生物医用纳米材料在增强肿瘤细胞免疫原性死亡中的应用

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摘要 激活机体的适应性免疫反应是提升长期抗肿瘤疗效的关键因素. 化学治疗、放射治疗、光动力治疗(photo-dynamic therapy, PDT)等方法可诱导肿瘤细胞发生凋亡并伴随着免疫原性死亡(immunogenic cell death, ICD). ICD引起的损伤相关分子模式(damage associated molecular patterns, DAMPs)分子的暴露或释放可刺激免疫系统发挥抗肿瘤免疫作用, 招募抗原递呈细胞(antigen-presenting cell, APC), 激活T细胞适应性免疫应答. 因此, 在肿瘤免疫治疗中ICD诱导剂可以改善其治疗效果, 从而提高患者生存率. 越来越多的研究表明, 基于纳米材料的癌症治疗平台不仅可以实现特定肿瘤微环境(tumor microenvironment, TME)刺激响应的药物控制释放, 并且其可以调节TME进而诱导肿瘤细胞发生ICD, 这撞击出了癌症纳米医学的新火花. 自此以后, 设计和构建增强肿瘤ICD效应的生物医用材料的相关研究受到了极大关注. 基于此背景, 本文首先介绍了肿瘤ICD的成因以及纳米材料在诱导肿瘤ICD中发挥的多重功能. 其次, 阐述了纳米材料在调控TME, 改善肿瘤治疗效果方面所具有的巨大潜力. 最后, 对纳米材料在诱导肿瘤ICD研究中所面临的挑战也进行了展望性的深入探讨.

关键词 纳米材料, 免疫原性死亡, 药物递送, 免疫治疗, 联合治疗

恶性肿瘤已经成为困扰世界公共卫生的主要难题. 尽管目前临床上普遍使用的手术治疗、化疗、放疗等治疗手段通过直接去除或者杀死癌细胞实现了差强人意的治疗效果^[1], 但是其存在的固有的靶向性差、易引发肿瘤耐药性以及损伤机体免疫系统局限性严重影响了病患的生活质量, 并且制约了其进一步的临床应用^[2]. 因此, 迫切需要发展更高效的策略来克服这些棘手的问题, 以安全有效的方式更好地治疗癌症. 免疫治疗作为一种独特的癌症治疗方式, 其旨在诱导固有和适应性免疫系统识别和消灭恶性肿瘤细胞, 以防止肿瘤的转移和复发, 已成为目前癌症治疗方式中最具

有吸引力的治疗选择之一^[3]. 自20世纪90年代首个免疫试剂获批用于临床后, 目前已有多种肿瘤免疫疗法(包括癌症疫苗、免疫检查点封锁疗法、过继细胞疗法)相继获批^[4].

尽管肿瘤免疫治疗在根除已形成的肿瘤、防止肿瘤复发和转移方面具有令人信服的潜力, 但其在实际的临床应用过程中仍面临着诸多的挑战. 例如, 由于肿瘤细胞的免疫逃逸机制, 免疫系统难以对肿瘤细胞实现有效的免疫监视和清除; 肿瘤细胞表面抗原暴露少, 对免疫疗法响应率低等^[5]. 基于此, 增强肿瘤细胞免疫原性, 激活适应性免疫成为当前肿瘤免疫治疗研究的

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热点.

长期以来,人们普遍认为,细胞凋亡是一种免疫沉默(甚至免疫耐受)的细胞死亡方式.然而在实际的临床放疗中,研究人员发现,不仅放疗照射部位的肿瘤有明显消除,而且未辐照部位的转移病灶也受到一定程度的抑制^[6],并将此现象称为“远位效应”.通过进一步研究发现,这种“远位效应”现象与肿瘤细胞的“免疫原性细胞死亡(immunogenic cell death, ICD)”过程直接相关.当肿瘤细胞发生ICD,濒死的细胞会暴露抗原表位并释放损伤相关分子模式(damage associated molecular patterns, DAMPs)分子,产生免疫刺激内源性危险信号,招募抗原递呈细胞(antigen-presenting cell, APC)提呈抗原,激活适应性免疫反应并产生持久的抗肿瘤效应^[7].

纳米技术的快速发展为肿瘤治疗提供了新策略.以生物医用纳米材料为载体的药物递送系统可提高药物吸收利用率^[8],延长药物半衰期,实现高效靶向递送^[9].此外,协同化疗^[10]、放疗^[11]、光动力治疗(photo-dynamic therapy, PDT)^[12]及各种联合治疗^[13]方式,纳米材料可发挥肿瘤微环境(tumor microenvironment, TME)刺激响应、药物缓释等作用.更重要地,纳米材料在肿瘤ICD治疗中作为有效的ICD诱导剂载体,对于激活机体抗肿瘤免疫、产生长效抗肿瘤效果具有重要意义.基于此,本文从肿瘤ICD的特征出发,就生物医用材料在多种肿瘤治疗模式中诱导ICD发挥机体抗肿瘤作用的研究进展进行总结,以期对纳米材料在ICD治疗的临床应用提供重要的理论指导和实践参考.

