥重要调控作用。靶向线粒体的免疫治疗是一种新兴的癌症治疗策略。构建的线粒体靶向免疫制剂通过诱导肿瘤免疫原性细胞死亡、调节线粒体动力学和代谢、激活免疫信号通路等多种免疫策略, 显著改善抗癌功效。本文聚焦于癌症免疫治疗领域, 介绍了线粒体与肿瘤免疫的关系, 并总结了近5年来靶向线粒体纳米制剂的设计、开发及其在癌症免疫治疗中的应用进展。最后讨论线粒体靶向纳米制剂在抗癌免疫治疗方面所面临的挑战与前景, 以期为开发用于癌症免疫治疗的新型线粒体靶向制剂提供依据。

关键词: 癌症; 线粒体; 纳米制剂; 靶向治疗; 免疫治疗

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Recent advancements in mitochondria-targeted nanoformulations for cancer immunotherapy

CAI Jia, HUANG Hong-wu, PENG Bing-cong, TANG Jia-si, XIE Pei-kang, CHEN Xiang-yu, HE Dong-xiu*

(*School of Pharmacy, Hengyang Medical School, University of South China, Hengyang 421001, China*)

Abstract: Mitochondria plays an important regulatory role in the anticancer immune response by directly participating in the activation, proliferation and differentiation of immune cells, regulating multiple immune signaling pathways and affecting the activation and function of tumor-infiltrating immune cells with the help of the change of mitochondrial dynamics and metabolic. Mitochondria-targeted immunotherapy is an emerging cancer treatment strategy. The constructed mitochondrial targeted nanoformulation significantly improves the anti-cancer efficacy by inducing immunogenic cell death, regulating mitochondrial dynamics and metabolism, activating immune signaling pathways and other immune strategies. This review focuses on the field of cancer immunotherapy, introduces the relationship between mitochondria and tumor immunity, and summarizes the design of mitochondria-targeted nanomaterials in the past five years. Finally, the challenges and prospects of mitochondria-targeted nanoformulations in anti-cancer immunotherapy are discussed in this paper, which offers support for the development of novel mitochondria-targeted agents for cancer immunotherapy in the future.

Key words: cancer; mitochondria; nanoformulation; targeted therapy; immunotherapeutic

近年来, 尽管新开发的抗癌策略加速了一些癌症的治疗进展, 并推动了整体癌症死亡率的下降, 但癌症仍然是重要的死亡原因[1]。癌症免疫疗法是一种通过激活或增强人体免疫系统功能来对抗癌症的治疗方法。它能够抑制多种癌症的生长并预防复发, 已成为一种有效的癌症治疗策略[2]。免疫疗法增强了免疫反应的特异性和能力, 可以消除多种癌细胞, 从而产生持

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*通讯作者 Tel: 86-734-8282614, E-mail: 1025165380@qq.com

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久的抗肿瘤效应。因此, 它比传统治疗更有效地减少肿瘤转移和复发。目前, 最有前途的抗肿瘤免疫治疗策略主要包括肿瘤疫苗、免疫检查点阻断疗法、双特异性T细胞接合器和过继细胞疗法等[3]。

线粒体作为真核细胞的重要细胞器, 不仅负责电子传递、ATP生成、脂肪酸合成、活性氧 (reactive oxygen species, ROS) 产生、氧化磷酸化 (oxidative phosphorylation, OXPHOS) 和钙稳态等许多重要功能, 还参与肿瘤细胞的代谢重编程和免疫稳态[4]。最近的研究证明, 线粒体不仅参与调节巨噬细胞和自然杀伤 (natural killer, NK) 细胞的生长与分化[5], 还通过线粒体自噬相关蛋白BNIP3-BNIP3L调控NK细胞的记忆形成[6]。线粒体能够聚集在T淋巴细胞和抗原提呈细胞形成的免疫突触中, 且T细胞受体的激活可刺激线粒体生成ROS和ATP[7]。释放的线粒体ROS (mitochondrial reactive oxygen species, mtROS) 及其他物质能够参与调节免疫反应[8]。这些研究表明, 线粒体在癌症免疫中具有重要调控作用[9,10]。此外, 与健康的线粒体 (−160 mV) 相比, 癌细胞的超极化线粒体膜 (−220 mV) 有助于正电荷分子快速且选择性地进入线粒体[11]。因此, 线粒体成为癌细胞中脆弱的重要靶标细胞器[12], 并且是癌症免疫治疗的一个重要靶点。通过设计与开发线粒体靶向的纳米制剂, 以恢复或增强免疫系统对癌细胞的识别和消灭能力, 实现癌症免疫治疗, 已成为当前抗肿瘤策略研究的重要方向

近年来, 随着对线粒体在肿瘤生物学中关键作用的深入认识[13], 靶向线粒体的抗癌策略已成为研究热点, 相关治疗进展已有多篇系统综述报道[14-18]。现有研究不仅阐明了生理和肿瘤微环境 (tumor microenvironment, TME) 中线粒体的动态特征, 更揭示了线粒体异常如何影响免疫逃逸和免疫细胞 (特别是T细胞) 的功能, 为开发靶向线粒体的免疫治疗策略奠定了理论基础[9,19]。然而, 关于靶向线粒体纳米制剂在癌症免疫治疗中的应用, 目前仍鲜见系统性综述。本文聚焦于癌症免疫治疗领域, 重点阐述线粒体在肿瘤免疫中的调控作用机制, 系统探讨线粒体靶向纳米制剂的设计策略及其在基于线粒体调控的抗肿瘤免疫治疗中的应用 (图1)。分析了该领域面临的主要挑战与发展前景, 以期为开发新型线粒体靶向免疫治疗纳米制剂提供理论依据和创新思路。

1　线粒体靶向纳米制剂在癌症免疫治疗中的应用基础

正常细胞通过线粒体裂变与融合、生物合成、蛋白质稳态及线粒体自噬等质量控制系统, 维持其结构和功能的完整性[20]。肿瘤细胞与正常细胞的关键差异之一是代谢重编程, 其中线粒体作为核心细胞器发挥重要作用。TME由癌细胞、宿主细胞、免疫细胞及分泌因子等共同构成, 在癌症免疫应答中至关重要[9,21]。目前, 靶向线粒体的抗肿瘤免疫治疗主要集中在调控肿瘤或免疫细胞内的线粒体动力学、代谢、线粒体DNA (mitochondrial DNA, mtDNA) 释放、ROS生成及相关蛋白质表达, 以激活或增强免疫系统功能。本节将系统探讨线粒体在癌症免疫中的作用 (图2), 为线粒体靶向纳米制剂的免疫治疗提供理论基础。

1.1　线粒体动力学与代谢在癌症免疫中的作用

线粒体通过裂变、融合、运输和自噬等过程表现出高度的动态性, 这些过程统称为线粒体动力学[9,22]。线粒体动力学不仅调控肿瘤进展及免疫细胞功能[9,22-24]。如在免疫应答中, 线粒体动力学直接影响T细胞活化与分化: 裂变促进T细胞的迁移、浸润和细胞毒性, 并调节其他免疫细胞的代谢转化; 而融合则驱动记忆T细胞形成[9]。动力相关蛋白1是介导线粒体裂变和维持线粒体动态网络的关键蛋白, 其激活可增加线粒体数量并松弛内膜嵴结构, 从而调节T细胞的功能[25,26]。当活化的T细胞分化为记忆T细胞或调节性T细胞 (regulatory T-cell, Tregs) 时, 其线粒体会发生显著变