1 ICD概述

肿瘤细胞免疫原性差导致肿瘤免疫治疗响应率低^[14].将胶质母细胞瘤、卵巢癌和前列腺癌等具有肿瘤深部细胞毒性T细胞(cytotoxic T lymphocytes, CTLs)浸润不足特点的“冷肿瘤”转变为“热肿瘤”是提升免疫治疗响应率的重要手段^[15-17].此外,诱导肿瘤细胞ICD被证明能够克服肿瘤免疫原性差和抗原敏感性低的问题,也是一种有效提升免疫治疗响应率的策略.

当肿瘤细胞发生ICD时,其释放的“危险信号”DAMPs分子可刺激免疫系统,有效激活T细胞,参与人体免疫调节^[18,19](图1).DAMP分子主要包括钙网蛋白(calreticulin, CRT)、三磷酸腺苷(adenosine triphosphate, ATP)和高迁移率族蛋白B1(high mobility group protein B1, HMGB1)^[20].ICD前期,内质网(endoplasmic

reticulum, ER)分子伴侣CRT外翻释放“eat me”信号,募集APC, CRT与树突状细胞(dendritic cell, DC)表面分子结合,刺激DC吞噬抗原,并可促进巨噬细胞活化,从而吞噬肿瘤细胞.在ICD前期、早期、中期,濒死的肿瘤细胞释放ATP作为“find me”信号,与APC上表面嘌呤受体P2X7和P2Y2结合,刺激NLRP3复合物产生及APC成熟,从而促进CTLs增殖. ICD后期,肿瘤细胞分泌的高度保守、高度表达、炎症反应相关的HMGB1蛋白分子可与APC上TLR2/4等受体结合,诱导DC成熟,激活炎症反应^[18,19]. CRT转位、HMGB1释放和ATP分泌是ICD发生的3个必要条件.此外, ER应激引起的胞内相关信号通路的激活也可作为ICD的分子标记^[21,22].

2 纳米材料用作ICD诱导剂载体

ICD具有应激源依赖性,其诱导需基于活性氧(reactive oxygen species, ROS)的ER应激.根据诱导细胞死亡方式的不同,ICD诱导可分为I型、II型^[14,16-20].其中, I型ICD诱导剂主要作用于细胞核,诱导肿瘤细胞非ER靶向的凋亡,引起温和的ER应激及相关免疫原性分子释放; II型ICD诱导剂选择性靶向ER,通过ROS依赖的ER应激释放危险信号和凋亡信号.阿霉素(doxorubicin, DOX)、米托蒽醌(mitoxantrone, MIT)、奥沙利铂(oxaliplatin, OXA)、紫杉醇(paclitaxel, PTX)、环磷酰胺(cytosine, CTX)等大多数临床抗肿瘤药物及放射治疗均属于I型ICD诱导剂;而光动力、光热疗法和RNA溶瘤病毒(coxsackievirus B3, CVB3)疗法等属于II型ICD诱导剂.

然而,小分子药物和其他效应分子作为ICD诱导剂存在生物利用度不高、药物溶解性差、无法精准释放等问题. ICD诱导剂需靶向肿瘤部位,而纳米载体可利用其增强的渗透和滞留效应(enhanced permeability and retention effect, EPR)实现肿瘤组织靶向,增强肿瘤组织选择性富集,将最佳剂量的ICD诱导剂有效递送至特定组织,在降低其毒副作用的同时增强其效能^[23].各类纳米材料(如脂质体、胶束、纳米粒、纳米凝胶、金属纳米氧化物等)作为ICD诱导剂和其他药剂的载体可通过多种治疗方式激活免疫反应,具体内容见表S1. Zhao等人^[24]报道称包裹在聚乙二醇(poly(ethylene glycol), PEG)-聚乳酸-羟基乙酸(poly(lactic-co-glycolic acid), PLGA)共聚物纳米粒中的ICD诱导剂OXA比游离的OXA引起更强的ICD效应和DAMPs分子释放,并诱导

图1 (网络版彩色) ICD周期图及其类型^[14]. (a) 诱导肿瘤ICD过程; (b) ICD的种类. Copyright © 2019, Frontiers Media SA
 Figure 1 (Color online) Immunogenic cell death cycle and kinds of ICD^[14]. (a) The process of inducing ICD of tumor cells; (b) kinds of ICD. Copyright © 2019, Frontiers Media SA

更多的DC细胞和T细胞激活. Liu等人^[25]设计制备的一种血清白蛋白(serum albumin, SA)包裹的勃姆石(boehmite, B)高分子纳米材料, 可共负载蜂毒肽(melittin, MLT)和光敏剂二氢卟吩(Chlorin e6, Ce6). 相较单一的载体Ce6@SAB, 大分子细胞溶解肽MLT的共负载可明显增强肿瘤细胞对Ce6的摄入, 有效激活DC细胞, 促进机体免疫应答; 相较单独的MLT, 该材料可显著降低溶血现象, 并实现MLT协同增强的PDT抗肿瘤效果.

3 纳米材料用作ICD诱导剂联合载体

纳米材料作为递送载体, 不仅能提高药物递送效率, 利用其可修饰的表面还可设计具有TME刺激响应性的功能化载体材料, 实现分级和可控的ICD诱导剂释放. 同时, 纳米材料可装载多组分进行共递送, 保护有效载荷免于降解和过早释放, 实现各种疗法与ICD诱导剂的联合治疗, 增强抗肿瘤效果. 此外, 某些特殊结构

的材料自身也可引起ICD, 增强肿瘤免疫原性. 因此, 基于纳米材料的化疗、放疗、PDT及各种联合治疗可以发挥TME刺激响应、药物缓释等诸多作用, 增强肿瘤免疫治疗.

3.1 化学治疗

DOX、PTX、MIT、OXA等药物可诱导细胞发生ICD, 但小分子药物在治疗过程中存在半衰期短、肿瘤部位递送效率低、毒性大, 且易引起多器官的不良免疫反应等问题. 基于纳米材料易于表面修饰的特征, 其被广泛用于制备工程化的纳米药物递送平台以应对不同的TME(如酶、低氧、弱酸性、高还原性等), 显示出可控的药物释放能力, 大大提高治疗效果^[26].

TME独特的物理化学特性激发了研究者设计和构建不同纳米材料的热情. 例如, 基于肿瘤内磷脂酶(human secretory phospholipase A2)、磷酸酶(acid phosphatase, alkaline phosphatase)、蛋白酶(prostate specific antigen, cathepsin B, matrix metalloproteinase)、 β -葡萄糖苷酸酶(β -glucuronidase)等的酶异常环境可将适当酶底物与高分子偶联; 基于低氧环境可将乏氧响应性偶氮苯基团连接至材料; 基于弱酸性环境可将席夫碱、羧酸酯、缩醛或缩酮、磷脂酰胺等引入设计体系; 基于谷胱甘肽(glutathione, GSH)环境可引入二硫键、二硒键、硫醚键等响应性化学键或化合物^[23].

Zheng等人^[27]将DOX载入介孔二氧化硅纳米粒中, 设计了具有pH和GSH双重响应的递送系统, 可诱导DC成熟和抗肿瘤细胞因子释放, 最终系统治疗高度转移性三阴性乳腺癌. Wang等人^[28]设计了可响应性拆卸的纳米平台, 将亲水性透明质酸(hyaluronic acid, HA)接枝的DOX前药(HA@DOX)与疏水性3-二乙基氨基丙基(3-diethylaminopropyl isothiocyanate, DEAP)偶联成两亲性嵌段聚合物, 随后自组装构建负载药物塞来昔布(celecoxib)的纳米粒. 利用基质金属蛋白酶-2(matrix metalloproteinase-2, MMP-2)和聚合物纳米粒的pH敏感性, 该纳米粒子可靶向肿瘤部位并释放DOX, 触发ICD. Fan等人^[29]采用温和的生物标记方法将功能化DNA量子点(quantum dots, QDs)锚定在外泌体表面, 该外泌体可被肿瘤细胞迅速吞噬, 从而作为肿瘤的特异性标记物. 同时, 构筑M1巨噬细胞囊泡可有效杀死肿瘤细胞, 结合靶向给药系统实现可视化肿瘤治疗和特异性药物递送. 除引入刺激响应化学键或化合物外, Zhang等人^[30]报道了一种可自身诱导ICD的半导体聚合物

(semiconducting polymer nanoparticles, SPN)纳米蛋白降解靶向嵌合体(proteolysis targeting chimera, PROTAC). 该SPN由一个半导体聚合物与PROTAC片段通过肿瘤生物标志物可裂解肽结合而成, 在近红外下可产生单线态氧, 诱导ICD, 增强肿瘤免疫原性, 杀死肿瘤细胞. 此外, 纳米材料可以克服机体某些部位的“屏障”作用, 有利于药物靶向发挥作用. “冷肿瘤”胶质母细胞瘤可形成血脑屏障, 阻挡免疫系统内多数T细胞进入肿瘤内部并隔绝药物作用^[31]. Zhang等人^[32]设计了载有DOX的PEG-PLA纳米颗粒, 可有效透过血脑屏障靶向胶质母细胞瘤, 并触发肿瘤细胞ICD, 最终显著提高小鼠存活率并延长中位生存期.

综上, 纳米材料广泛应用于化学免疫治疗, 其可变尺寸、可修饰表面、可调控的刺激响应性及相关协同作用等有助于诱发肿瘤细胞ICD, 提高肿瘤免疫原性, 促进抗肿瘤效果, 具有很高的临床应用潜力.