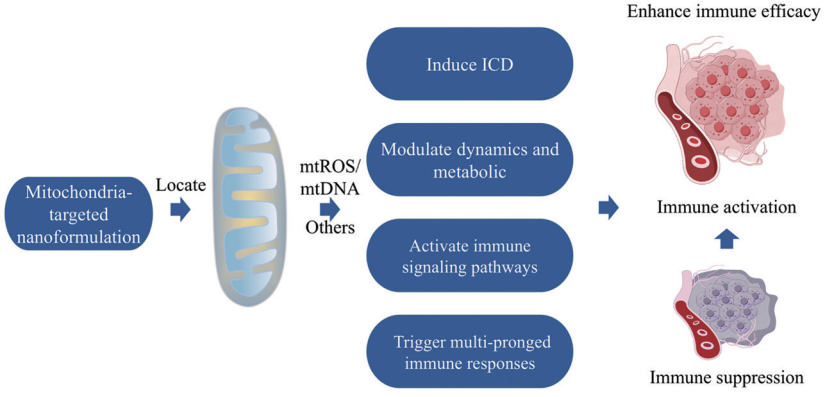


Figure 1　Schematic of mitochondria-targeted nanoformulation for cancer immunotherapy. mtROS: Mitochondrial reactive oxygen species; mtDNA: Mitochondrial DNA; ICD: Immunogenic cell death

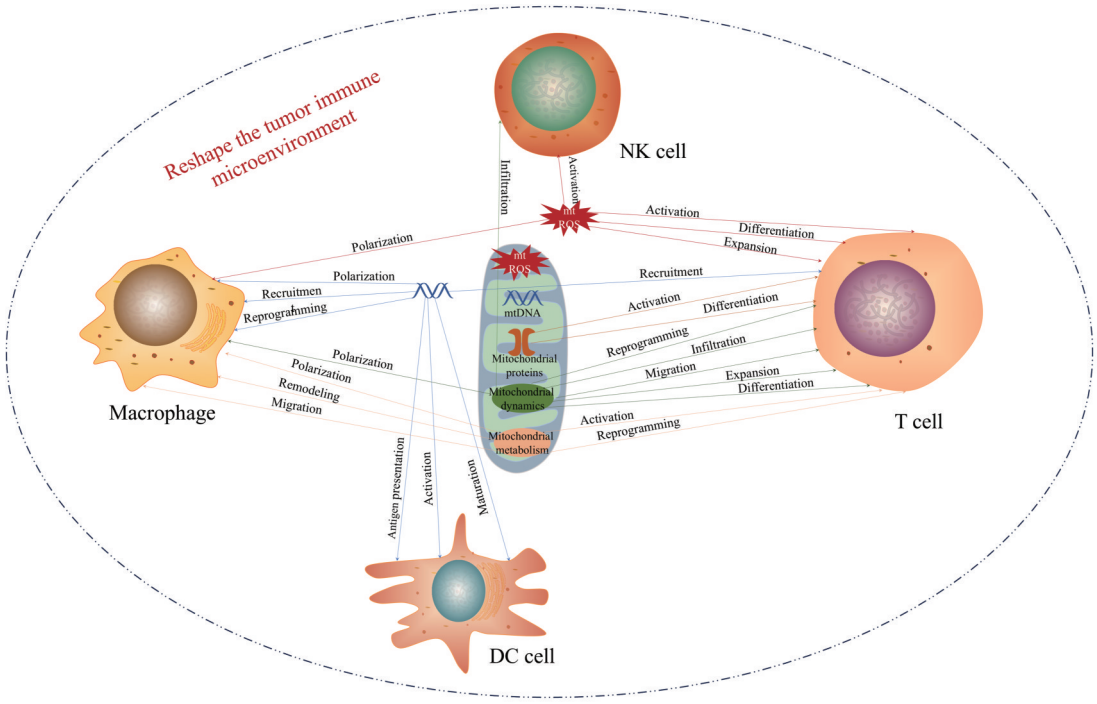


Figure 2 The role of mitochondria in cancer immunity. NK: Natural killer; DC: Dendritic

化: 从分裂状态逐渐转变为融合状态, 形成长管状结构, 同时线粒体内膜的嵴也变得更为致密。这一过程在效应T细胞的活化中起着关键作用。同时线粒体内膜的嵴也变得更加紧密。这一动态变化过程在调控效应T细胞的活化中起着关键作用[26]。

线粒体代谢 (如TCA循环、脂肪酸代谢、谷氨酰胺代谢、OXPHOS 等) 不仅参与生物分子和能量的生成[27], 还影响巨噬细胞的极化和免疫细胞的活性。当巨噬细胞向M1型促炎巨噬细胞极化时, 线粒体裂变增强, 代谢途径从OXPHOS转变为有氧糖酵解, ROS水平升高; 而当巨噬细胞向M2型抗炎巨噬细胞极化时, 线粒体呈现融合变长的状态[5]。糖酵解的上调还可以增强Tregs的活性。此外, 线粒体裂变诱导的mtDNA损伤通过趋化因子配体2的分泌促进肿瘤相关巨噬细胞 (tumor-associated macrophages, TAMs) 的招募和M2极化, 从而加速肝细胞癌的进展[28]。

此外, 线粒体动力学的失衡会损害OXPHOS的活性和效率, 并干扰T细胞的代谢重编程[29]。研究发现, 浸润肿瘤的NK细胞的线粒体体积较小且呈现碎片化, 其活性和肿瘤杀伤能力显著降低, 这使肿瘤能够逃避NK细胞的监测。抑制线粒体裂变可改善NK细胞的线粒体代谢、存活和抗肿瘤能力[30], 并增强癌细胞主要组织相容性复合体-I的表达, 从而提升免疫治疗的效果[31]。在三阴性乳腺癌 (triple-negative breast cancer, TNBC) 中, 调控线粒体动力学可提高NK细胞对TNBC的抗肿瘤功效[32]。此外, 靶向线粒体代谢的化合物 (如三苯基磷修饰的CuET) 还能诱导巨噬细胞向M1型极化, 重塑肿瘤微环境[33]。

1.2 线粒体DNA在癌症免疫中的作用

mtDNA是一个16.5 kb的环状分子, 编码OXPHOS复合物形成所需的13种蛋白质、22种tRNA和2种线粒体RNA翻译所需的核糖体RNA[34]。mtDNA作为一种有效的炎症激动剂, 在先天免疫中发挥着积极作用[34]。mtDNA可通过多种机制激活抗肿瘤免疫应答。例如, 应激释放的mtDNA被cGAS识别后, 生成第二信使2′,3′-cGAMP。随后, 2′,3′-cGAMP通过激活STING蛋白, 介导I型干扰素信号通路和相关炎症反应的活化[35], 促进细胞毒性T细胞 (CD8+ T细胞) 的活化[36]。在树突状细胞 (dendritic cells, DCs) 中, mtDNA激活STING通路增强抗原交叉激活功能[37]。最近的研究发现, 植物来源mtDNA通过囊泡内化到TAM中后, 能诱导cGAS-STING通路重编程巨噬细胞, 促使其向抗肿瘤表型M1巨噬细胞转变[38]。研究进一步证实, Mn^{2+}[39]、线粒体转录因子A的缺失[40]和抑制共济失调毛细血管扩张突变[41]等均可诱导mtDNA释放, 并激活cGAS-STING通路, 从而分别增强DCs的成熟[39]、抗原呈递[40]和免疫检查点阻断 (immune checkpoint blockade, ICB) 疗效[41]。

mtDNA不仅能够激活cGAS-STING通路, 还可通过多种途径激活免疫反应。如mtDNA被模式识别受

体NLRP3识别后, 激活caspase-1, 促进IL-1和IL-18前体的剪切和活化, 并招募巨噬细胞、中性粒细胞和T淋巴细胞参与相关免疫反应[42]。此外, 细胞外mtDNA的CpG结构域能够被模式识别受体TLR9识别, 进而激活MAPK/NF-κB通路, 促进炎症反应的发生[43]。基于这些机制, 开发能够刺激mtDNA释放的线粒体靶向纳米制剂, 有望增强抗癌免疫治疗的效果。

1.3　线粒体ROS在癌症免疫中的作用

线粒体是产生ROS的主要细胞器。尽管ROS曾被认为是有害分子, 但近年来越来越多的研究表明, ROS在生物过程的几乎所有方面都具有重要作用[44]。在免疫系统中, ROS参与宿主防御、免疫反应和免疫调节, 且其水平对肿瘤微环境中T细胞和巨噬细胞的功能具有重要影响[45]。例如, 生理水平的ROS促进T细胞活化与增殖[45], 并参与巨噬细胞极化[46,47]和免疫应答调控[48]。在肿瘤微环境中, 肿瘤细胞通过代谢重编程、癌基因的激活和线粒体功能障碍来升高ROS水平[49]。然而, 高水平的ROS会抑制T细胞功能, 干扰TME中浸润性T细胞的表面受体与MHC肽复合物的识别, 进而减弱T细胞的免疫反应[19]。此外, 过量的ROS也会损害巨噬细胞[50]。最近研究报道TLR7诱导的线粒体ROS可增强DCs分泌IL-12, 进而激活NK细胞的抗肿瘤功能[51]。基于此, 靶向调控mtROS的纳米制剂有望成为调节抗肿瘤免疫的新策略。

1.4　线粒体其他组分在癌症免疫调控中的作用

多种线粒体蛋白或蛋白复合体参与调节T细胞功能。例如, 线粒体外膜融合蛋白 (mitofusin 1, MFN1)的下调, 及miR-24的上调, 会影响T细胞衰竭的表型[52]。由核编码并定位于线粒体的ATP依赖性金属蛋白酶在去乙酰化后能够促进OXPHOS和线粒体融合, 从而促进T细胞存活和记忆形成[53]。线粒体丙酮酸载体 (mitochondrial pyruvate carrier, MPC) 由两个分子质量为15 kDa的高度保守的蛋白亚基组成, 存在于线粒体内膜, 负责将丙酮酸从线粒体外运输到线粒体内, 调控线粒体丙酮酸代谢和摄取。MPC的基因缺失可促使CD8+ T细胞向记忆表型分化[54]。然而, 线粒体转运蛋白通过Nrf2介导的转录上调PD-L1的表达, 促进肝癌免疫逃避[55]。这些发现揭示了线粒体蛋白在免疫调控中的关键作用, 为开发靶向线粒体的免疫治疗策略提供了新方向。

2　线粒体靶向纳米制剂的设计、开发及其在癌症免疫治疗的应用

2.1　线粒体靶向纳米制剂的设计策略

随着对线粒体认识的不断深入, 新型的线粒体靶向策略的发展推动了线粒体靶向纳米制剂的创新设计。为了开发能够靶向线粒体并激发机体抗肿瘤免疫的纳米制剂, 必须重点考虑以下两个关键因素: ① 纳米制剂如何有效定位至线粒体并响应环境释放药物; ② 纳米制剂增强抗肿瘤免疫应答。

2.1.1　线粒体定位与递送　线粒体靶向纳米制剂的设计关键在于实现精准定位和有效递送。为确保制剂中的治疗成分能够有效到达线粒体并发挥其作用, 设计时需综合考虑3个核心要素: 血液运输稳定性、溶酶体逃逸能力和特异性靶向识别能力。值得注意的是, 线粒体对肿瘤免疫反应的调控不仅涉及癌细胞, 还与肿瘤微环境中的各类免疫细胞密切相关。因此, 从理论角度而言, 可以设计分别靶向肿瘤细胞线粒体和免疫细胞线粒体的纳米制剂。然而, 现有文献[56]报道显示, 靶向肿瘤细胞线粒体的纳米制剂仍占据主导地位, 而针对免疫细胞线粒体的靶向制剂研究则相对匮乏。

研究发现, 癌细胞线粒体膜电位通常低于健康细胞, 这一特性为靶向设计提供了重要依据。目前主要采用带正电荷的分子或离子作为靶向配体, 通过直接载药或载体修饰的方式实现线粒体递送。尽管已有多种靶向策略被开发, 包括阳离子聚合物、核酸适配体、多肽、抗体、小分子化合物和脂质体等[57]。但针对抗肿瘤免疫反应设计的纳米制剂所使用的线粒体靶向配体相对较少, 主要包括阳离子聚合物[58]、小分子化合物[59]、多肽[60]和有机染料[61,62]等。在靶向纳米制剂的设计中, 常用的药物载体包括聚合物[58-61]和金属多酚化合物[63]等。值得注意的是, Chen等[58]创新性地使用聚 (2-(*N*-氧化物-*N*,*N*-二乙氨基)甲基丙烯酸乙酯)-b-聚 (ε-己内酯) 共聚物 (OPDEA-PCL) 同时作为靶向配体和药物载体, 成功构建了具有线粒体共定位能力的纳米颗粒, 有效诱导了肿瘤细胞的免疫原性细胞死亡 (immunogenic cell death, ICD)。

针对带正电荷的线粒体靶向载体易被清除的问题, 研究者开发了多种创新策略。例如, Peng等[59]开发了一种具有pH控制电荷反转功能的线粒体靶向胶束顺序递送系统。该系统在中性pH时带负电 (2,3-二甲基马来酸酐改性的生物素-PEG4000-NH_2外壳), 在靶向肿瘤阶段能够保留更长时间; 在肿瘤微酸性环境下转为正电, 促进细胞摄取。此外, 暴露的三苯基膦 (triphenylphosphine, TPP) 基团有助于将制剂中的药物定位线粒体。Li等[60]利用线粒体靶向杂合多肽修饰的*N*-(2-羟丙基)甲基丙烯酰胺共聚物偶联多柔比星 (doxorubicin, DOX), 显著增加DOX的线粒体积累和细胞内ROS水平。此外, Ge等[63]利用千层纸素A (oroxylin A, OA) 固有的溶酶体自我修饰特性, 合成了金属多酚复合物, 实现了溶酶体逃逸和线粒体靶向递

送药物。近年来, 针对线粒体组分的靶向制剂研究报道逐渐增多。研究表明, 易位蛋白 (translocator protein, TSPO) 主要位于线粒体外膜, 并在多种肿瘤中广泛表达[64]。基于这一发现, Xie等[65]利用结直肠癌细胞中过表达的TSPO, 成功开发了线粒体靶向制剂。这些创新设计有效解决了传统阳离子载体的局限性, 为线粒体靶向治疗提供了新思路。

2.1.2 增强抗肿瘤免疫的多维调控策略 抗肿瘤免疫是一个极其复杂的过程, 主要涉及抗原释放和呈递、效应T细胞增殖和分化、免疫细胞向肿瘤组织的浸润, 及免疫细胞对肿瘤细胞的识别和清除。目前的研究主要采用单一或多种不同药物来调控上述一个或多个阶段。例如, 某些天然活性成分[58]、光敏剂[59,65]、化疗药物 (如DOX)[60]和一氧化氮 (nitric oxide, NO)[66]常用于诱导ICD, 促进抗原暴露和呈递。免疫检查点抑制剂常被用于增强T细胞的活性[67]。然而, 由于抗肿瘤免疫可能会在某些阶段产生免疫逃逸, 单一的调控措施可能不足以有效增强肿瘤免疫疗法的效果。因此, 研究者们常常使用一种制剂来同时调控抗肿瘤免疫的多个阶段。