3.2 放射治疗

放射治疗通过将X射线、 γ 射线或电子束等电离辐射束局部施加在肿瘤部位以诱导DNA损伤和细胞凋亡, 并诱导肿瘤细胞原位ICD. 研究表明, 放疗可以激活宿主的免疫系统进而攻击非照射部位的肿瘤细胞, 这种免疫驱动作用不仅可以消除局部照射部位的肿瘤, 也可消除远处转移灶^[6]. 但是, 照射区域内的放疗效果不是肿瘤特异性的, 其治疗率取决于电离辐射对肿瘤部位的靶向性和富集能力. 此外, 由于高氧浓度可以稳定放疗诱导产生的DNA损伤进而阻止肿瘤细胞DNA自我修复, 肿瘤细胞自身的乏氧环境会导致治疗抗性和放疗失败. 因此, 提升肿瘤组织对放射线的敏感性及肿瘤组织靶向性是改善肿瘤放疗效果的核心.

纳米材料功能可集成化及EPR效应可有效促进放射线在肿瘤内的富集^[33]. Deng等人^[34]基于核碱基配对原理, 将聚胸腺嘧啶和光异构化的聚偶氮苯(polythymine and photoisomerized polyazobenzene, PETAzo)与腺嘌呤修饰的硫化锌ZnS(adenine-modified ZnS, ZnS-A)组合构建了一种仿生纳米胶囊. 该材料可将放疗X射线转换成紫外线辐射, 诱导偶氮苯基团异构化, 从而降低偶氮苯的 π - π 堆积作用和疏水性, 诱导纳米胶囊溶胀, 增强对双层磷脂膜的渗透性, 实现药物在细胞膜上可控释放. 此外, PETAzo和ZnS-A之间的核碱基配对相互作用使其在体内循环周期延长, 阻止药物泄漏, 从而保持药物在肿瘤处的长效稳定性. Chen等人^[11]利用水/

油/水双乳化法制备了多功能核壳结构的PLGA纳米粒子,在其亲水性内核中装载可引发过氧化氢(H_2O_2)快速分解的水溶性酶(catalase, Cat),在疏水外壳中装载免疫佐剂(imiquimod, R837)(图2)。PLGA-R837@Cat纳米粒子内核中的Cat可调节肿瘤缺氧和免疫抑制性微环境,并触发肿瘤细胞ICD,借助外核中的免疫佐剂协同强化

机体适应性免疫应答,并实现增强的局部肿瘤放射疗效。

放疗与免疫佐剂的联合使用能够有效增强抗肿瘤免疫反应,达到协同治疗效果^[35]。但由于单次、大量注入免疫佐剂或引起机体严重副作用,目前多在肿瘤部位实施局部、重复、少量注射免疫佐剂的方法以减少

图2 (网络版彩色)基于核壳结构PLGA纳米粒子的放射-免疫检查点联合疗法^[11]。(a) PLGA-R837@Cat诱导的抗肿瘤免疫反应机制图;(b) PLGA-R837@Cat放疗后引起的免疫反应,包括乏氧缓解后TAM极化、放疗诱导ICD及DC活化、Tregs上调;(c)小鼠继发肿瘤中不同类型的T细胞流式细胞图,显示放疗-检查点封锁联合疗法的抗肿瘤效果。Copyright © 2019, John Wiley and Sons

Figure 2 (Color online) The combined therapy of radio and checkpoint-blockade therapy based on PLGA core-shell structure nanoparticles^[11]. (a) The schematic illustration for mechanism of antitumor immune responses induced by PLGA-R837@Cat; (b) the immune responses after radiotherapy with PLGA-R837@Cat, including TAM polarization post hypoxia relief, radiotherapy-induced ICD, the subsequent DC activation, as well as upregulated Tregs in the tumors; (c) representative flow cytometry plots showing different types of T cells in secondary tumors from different groups of mice to show the antitumor immune effects of radiotherapy in combination with checkpoint blockade. Copyright © 2019, John Wiley and Sons

副作用。然而在临床治疗中,这种少量多次的注射方法并不适用于每个化疗或放疗过程。面对该问题, Sun等人^[36]构筑了一种原位ATP响应的智能水凝胶,该水凝胶可在肿瘤组织处原位形成并长期停留;在诱导ICD过程中,该水凝胶可在肿瘤细胞释放的ATP刺激下,同步释放免疫佐剂胞嘧啶鸟嘌呤二核苷酸(CpG oligonucleotide, CpG ODN),在消除肿瘤方面具有显著的协同效应。

由此看出,纳米材料在放射疗法中一方面提高了生物相容性、安全性,另一方面通过与其他疗法的结合显著增强了放疗治疗的效果。通过局部放疗触发全身免疫治疗的设想可为下一代癌症放疗提供新的思路 and 临床参考。

3.3 光动力治疗

PDT是基于光、光敏剂和O₂分子的副作用小的微创肿瘤免疫治疗手段^[37]。富集在肿瘤部位的光敏剂被特定波长的光激发,产生电子和空穴,可将组织周围O₂分子活化为单线态氧(¹O₂)、超氧阴离子自由基(O₂^{·-})、羟基自由基(·OH)等具有细胞毒性的ROS,引起生物大分子氧化损伤,进而诱导ICD^[38]。TME的乏氧环境导致ROS依赖的PDT治疗手段效率较低。近年来,研究者设计了多种策略来克服PDT治疗的这一局限性。