为了精准靶向胶质母细胞瘤并实现多步调控的协同效应, Chen等[68]开发了一种多功能纳米制剂。该制剂通过以下协同机制实现多维度免疫调控: 首先, NO诱导ICD增强肿瘤免疫抗原的产生, 进而促进抗原呈递细胞的成熟和T细胞活化; 其次, NO使肿瘤组织中的异常血管正常化, 改善T细胞运输; 最后, NO通过与ROS反应生成过氧亚硝酸盐 ($ONOO^-$), 降解肿瘤细胞外基质, 从而增强T细胞浸润。

2.2 线粒体靶向纳米制剂在癌症免疫治疗中的应用

研究表明, 线粒体靶向纳米制剂可通过多种策略增强抗肿瘤免疫反应, 包括: 触发线粒体介导的ICD、调节线粒体动力学与代谢、激活免疫相关信号通路等, 从而显著提升免疫治疗效果。

2.2.1 线粒体靶向纳米制剂诱导线粒体介导的ICD ICD是一种由应激压力驱动的生物学过程, 能将垂死癌细胞转化为特异性抗原, 促进DCs成熟和抗原呈递, 进而激活肿瘤特异性免疫反应, 有效改善免疫抑制性TME[58,60-62]。与传统ICD诱导剂相比, 线粒体应激诱导的ICD效率更高、细胞毒性更强。目前, 已开发出多种线粒体靶向ICD诱导剂, 如光敏/光热剂、化疗药物 (如蒽醌类)、天然药物及多组分纳米粒子等, 单独或联用均可显著增强癌症免疫治疗的效果。

光敏/光热剂是目前研究较多的ICD诱导剂之一[69-71]。值得注意的是, 部分光敏剂通过靶向内质网来诱导ICD[72,73]。近年来, 研究者开发了多种线粒体靶向纳米制剂, 通过负载光敏/光热剂靶向破坏线粒体, 促进肿瘤相关抗原 (tumor-associated antigens, TAAs) 暴露, 从而增强抗肿瘤免疫应答[62,65,74,75]。例如, 基于光敏剂IR700DX-6T (靶向线粒体易位蛋白) 的靶向制剂, 在结直肠[65]和胰腺癌[74]模型中均能有效诱导ICD, 激活DCs和CD8+ T细胞, 减少Treg细胞, 显著激发宿主的抗肿瘤免疫并抑制肿瘤生长。Wang等[75]开发的透明质酸修饰的线粒体纳米粒 (DIH), 其负载的花青染料dc-IR825在近红外光照射下可同时产生ROS和温和光热效应, 通过诱导线粒体应激引发强烈ICD, 从而有效抑制肿瘤生长, 甚至根除肿瘤。另有研究设计出双靶向光敏剂Cy5-I-CF3, 可同时作用于内质网和线粒体, 在4T1肿瘤模型中诱导广泛的ICD并激发显著抗肿瘤免疫应答[76]。基于其他线粒体靶向光敏剂在癌症免疫治疗中的应用见表1[75-99]。

Table 1 Some examples of photosensitization, chemotherapy medication, natural active et al that induce ICD to enhance the effect of cancer immunotherapy. ROS: Reactive oxygen species; RNS: Reactive nitrogen species; DCs: Dendritic cells; CTLs: Cytotoxic T lymphocytes; ICT: Icaritin; CAT: Catalases; CA: Cinnamaldehyde; CPT: Camptothecin; DOX: Doxorubicin; PTXL: Paclitaxel; I3A: Indole-3-carboxaldehyde; US: Ultrasound; MHT: Magnetic hyperthermia treatment; KET: Ketoconazole; TI: A triphenylphosphonium conjugate of 5-carboxy-8-hydroxyquinoline; MWTT: Microwave thermotherapy

Composition	Stimulus trigger of ICD	Targeting ligand	Research subject	Therapeutic outcome	Ref.
DIH	Dc-IR825 + light	Dc-IR825	4T1 cell, 4T1 tumor model	Inhibit tumor growth and eradicate tumors by releasing DAMPs and stimulating maturation of naive DCs and inducing robust immune responses	[75]
THTTPy-PTSA	Tetrahydropyridine group + light	Pyridine group	4T1 cell, 4T1 tumor model	Inhibit tumor growth by enhancing the infiltration of CD8+ T cells and NK cells into TME while suppressing Treg cell expression	[76]
Rh-PTZ	Rh-PTZ + light	Rhodanine	4T1 cell, 4T1 tumor model	Stimulate the immune response, promote the maturation of sufficient DCs, enhance the infiltration of CD8+ T cells, and alleviate the tumor immunosuppressive microenvironment	[77]

Continued

Composition	Stimulus trigger of ICD	Targeting ligand	Research subject	Therapeutic outcome	Ref.
Cy5-I-CF3	Cy5-I-CF3 + light	Cy5	MCF-7 cell, 4T1 tumor model,	Suppress both distant and primary cancers by enhancing the endogenous antigen presentation machinery to promote the DCs maturation, infiltration of CTLs and reduce the expression of Treg cells	[78]
FE-T	IR-FE-TPP + light	TPP	4T1 cell, 4T1 tumor model	Boost the immune response by remarkably improving the immunosuppressive environment, showing good immune therapy efficacy for antitumor therapy	[79]
CAT/CPT-TPP/PEG-Ce6	CAT, CA, Ce6 + light	TPP	4T1 cell, 4T1 tumor model	Remodel immunogenicity, foster the phagocytosis and presentation of tumor antigens by DCs, and amplify CD8+ T cells infiltration	[80]
CS@KET/P780)	P780 + light	P780	Hepa 1−6 cell, Hepa 1−6 tumor model	Activate the immune system in vivo and reshape the immunosuppressive microenvironment within tumors	[81]
BSA@T780/DOX	DOX, T80 + light	T780	4T1 cell, 4T1 tumor model	Promote DCs maturation, increase proportions of CD4+ T cells, CD8+ T cells, memory T cells and related cytokines, decrease Tregs proportion and regulate the ratio of M1/M2 macrophages to demonstrate excellent immunotherapy efficacy on ablation of primary tumor, inhibition of bilateral tumors and prevention of lung metastasis and postsurgical recurrence	[82]
mPEG-SS-PGG-SS-IR780	PTXL, IR-780 + light	IR-780	A549 cell, A549 tumor model	Inhibit tumor growth by promoting the maturation and migration of DCs, and the activation and proliferation of T cells	[83]
Mito-ZS-I	I, cyanine chromophore + light	Cyanine chromophore	4T1 cell, 4T1 tumor model	Facilitate both innate antitumor immunities and maturation of DCs, T lymphocytes and memory T cells for specific anti-immunities maturation	[84]
NRh-Ph-NO	NRh-Ph-NO + light	Rhodamine	4T1 cell, 4T1 tumor model	Induce NO/ROS to generate RNS, causing a decrease in the mitochondrial membrane potential and initiate apoptosis by caspase-3 activation	[85]
DOX-MitoNVs	DOX	Mitochondrial membrane	C6 cell, C6 tumor model	Improve activation of CD4+ and CD8+ T cells and their subsequent infiltration into the tumor and modify the local cytokine environment, promoting a shift from an immunosuppressive to an immunostimulatory state	[86]
ACUPA/TPP-I3A	I3A	TPP	Panc02 cell, Panc02 tumor model	Increase the number of tumor-infiltrating T lymphocytes, activate adaptive immunity, and achieve superior survival time reshaping of the tumor microenvironment	[87]
PLA-PEG-ACUPA/TPP	I3A, DOX	TPP	RM-1 cell, RM-1 tumor model	Reverse the immunosuppressive microenvironment, transform cold tumors into hot tumors and elicit effective innate and adaptive antitumor immune responses	[88]
TPP-DHA	TPP-DHA	TPP	4T1 cell, 4T1 tumor model	Promote DCs maturation, tumor-specific CTLs proliferation, as well as a large-scale release of proinflammatory cytokines such as IL-6, TNF-α, and IFN-γ to inhibit metastasis to the lungs and tumor growth	[89]
MON-CA-TPP@HA	CA, MONs	TPP	4T1 cell, 4T1 tumor model	Promote DCs maturation, CD 8+ T cell activation and regulate the ratio of M1/M2 macrophages to improve tumor immunosuppressive microenvironment	[90]
NP-I-CA-TPP	CA, Iodides	TPP	K7M2 cell, K7M2 tumor model	Down-regulate the ratio of Tregs in the tumor immune microenvironment, promote the polarization of TAMs to M1 phenotype, ultimately reshape the tumor immune microenvironment and sensitize the immune checkpoint blockade response	[91]
MLipRIR	US + IR780	TPP	4T1 cell, 4T1 tumor model	Activate antitumor immunity for the suppression of both primary and distant tumors with the aid of immune checkpoint blockade	[92]
MNPs-RGD-TPP	MHT	TPP	Hepa 1−6 cell, Hepa 1−6 tumor model	Activate the pro-tumor TAMs (M2) into anti-tumor M1 phenotype, release cytotoxic cytokines and promote phago- cytosis of macrophages against tumor cells	[93]