血红蛋白(hemoglobin, Hb)作为氧纳米载体可通过增加TME中氧浓度来提高PDT触发ICD的效率^[39]。Chen等人^[40]利用二硫键将纳米载体与Hb连接并负载Ce6,构建了杂合蛋白氧纳米载体,载体将Hb递送至肿瘤细胞内并在肿瘤低氧环境中逐渐释放O₂,使得ROS产量显著提高,触发DAMPs分子释放和DC细胞成熟,增强PDT治疗效果。二氧化锰(manganese dioxide, MnO₂)在酸性和富含H₂O₂的TME中可被降解产生足够的O₂并增加ROS,进而提高光动力效率。Chung等人^[41]开发的基于GSH敏感的负载光敏剂维替普芬(verteporfin, VP)和MnO₂纳米颗粒共组装的聚酰胺-胺型树枝状高分子(polyamidoamine, PAMAM)-多糖褐藻糖胶多功能纳米颗粒也可被动靶向肿瘤部位,诱导ICD,提高PDT效果。

据报道,除氧载体及ROS环境响应外,肿瘤细胞也可通过其细胞核内一种硫氧化还原蛋白-1(thioredoxin 1, Trx-1)的表达移除ROS或修复氧化蛋白,从而实现抗氧化,加剧肿瘤组织内乏氧微环境。基于此, Lu等人^[42]构建了卟啉(meso-tetrakis(4-aminophenyl) porphyrin,

TAPP)基共价有机框架(nanoscale covalent organic polymer, nCOP)纳米材料,并装载Trx-1抑制剂(PX-12)。nCOP-PX-12可在酸性条件下释放TAPP并实现线粒体靶向,随后在光照射下诱发线粒体依赖的ICD,所释放的PX-12可抑制Trx-1表达以改善肿瘤乏氧微环境。综合来看, TAPP和PX-12的协同效应能显著诱导肿瘤细胞ICD和机体APC活化。

PDT是诱导ICD的有力策略,克服TME中的缺氧对于提高PDT效率至关重要,对PDT和增氧疗法之间相互作用的进一步了解可为新型癌症免疫疗法的发展提供新的依据。近年来,研究者通过直接抑制肿瘤线粒体的氧化磷酸化作用(oxidative phosphorylation, OXPHOS),设计基于线粒体呼吸链抑制剂(atovaquone, ATO)和光敏剂共负载的纳米材料可很好地缓解肿瘤乏氧^[43,44],该策略与ICD的结合也有很好的研究潜力。此外,靶向ER^[45,46]在ER中积聚并原位产生ROS,导致ER应激,激活ICD,诱导肿瘤免疫应答触发的PDT增强治疗在基于PDT和ICD的癌症治疗中也有很高的研究价值(图3)。

3.4 新兴治疗

超声触发的声动力治疗(sonodynamic therapy, SDT)通过声敏剂在超声刺激下产生ROS消除肿瘤,其具有非侵入性、高组织渗透性以及低副作用等特点,但无机声敏剂存在肿瘤富集效果差及量子产率低等问题,限制了SDT法临床应用。针对该问题, Jiao等人^[47]构建了一种具有丰富表面氧缺陷的纳米氧化锆(oxygen-deficient zirconia, ZrO_{2-x})作为声敏剂,通过PEG和cRGD(cyclic-Arg-Gly-Asp, cRGD)肽修饰ZrO_{2-x}表面,增强其在肿瘤部位的特定富集和深层组织渗透。在超声激发作用下,所制备的ZrO_{2-x}@PEG/cRGD纳米粒子利用表面的氧缺陷有效分离产生的电子-空穴对,进一步活化ROS诱导ICD,引发全身抗肿瘤免疫响应,实现治疗后肿瘤的完全根除^[47]。此外, Fu等人^[48]采用溶剂热法合成了具有多种酶活性的聚乙二醇化铁酸钴纳米花(PEGylated CoFe₂O₄ nanoflowers, CFP), CFP作为一种声敏剂,其中的多价元素(Co^{2+/3+}、Fe^{2+/3+})具有较强的类H₂O₂酶活性,其可与内源性的H₂O₂反应生成¹O₂,在声动力下可促进¹O₂的产生进而有效触发ICD,并可与免疫检查点阻断相结合以抑制原发性和远端肿瘤的生长及肺转移。

基于生物体内诸多气体信号分子的气体疗法,与多功能纳米技术结合也可达到精准的治疗效果。一氧

图3 (网络版彩色)ER靶向增强ICD的PDT示意图^[46]. Copyright © 2020, American Chemical Society

Figure 3 (Color online) Schematic illustration of enhanced immunogenic cancer cell death and anticancer effect induced by ER-targeting photodynamic therapy^[46]. Copyright © 2020, American Chemical Society