Continued

Composition	Stimulus trigger of ICD	Targeting ligand	Research subject	Therapeutic outcome	Ref.
F-pY-T	ICD: F-pY-T; ICB: Anti-PD-L1	TPP	CT26 cell, CT26 tumor model	Induce cancer cells apoptosis and DAMPs release to promote DCs maturation and CTLs activation *in vivo* and combine with anti-PD-L1 to enhance antitumor efficiency in ICB	[94]
CS@KET/P780	KET, P80 + light	P780	Hep3B cell, Hepa1-6 cell, Hep3B, Hepa1-6 tumor model	Release TAAs and DAMPs to enhance the treatment outcomes in an HCC	[95]
MCTH	GaMOF-Arg + US	TPP	PC-3 cell, RM-1 cell, PC-3 tumor model, RM-1 tumor model	Promote the maturation of sufficient DCs and the infiltration of CD8+ T cells into the tumor, and alleviate the immunosuppressive TME by upregulating the expressions of TNF-α and IFN-γ	[96]
TPP-HA-TDV	2,4-Dinitrophenol uncoupling	TPP	H22 cell, H22 tumor model	Cooperate with anti-CTLA-4 to achieve HCC immunotherapy and develop a durable antitumor memory response	[97]
GaMOF-Arg-TPP	MWTT, NO	TPP	4T1 cell, 4T1 tumor model	Inhibit tumor metastasis and recurrence by increasing tumor tissue CD4+ T cells and CD8+ T to activate the body's own systemic anti-tumor immune response	[98]
Cu/TI	Cu/TI	TPP	4T1 cell, 4T1 tumor model	Promote the infiltration and activation of CTLs and downregulated PD-L1 expression to inhibit the growth of colorectal carcinoma and triple-negative breast cancer	[99]

除了使用单一光敏剂诱导ICD外, 研究者们也探索了联合光敏剂与其他试剂协同诱导ICD的策略。例如, 通过将光敏剂Ce6与TPP-PEG-CA-TA-TK偶联的喜树碱 (camptothecin, CPT) 及过氧化氢酶 (catalases, CAT) 共组装成线粒体靶向聚合物胶束, 在激光照射下, 通过多重协同作用扩增ROS水平, 从而实现有效的ICD诱导 (图3), 显著抑制乳腺癌生长[80]。类似地, 在线粒体靶向纳米制剂 (CS@KET/P780) 中, P780 (一种线粒体靶向光敏剂) 靶向并破坏线粒体的完整性, 增强ROS的产生, 诱导细胞凋亡。凋亡的肿瘤细胞通过释放TAAs和损伤相关分子模式引发ICD及更长期的抗肿瘤反应, 对肝细胞癌表现出良好的治疗效果[81]。基于光敏剂联合其他试剂[82-85]诱导ICD开发的线粒体靶向制剂在癌症免疫治疗中的应用总结见表1。

传统化疗药物也是广泛使用的ICD诱导剂之一。尽管米托蒽醌 (mitoxantrone, MITX)[61]、顺铂 (cisplatin, CDDP)[61]和DOX[84,86]等传统化疗药物可诱导ICD, 但单一药物的效果有限。因此大多数研究采用多药联合策略以增强ICD的诱导效果。研究发现, MITX不仅可作为ICD诱导剂, 还可以作为光动力免疫治疗的光

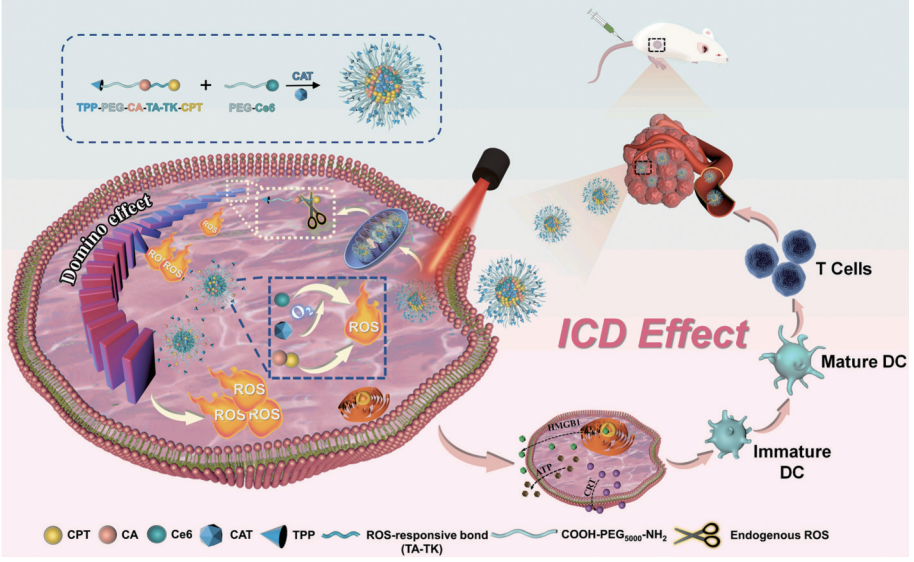


Figure 3 Schematic diagram illustrating the ROS-responsive and triple synergistic mitochondria-targeted polymeric micelles inducing ICD *via* ROS-triggered domino effect upon cellular entry. Adapted from Ref. 80 with permission. Copyright © 2024 KeAi Communications Co. Ltd.

敏剂。Zhang等[61]利用罗丹明B作为线粒体靶向配体, 联合CDDP和MITX, 制备了聚前药纳米颗粒, 协同诱导ICD, 显著提高了对免疫抑制性卵巢癌的治疗效果。此外, 英基诺-3-当归酸酯 (ingenol-3-angelate, I3A) 通过PKC信号通路促进T细胞增殖和存活, 并诱导肿瘤细胞的ICD[87]。基于此, Wang等[88]设计了一种双靶向递送系统 (PLA-PEG-ACUPA/TPP), 共同递送I3A和DOX至肿瘤细胞线粒体, 使两种药物协同诱导强烈的ICD, 从而抑制前列腺癌的生长。

近年来研究表明, 天然活性成分和小分子化合物也可作为ICD诱导剂[58,88,89]。Chen等[58]开发了一种靶向递送系统装载淫羊藿素 (icaritin, ICT), 通过线粒体自噬有效诱导ICD, 使肝癌抑制率达到60%。此外, 另有研究用TPP与二氢青蒿素 (dihydroartemisinin, DHA) 缀合制备了二氢青蒿素衍生物TD, 触发ROS生成, 比其母体化合物更有效地诱导ICD, 并且可抑制肺部转移和乳腺癌生长[89]。

关于多组分纳米粒子作为ICD诱导剂的研究展现出独特优势。例如, 纳米制剂MON-CA-TPP@HA在透明质酸 (hyaluronan, HA) 的帮助下靶向进入肿瘤细胞, 并通过TPP残基靶向线粒体, 诱导乳腺癌细胞凋亡和ICD, 有效促进DCs成熟和CD8+ T细胞活化, 同时调节M1/M2巨噬细胞的比例, 改善肿瘤免疫抑制微环境[90]。Wan等[91]设计开发的多组分聚合物纳米颗粒 (NP-I-CA-TPP) 通过GSH耗竭来放大肉桂醛 (cinnamaldehyde, CA) 诱导的癌细胞线粒体氧化应激, 诱导ICD并触发宿主的抗肿瘤免疫反应, 从而增强癌症免疫治疗效果。

此外, 新型物理刺激响应型ICD诱导策略不断涌现, 主要包括以下几类: ① 超声响应型纳米粒通过声动力效应特异性破坏线粒体功能, 当其与免疫检查点阻断联用时, 能显著抑制原发性灶和远端转移灶的生长[92]; ② 磁性纳米粒在线粒体靶向蓄积后, 通过磁热效应诱导线粒体热应激, 显著抑制肝癌生长[93]; ③酶响应型自组装纳米粒特异靶向肿瘤线粒体, 高效诱导ICD并增强抗肿瘤免疫应答[94]。

线粒体靶向ICD诱导剂较传统ICD诱导剂具有显著优势: 其能够通过光热、药物等多重策略高效诱导mtDNA泄漏、mtROS产生及激活cGAS-STING通路, 从而显著增强抗肿瘤免疫。然而, 该领域仍存在以下关键挑战: 首先,“冷肿瘤”对ICD诱导剂的响应不足, 需联合其他治疗手段; 其次, 过量ROS可能对正常细胞组织造成损伤; 最后, 光热、磁热等物理刺激需要精准控制以避免引发炎症风暴。未来发展方向包括: 开发诊疗一体化系统以实时监控ICD疗效, 优化ICD联合诱导方案, 及提高治疗的精准性。基于其他刺激诱导ICD的线粒体靶向制剂[95-99]在癌症免疫治疗中的应用见表1。

2.2.2　线粒体靶向纳米制剂通过调节线粒体动力学与代谢提高抗癌免疫　线粒体动力学和代谢调控在免疫细胞功能中具有重要作用[9]。目前, 基于此开发的抗肿瘤免疫治疗的线粒体靶向制剂相对较少[100-103]。Hou等[100]设计的线粒体靶向的吉西他滨 (gemcitabine, Gem) 偶联物pG2-Gem, 通过调节线粒体融合和代谢增强MHC-1抗原呈递, 与PD-1抗体联用实现了87.5%的肿瘤清除率。Ye等[101]开发的巨噬细胞膜包被黑鳞纳米制剂M@BPTLD (负载洛尼达明) 展现出显著的免疫调节作用。该制剂通过双重机制发挥作用: 一方面阻断线粒体自噬过程; 另一方面增强细胞焦亡效应, 从而促进免疫激活因子的释放并促进DCs成熟。此外, 线粒体靶向制剂阿托伐醌 (Mito-ATO) 通过特异性抑制线粒体电子传递链 (复合体I和V) 有效调控肿瘤免疫微环境代谢[102,103]。其作用机制表现为: ① 抑制Tregs的糖酵解和OXPHOS过程, 诱导其凋亡; ② 显著上调效应T细胞和M1型巨噬细胞的OXPHOS活性, 诱导CD8+ T细胞分化。这种代谢重编程策略有效重塑了抗肿瘤免疫应答。这些创新制剂通过靶向调控线粒体功能增强抗肿瘤免疫反应, 为基于线粒体代谢干预的免疫治疗提供了新思路。

2.2.3　线粒体靶向纳米制剂通过激活免疫相关信号通路增强抗癌免疫　线粒体应激介导的mtDNA释放可激活胞质DNA感受通路, 进而触发抗肿瘤免疫应答。基于此, 研究者开发了多种线粒体靶向的纳米免疫治疗制剂。

在众多免疫调控通路中, cGAS-STING途径是目前研究较为广泛且具有有效免疫刺激作用的信号通路。研究者通过利用光动力效应[104,105]、超声刺激[106]、纳米酶[107]、三苯胺类似物[108]等作为cGAS-STING信号通路的激动剂, 设计并开发了多种能激活抗肿瘤免疫的线粒体靶向纳米制剂。如Zhao等[105]开发的纳米颗粒ALA&Dz@ZIF-PEG通过Zn^{2+}释放和光动力效应双重激活mtDNA/cGAS-STING通路, 导致IFN的产生 (图4), 显著促进肿瘤消退。Lei等[106]构建的钴有机框架纳米片实现了超声可控的STING信号放大, 成功激活抗骨转移瘤的T细胞免疫。此外, 新型纳米酶MDP凭借其过氧化物酶/过氧化氢酶双活性, 通过激活cGAS-STING途径激发免疫反应, 显著提高了放射–免疫联合疗法的治疗效果[107]。Wang等[108]针对线粒体组分mtDNAG4结构开发的三苯胺类似物, 通过稳定mtDNA G4结构诱导mtDNA损伤, 进而激活cGAS-

STING途径, 重塑巨噬细胞并激活T细胞, 从而抑制4T1细胞小鼠的肿瘤生长和转移。这些研究为基于cGAS-STING通路的线粒体靶向免疫治疗提供了多样化的策略, 展现了广阔的临床应用前景。

除了cGAS-STING信号通路外, 近年来也有通过激活其他信号通路来增强抗癌免疫的报道。Feng等[109]开发的手性超分子纳米纤维CNF通过特异性靶向癌细胞线粒体, 促进线粒体ROS的产生, 激活Caspase1/gasdermin D通路, 诱导焦亡, 促进M1型巨噬细胞的极化, 并增强CD8+ T细胞的免疫应答, 显著抑制原发性和转移性肿瘤生长 (效果提升1.8倍)。

2.2.4 线粒体靶向纳米制剂触发多重抗癌免疫反应 成功启动抗肿瘤免疫需满足3个必要条件: 肿瘤特异性抗原的存在、多种免疫细胞的参与及免疫抑制微环境的逆转。针对这些需求, 研究者开发了多功能线粒体靶向免疫制剂, 可同步增强肿瘤抗原产生, 促进抗原呈递细胞成熟, 激活T细胞并改善肿瘤T细胞浸润。