化氮(nitric oxide, NO)分子在肿瘤细胞中具有“两面性”: 低浓度NO可促进肿瘤细胞生长, 而高浓度NO通过介导巨噬细胞、能量代谢、增强化疗敏感等诱导肿瘤细胞凋亡。纳米材料可高效递送NO至肿瘤脉管系统中发挥治疗效果。Wang等人^[49]利用苯二胺脂质体构建了可智能响应NO气体的纳米载体, 并在脂质体表面包裹了负载有L-精氨酸(L-Arginine, L-Arg)和DOX的Au@CuS纳米粒子。通过共振能量转移, 该纳米材料可在ROS存在的情况下将L-Arg转化为NO, 使磷脂双层结构发生失稳且释放NO。随着体内NO的积累, NO响应的苯二胺脂质体被破坏并释放DOX, 增强机体化疗敏感性和ICD治疗效果^[49]。

一氧化碳(CO)分子生理学功能复杂, 在肿瘤细胞中其可锚定线粒体并在线粒体中积累, 导致O₂消耗迅速增加, 使肿瘤细胞发生线粒体源性凋亡。因此, 利用CO分子治疗肿瘤也是一重要策略。其中, 控制CO分子在肿瘤处精准释放是这一策略推广应用的核心。Wang等人^[50]设计了基于化疗药物MIT、羰基锰(manganese carbonyl, MnCO)的PLGA-PEG纳米平台, 通过EPR效应, 材料可在肿瘤部位聚集, 瘤内H₂O₂和MIT的光热效应可触发MnCO生成CO, 进而消耗氧分子并产生氧自由基使线粒体破损, 且CO可增强肿瘤细胞的化疗敏感性, 大大提高肿瘤治疗效果。此外, 抗血管生成治疗、基因治疗、氧化应激疗法等其他疗法也可与ICD结合, 提高抗肿瘤效果。

4 纳米材料用作增强ICD的联合治疗

单一疗法具有诸多局限性, 如化学疗法和放射疗法虽可杀伤癌细胞, 但对其他正常组织细胞及免疫细胞也会造成不可逆的损伤; PDT受限干乏氧的TME等。此外, 单一疗法也易受肿瘤异质性限制。基于以上考虑, 多模式协同的联合治疗模式更具优势。目前, 化学治疗、放射治疗和PDT的联合疗法已体现出明显优于单一疗法的效果。上述疗法与免疫检查点、免疫抑制因子、免疫佐剂、免疫细胞等的联用策略也得到广泛研究。

4.1 基于免疫检查点的联合治疗

免疫检查点是免疫系统的“刹车装置”, 在免疫系统中可调节免疫激活程度, 维持自身免疫耐受和调节组织免疫反应, 防止免疫系统过度活化。然而, 肿瘤细胞会激活免疫检查点, 阻断肿瘤免疫的提呈抗原过程, 抑制T细胞进而实现免疫逃逸。常用的免疫检查点有程序性细胞死亡1(programmed cell death protein 1, PD-1)及其配体(programmed cell death 1 ligand 1, PD-L1)、CTLs相关抗原4(cytotoxic T-lymphocyte associated protein 4, CTLA4)等^[51]。免疫检查点治疗常常受到低免疫原性、免疫细胞低浸润性、免疫抑制微环境等的限制^[52], 多种治疗手段的协同作用可改善上述问题。

Su等人^[53]制备了一种pH和MMP-2双重敏感的高分子胶束, 用于装载PD-1抗体和药物PTX。在肿瘤弱酸性的微环境和高表达MMP-2酶的作用下, 触发负电性PD-1抗体释放, 使得胶束表面呈正电性, 增加肿瘤细胞摄取。pH敏感的胶束可在TME中释放PTX, 从而诱导肿瘤细胞发生ICD。PTX和PD-1抗体在肿瘤组织中的可控靶向释放实现了协同的化学-免疫联合治疗, 进而达到快速清除肿瘤的目的。Ruan等人^[54]制备了豆荚蛋白响应金纳米颗粒, 其可被动靶向胶质瘤细胞, 在豆荚蛋白的作用下原位形成聚集物, 提高药物DOX和羟化氯喹的富集, 从而增强ICD效应。另外, 该材料和PD-L1抗体的协同能够逆转免疫抑制的TME, 实现化疗、自噬抑制和阻断PD-L1免疫检查点治疗联合治疗过程中的快速免疫应答, 有效预防肿瘤复发。

除与化学疗法结合外, 研究者还对免疫检查点与其他疗法的联合进行了一系列研究, 如Zhang等人^[55]利用仿生纳米乳共递送光敏剂和PD-1蛋白, 实现了协同的光动力-免疫治疗, 可触发ICD, 促进DC细胞的成熟

和CTLs细胞的肿瘤浸润。Chen等人^[11]将具有多功能核壳结构的PLGA纳米粒子与抗CTLA4检查抑制剂结合,放射疗法与免疫疗法的联合可有效抑制远处转移灶的生长,实现通过增强局部肿瘤放疗触发全身抗肿瘤免疫反应的治疗结果。