ICB剂通过解除T细胞抑制信号, 已在临床取得显著功效。近年来, 研究者将其与ICD诱导剂[93,94,110,111]、焦亡诱导剂[112]及cGAS-STING激动剂[63,113,114]联用, 开发出能协同调控多阶段抗肿瘤免疫的线粒体靶向纳米制剂。例如, Bai等[110]开发的Ag@CuS-TPP@HA核壳纳米粒子, 经TPP和HA修饰后具备线粒体靶向性和1 064 nm激光响应特性。该制剂通过银介导的类芬顿反应产生ROS, 与光热效应协同诱导强效ICD, 同时增强免疫检查点阻断效果, 能够消除原发肿瘤并有效抑制远处肿瘤的生长。

研究表明, 部分ICD诱导剂治疗后会导致PD-L1表达上调[97,98,113,114]。基于此, Li等[111]开发了一种由ICD诱导共聚物 (PD-R8MTS) 和PD-L1阻断共聚物 (PMSP-SP-SP-L1) 组装的多功能线粒体靶向制剂SNV。该制剂同时具有ICD诱导和PD-L1阻断功能, 可增强CD8+ T细胞的细胞毒性, 并具备长期循环特性。SNV在免疫原性B16F10黑色素瘤和非免疫原性4T1乳腺癌小鼠模型中显示出强大的抗肿瘤效果。此外, Jin等[112]合成了一种线粒体靶向聚合物胶束 (OPDEA-PDCA), 通过抑制线粒体PDHK1、诱导mtROS生成和细胞色素C激活来引发骨肉瘤细胞焦亡, 从而导致包括HMGB1、ATP和CRT在内的免疫原性物质的大量释放。此外, OPDEA-PDCA通过改变PD-L1的表达模式, 当联合抗PD-L1单抗时, 可有效逆转T细胞耗竭 (图5), 显著抑制骨肉瘤进展并延长T细胞的活化时间。

最新研究开发了一种整合PD-1抑制剂与DNA表观遗传激活剂 (EnPGC-1) 的线粒体靶向系统。EnPGC-1通过增强线粒体代谢活性, 显著促进CD8+ T细胞活化与增殖。EnPGC-1与PD-1阻断的协同作用显著增强了抗肿瘤免疫力, 并提高了宿主的存活率[113]。Ding等[114]设计的脂质体BQR@MLipo能够选择性地积聚

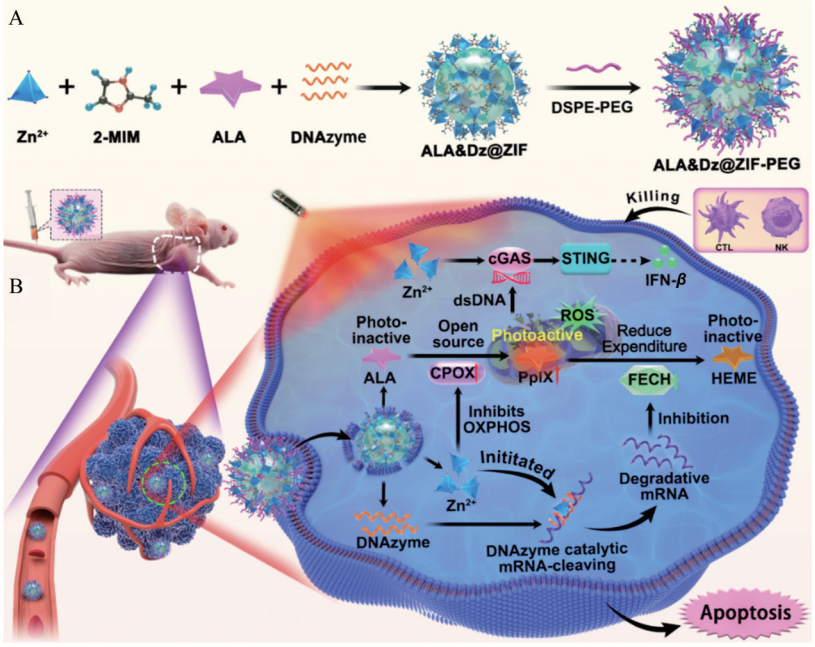


Figure 4 Schematic illustration of a photosensitizer metabolism-regulating strategy using ALA/DNAzyme-co-loaded nanoparticles (ALA&Dz@ZIF-PEG) for mitochondria-targeting photodynamic immunotherapy. A: The preparation of ALA&Dz@ZIF-PEG nanoparticles; B: The mechanism in promoting mitochondria-targeted photodynamic immunotherapy. Adapted from Ref. 105 with permission. Copyright © 2023 American Chemical Society

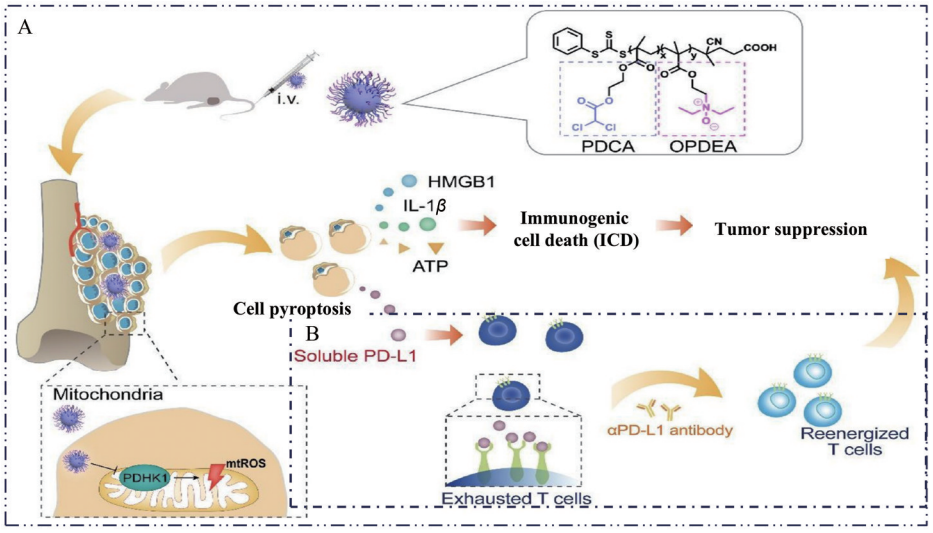


Figure 5　Schematic diagram illustrating the antitumor mechanism of mitochondria-targeted polymer micelle (OPDEA-PDCA). A: The induction of pyroptosis in osteosarcoma cells by mitochondria-targeted micelles OPDEA-PDCA; B: The synergistic antitumor mechanism enhanced by combination therapy with anti-PD-L1 monoclonal antibody. Adapted from Ref. 112 with permission. Copyright © 2022 American Chemical Society

在线粒体, 通过抑制二氢乳酸脱氢酶诱发脂质过氧化和 ROS 的产生, 触发铁死亡释放 DAMPs, 同时, mtDNA 泄露激活 cGAS-STING 通路, 促进 IFN-β 分泌及抗原的交叉呈递。联合 PD-1 抑制剂后, 显著增强了膀胱癌模型中 CD8+ T 细胞的浸润及肿瘤控制。

诱导 ICD 和激活 cGAS-STING 途径是目前两种主流的增强抗癌免疫策略。基于此, 研究者们开发了多款线粒体靶向纳米免疫制剂[81,115,116]。例如, Li 等[115]合成的靶向肝脏和线粒体的金 (I) 复合物 (9b) 能产生大量 ROS 并诱导 ICD, 而泄露的 DNA 激活 cGAS-STING 途径, 在肝癌患者来源的异种移植模型中实现了强效抑瘤。此外, 另有研究报道合成了可以共同递送 2′,3′-cGAMP 和 TPP 修饰的 Ce6 聚合物纳米颗粒 HTCS, 其中 TPP-Ce6 介导的线粒体 ROS 有效杀死肿瘤细胞。肿瘤细胞碎片进一步引发 ICD, 其中所含的 2′,3′-cGAMP 激活 STING 通路, 促进细胞因子风暴和 DCs 成熟, 有效抑制黑色素瘤[116]。

研究表明, 线粒体动力学调控联合其他治疗策略具有显著的协同效应。例如, Zhao 等[117]开发了一种新型孪生样电荷切换纳米颗粒 (shMFN1-NPs + DOX-NPs, 简称 MIX-NPs)。其中, shMFN1-NPs 通过抑制线粒体融合将 M2 TAMs 极化为 M1 TAMs, 而 DOX-NPs 则通过诱导 ICD 促进 DCs 的成熟及 CD8+T 细胞的浸润和激活。此外, MIX-NPs 还抑制髓源性抑制细胞和 Tregs, 从而重塑免疫抑制微环境。在乳腺癌模型中, MIX-NPs 实现了 83% 的肿瘤抑制率。另一项研究表明, OXPHOS 抑制剂 LND 不仅能诱导线粒体功能障碍, 还能通过协同抑制 PD-L1、胶原蛋白和转化生长因子-β (transforming growth factor-β, TGF-β) 等多条途径激活免疫系统。基于此, 研究人员开发了线粒体靶向纳米脂质体 IR-LND@Lip, 该制剂通过三通路抑制 (PD-L1/胶原/TGF), 与放疗协同实现冷肿瘤转化, 几乎完全抑制了膀胱肿瘤和乳腺肿瘤的生长[118]。

这类线粒体靶向纳米制剂通过整合物理治疗、免疫治疗和靶向治疗形成协同效应, 能够同时触发抗原释放、抗原呈递细胞成熟、T 细胞活化及免疫微环境重塑等关键环节, 从而实现高效抗肿瘤免疫应答。然而, 该技术仍面临临床转化的瓶颈: 首先, 复杂制剂的生产工艺存在挑战; 其次, 联合策略可能导致疗效冲突或过度免疫。未来需要重点突破智能化制剂开发、优化联合策略及临床转化体系建设, 以推动其临床应用。其他触发多重抗癌免疫反应的线粒体靶向制剂的应用实例如表 2 所示[110-114]。

3　展望与挑战

线粒体作为细胞能量代谢和免疫调控的中枢, 通过调节肿瘤微环境中免疫细胞的激活、增殖和分化, 深刻影响抗肿瘤免疫反应。这一特性使其成为克服当前免疫治疗局限性的理想靶点。近年来, 靶向线粒体的免疫治疗策略已成为肿瘤治疗的新方向, 并在基础与临床研究中展现出巨大潜力。目前开发的线粒体靶向纳米免疫制剂具有以下突出优势: 首先, 已成功开发多种线粒体靶向材料[119]和载体[120], 为设计个性化线粒体靶向免疫制剂提供了灵活选择; 其次, 通过诱导 mtDNA 泄漏、mtROS 生成及激活 cGAS-STING 通路等

Table 2 Some examples of mitochondrial targeting agents through multiple immune strategies to enhance the effect of cancer immunotherapy. ICB: Immune checkpoint blockade; TAAs: Tumor-associated antigens; DAMPs: Damage-associated molecular patterns

Composition	Stimulus trigger of immune	Targeting ligand	Research subject	Therapeutic outcome	Ref.
Ag@CuS-TPP@HA	ICB: αPD-L1; ICD: light + Ag	TPP	4T1 cell, 4T1 tumor model	Eradicate primary tumor and inhibit distal tumor growth by blocking immune checkpoints to trigger ICD, releasing TAAs, DAMPs, and promoting the maturation of DCs and the infiltration of CTLs into the tumor	[110]
SNV	ICD: P-D-R8MTS; ICB: PMSP-DMA	P-D-R8MTS	B16F10 cell, 4T1 cell, B16F10 tumor model, 4T1 tumor model	Amplify ICD, block PD-1/PD-L1 interaction and unleash the killing effect of CD8+ T cells to enhance antitumor immunity	[111]
OPDEA-PDCA	Pyroptosis: OPDEA-PDC; ICB: OPDEA-PDCA, anti-PD-L1	OPDEA	K7M2 cell, K7M2 tumor model	Suppress proliferation of osteosarcoma with prolonged T cell activation by resulting in immunogenic pyroptosis and combining with anti-PD-L1 monoclonal antibody	[112]
EnPGC-1	ICB: Anti-PD-L1; epigenetic strategy: EnPGC-1	EnPGC-1	MC38 cell, MC38 tumor model	Enhance antitumor immunity and improved host survival by enhancing oxidative phosphorylation, a feature of long-lived memory T cells and synergizing with PD-1 blockade	[113]
BQR@MLipo	ICD: Ferroptosis; ICB: αPD-1	TPP	MB49 cell, MB49 tumor model	Enhance innate and adaptive immune responses by inducing mitochondria-related ferroptosis to enhance DCs maturation and CD8+ T cells infiltration and activating cGAS-STING signaling pathway as well as trigger secretion of IFN-β	[114]

策略, 显著增强抗肿瘤免疫应答; 再者, 结合光热/磁热等物理治疗、免疫治疗与靶向治疗, 系统调控“抗原释放-APC成熟-T细胞活化−微环境重塑”的免疫循环, 提升疗效并降低传统治疗风险。这些进展凸显了线粒体靶向制剂在代谢调控和免疫激活方面的双重能力, 为癌症治疗提供了新思路。

尽管线粒体靶向纳米免疫制剂具有广阔的应用前景, 但其在基础研究和临床转化方面仍面临诸多挑战。首先, 生物安全性问题亟待解决: 现有带正电荷的靶向配体 (如聚合物或小分子) 可能存在潜在毒性, 因此需要开发更安全的替代策略, 如多肽或仿生人工线粒体; 其次, 联合治疗的复杂性也是一个重要问题: 单一免疫策略对“冷肿瘤”的效果有限, 而多策略联用可能导致制剂的可重复生产与质量控制困难, 甚至引发过度免疫反应等不良事件[121]; 最后, 机制研究不足: 线粒体应激与免疫应答的分子互作网络尚未完全阐明, 且临床前模型的预测性和标准化评价体系仍需进一步完善。

为突破当前研究瓶颈, 未来应着重关注以下3个研究方向: ① 精准靶向技术: 开发亚细胞器水平的递送系统, 以提升靶向精准度和生物相容性; ② 代谢异质性解析: 整合单细胞测序技术, 优化现有免疫治疗方案; ③ 信号转导机制研究: 深入探索线粒体与细胞核之间的信号串扰, 发掘新的免疫治疗靶点。随着材料科学、免疫学和人工智能等领域的交叉融合, 线粒体靶向免疫制剂有望突破实体瘤治疗响应率低的限制, 建立全新的治疗范式, 并加速从实验室向临床的转化。

作者贡献: 蔡嘉负责撰写论文; 黄红武、彭丙枞、唐嘉锶、谢培康、陈湘钰负责论文修改; 贺冬秀负责指导论文撰写并定稿。

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