4.2 基于免疫抑制因子IDO-1的联合治疗

吡啶胺2,3-双加氧酶1(ndoleamine-2,3-dioxygenase 1, IDO-1)能降低TME中色氨酸的水平,并提高其代谢物犬尿氨酸(kynurenine, Kyn)的水平,是肿瘤细胞实现免疫逃逸和大量增殖的关键作用酶。据报道,IDO-1抑制剂能够激活自身免疫系统并增强化疗药物的疗效^[56,57]。Wang等人^[58]设计的可共负载顺铂药物和IDO-1抑制剂的高分子纳米材料可同时释放IDO-1抑制剂与抗癌药物,通过这种增强的免疫-化疗联合疗法,实现有效的肿瘤免疫治疗。除IDO-1小分子抑制剂外,某些聚合物、酶也可实现免疫刺激信号和免疫抑制信号的调节。Zhang等人^[30]设计的PROTAC可被肿瘤细胞中高表达的组织蛋白酶B(cathepsin B)特异性激活,靶向小鼠肿瘤中的IDO-1使其分解,结合半导体聚合物的近红外光响应性,这种原位免疫代谢干预可以协同免疫原性的光疗法来增强T细胞的抗肿瘤免疫效应。此外,Zeng等人^[59]设计的可被近红外光激活的有机聚合物纳米酶(semiconducting polymer nanoenzyme, SPNK),由半导体聚合物内核与犬尿氨酸酶(kynureninase, KYNase)通过可被¹O₂裂解的PEG链连接而成,在近红外光照射下,SPNK会产生¹O₂,诱导ICD,同时释放KYNase降解IDO-1代谢下游免疫抑制型产物Kyn。光动力疗法、放射治疗与IDO-1的联合治疗策略也可增强诱导肿瘤ICD效果。Gao等人^[60]设计制备一种含有光敏剂和IDO-1抑制剂的前药囊泡,该囊泡可在TME中脱落,通过MMP-2介导的PEG裂解在肿瘤细胞内原位聚集,在激光照射下,囊泡可有效产生ROS,诱导肿瘤细胞发生ICD(图4)。

4.3 基于免疫抑制细胞的联合治疗

TME中的诸多免疫抑制细胞可通过表型交替、营养耗竭、细胞凋亡等方式抑制CTLs,促进肿瘤发生发展^[61]。M2肿瘤相关巨噬细胞(M2 tumor-associated macrophage, M2-TAM)可诱导产生肿瘤免疫抑制微环境。半乳糖凝集素-9(galectin-9, Gal-9)在胰腺导管腺癌细胞(pancreatic ductal adenocarcinoma, PDAC)中高表达,其

可被巨噬细胞表面表达的C型凝集素受体(dectin-1)识别,将巨噬细胞驱动到M2表型。基于此,Zhou等人^[62]设计了一种靶向PDAC细胞的外泌体生物平台,利用OXA触发ICD效应,并通过抑制DNA合成和修复杀死肿瘤细胞,同时结合Gal-9相关基因来阻断Gal-9/dectin-1通路,逆转由M2-TAM引起的免疫抑制。叶酸(folic acid, FA)受体在4T1乳腺癌细胞和M2-TAM中高表达,Deng等人^[63]利用FA受体介导的内吞作用靶向4T1乳腺癌细胞和M2-TAM,设计了由FA修饰、具有MMP-2响应性的脂质体。FA介导的M2-TAM靶向作用可重塑免疫抑制性TME,结合免疫佐剂CpG促进DC细胞成熟和免疫刺激性细胞因子分泌,触发效应T细胞免疫反应,发挥抗肿瘤作用。

肿瘤的乏氧环境已被证明有助于髓样来源抑制细胞(myeloid-derived suppressor cells, MDSC)上调,而MDSC可通过募集T调节细胞(regulatory T cells, Treg)并抑制T细胞活化诱导形成肿瘤免疫抑制微环境^[64]。Li等人^[65]利用氟-氟(fluorine-fluorine, F-F)相互作用,将Ce6、氟化顺铂药物载体(fluorinated cisplatin drug carrier, F-S-PAMAM-Pt)以及全氟化碳(perfluorocarbon, PFC)组装成FS@PMPt纳米簇。激光照射下,光敏剂Ce6促进ROS的产生,诱发ICD,并联合释放至肿瘤细胞中的PMPt,杀死肿瘤细胞内的MDSC和Treg。

5 总结与展望

近年来,免疫治疗逐渐成为多种肿瘤的重要治疗策略。在化疗、放疗、PDT及各种联合治疗中,纳米材料可作为多功能工具(载体、刺激响应剂、药物缓释剂等)调节肿瘤免疫微环境,增强肿瘤细胞ICD效应。随着相关研究的不断深入,该领域仍然存在一些亟待解决的问题。

(1) 纳米材料作为药物载体的递送效率亟须提高。据统计,实际能够到达肿瘤部位的纳米载体低于1%。尽管已开发了各种响应性的靶向策略可提高纳米材料的组织富集能力,但体内生物分布的具体情况仍无法精准调控。

(2) 纳米材料的降解和代谢过程亟须深入研究。相较于小分子药物,纳米材料具有更复杂的结构,其在代谢降解过程中产生的中间体可能存在某些生物学效应,从而影响肿瘤治疗效果。另外,纳米载体还可能具有系统毒性和副作用。因此,开发可重复、可放大、生物安全的纳米材料迫在眉睫,且亟须建立可靠的纳米材料

Figure 4 (Color online) The combined therapy of photodynamic and immunotherapy based on immunosuppressive factor IDO^[60]. (a) Schematic illustration of MMP-2-sheddable and GSH-activatable prodrug vesicle; (b) mechanism of nanomaterials-mediated photodynamic immunotherapy of cancer by combating IDO-1-induced adaptive immune resistance. Copyright © 2019, American Chemical Society

毒理学相关的体外模型, 为临床研究提供快速、廉价和可靠的参照方法.

(3) 诸多作用机制如纳米材料化学性质、表面性质、拓扑结构等对ICD的调控, 细胞与纳米基底在体内的相互作用还需进一步探讨。此外, ICD作为一种细胞死亡方式, 如何在临床中评判哪种纳米材料可诱导合适的ICD效应, 运用哪些方法和工具对其进行测试表征还有待探究。

(4) 目前的很多基础研究主要使用小鼠肿瘤模型,尚不能准确反映人类肿瘤的复杂性和异质性,将临床前研究的成果推向临床引用还需诸多探索。

虽然存在诸多挑战,我们仍期待该领域产生更多创新的想法和原创的理念,通过系统深入的研究和科学谨慎的评价,这些多功能的纳米材料有望为增强肿瘤细胞ICD效应和改善肿瘤免疫治疗提供新的范例.

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补充材料

表S1 用于增强肿瘤免疫原性死亡的纳米材料

本文以上补充材料见网络版csb.scichina.com. 补充材料为作者提供的原始数据, 作者对其学术质量和内容负责.

Summary for “生物医用纳米材料在增强肿瘤细胞免疫原性死亡中的应用”

Biomedical nanomaterials for the enhancement of immunogenic cell death-based cancer immunotherapy

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The activation of adaptive antitumor immune response is paramount for improving the long-term antitumor efficiency. Chemotherapy, radiotherapy, and photodynamic therapy (PDT) can induce cell apoptosis and immunogenic cell death (ICD). Subsequently, the exposure or release of damage-associated molecular patterns (DAMPs) caused by ICD can stimulate the immune system to exert an antitumor immune response, recruit the antigen-presenting cells, and activate the adaptive immune responses of T cells. As such, the application of ICD inducers in tumor therapy is of crucial role in improving the therapeutic effects and the survival rate of cancer patients. Recently, accumulating evidence has revealed that nanomaterials-based platforms for cancer treatment could not only achieve controlled drug release in response to stimulation of tumor microenvironment (TME), but also regulate TME to enhance ICD in the tumor. Hence, the construction of ICD effects-based biomedical nanomaterials has sparked tremendous attention. Benefiting from their unique size, biomedical nanomaterials are commonly applied as ICD inducers carriers to target tumor tissue and enhance selective enrichment in the tumor. By taking advantage of their easily modified surface properties and multi-selectivity of raw materials, nanomaterials can also be designed as functionalized carriers with stimulus responses to TME, thereby achieving stepwise and controlled release of ICD inducers. Meanwhile, biomedical nanomaterials are capable of co-delivering different components, protecting the payload from degradation and precise controlled release. These abilities enable nanomaterials to amplify the antitumor effects of chemotherapy, radiotherapy, PDT and many other emerging therapies. Of note, a single therapy has been limited by many factors. Chemotherapy and radiotherapy can bring about irreversible damage to normal tissue cells and immune cells. The hypoxic TME limits the function of PDT. On top of that, monotherapy has been also vulnerable to tumor heterogeneity. On this ground, combination therapy has become the prior option for cancer therapy. Furthermore, the synergistic of these therapies with immune checkpoints, immunosuppressive factors, immune adjuvants, immune cells and other strategies that can enhance ICD has been extensively estimated. In this paper, we first introduced the generation of the ICD, then emphasized the multifunctional roles of nanomaterials in inducing ICD and regulating the microenvironment of tumor cells. Ulteriorly, the tremendous potential, challenges and development trends of nanomaterials in therapeutic effects of ICD have been expounded and concluded. Finally, to make better use of nanomaterials and accelerate clinical transformation in the future, it is imperative to further explore the transfer efficiency, degradation and metabolism of nanomaterials, and propose a more specific and in-depth understanding of the molecular mechanism of ICD.

nanomaterials, immunogenic cell death, drug delivery, immunotherapy, combination therapy

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