基于纳米递药系统的肿瘤免疫检查点联合治疗研究进展

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摘要 免疫治疗已成为继手术治疗、化疗、放疗之外的重要肿瘤治疗手段。在肿瘤免疫疗法中, 免疫检查点阻断疗法临床疗效显著, 受到广泛关注。但是, 由于患者肿瘤组织免疫原性低、存在免疫抑制微环境和免疫细胞瘤内浸润缺乏等问题, 免疫检查点阻断治疗仍存在临床响应率低等局限性。近年来, 科研人员利用肿瘤区别于正常组织的生理和病理特性, 联合物理、化学等刺激手段, 发展了多种基于纳米递药系统的免疫检查点联合治疗策略, 显著提高了免疫检查点阻断治疗的疗效并有望降低其毒副作用。本文简要综述了本团队及国内外同行利用纳米递药系统高效递送免疫治疗药物, 将免疫检查点抑制剂与化疗、放疗和光疗等方法联合, 改善免疫检查点阻断疗法的疗效方面的研究进展, 并对该领域面临的挑战及未来发展趋势进行了探讨与展望。

关键词 纳米递药系统, 免疫治疗, 免疫检查点阻断, 联合治疗, 肿瘤微环境

恶性肿瘤已成为严重危害我国人民健康的重大疾病。近年来, 肿瘤免疫治疗在部分肿瘤患者中疗效显著, 已成为临床治疗恶性肿瘤的一项新策略。肿瘤免疫治疗是指利用机体自身免疫系统, 激活相关免疫细胞识别并杀伤肿瘤细胞的一种治疗策略^[1-4]。由于临床疗效显著, 患者耐受性好, 应用前景广阔, 肿瘤免疫治疗受到越来越多的关注。其中, 肿瘤免疫检查点阻断疗法(immune checkpoint blockade therapy, ICB therapy)已获得2018年诺贝尔生理学或医学奖^[5-7]。

免疫系统为机体提供一系列保障, 使机体免于病毒、细菌、真菌及其他外源有毒物质的侵害^[8]。在机

体细胞免疫应答中, T淋巴细胞的响应强度和应答质量受到共刺激因子与抑制信号的调节^[9,10]。这些免疫抑制信号即是免疫检查点。免疫检查点能够影响免疫进程, 调节免疫系统稳态。免疫检查点的过表达会抑制T细胞的激活, 使肿瘤细胞逃过免疫系统的监视和杀伤, 导致“免疫逃逸”。目前, 研究较深入的免疫检查点主要包括: 程序性死亡受体1(programmed cell death protein 1, PD-1)、程序性死亡受体-配体1(programmed cell death-ligand 1, PD-L1)^[11]、细胞毒性T淋巴细胞相关蛋白4(cytotoxic T lymphocyte associated protein 4, CTLA-4)和CD47(图1)。T细胞膜上的PD-1与肿瘤细胞

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图1 PD-1, PD-L1, CTLA-4和CD47免疫检查点的作用机制(网络版彩图)

Figure 1 Mechanisms of PD-1, PD-L1, CTLA-4, and CD47 immune checkpoints (color online)

表面的PD-L1结合后诱导CD8⁺ T细胞凋亡、失能或耗竭,抑制T细胞分泌穿孔素、颗粒酶等一系列能够杀伤肿瘤细胞的蛋白从而导致“免疫逃逸”^[12],导致肿瘤复发和转移。CTLA-4是T细胞上的一种跨膜受体,能调控T细胞功能,它的作用机制是与同源蛋白CD28竞争性地结合抗原提呈细胞(antigen presenting cells, APCs)的两个配体——CD80和CD86,向T细胞传递抑制信号^[12]。免疫检查点CD47在多种恶性肿瘤细胞表面过表达^[13],与信号调节蛋白 α (signal regulatory protein α , SIRP α)相互作用,作为“别吃我”的信号抑制APCs对肿瘤细胞的吞噬作用^[14,15]。

免疫检查点阻断疗法通过阻断肿瘤免疫检查点,使细胞毒性T淋巴细胞(cytotoxic T lymphocyte, CTLs)免疫系统的功能正常化而发挥抑瘤作用,现已成为一种具有巨大发展潜力和应用前景的肿瘤免疫治疗策略。抗PD-1抗体(anti-PD1 antibodies, α PD1)或抗PD-L1抗体(anti-PDL1 antibodies, α PDL1)能够有效阻断PD-1/PD-L1信号通路,解除肿瘤细胞对CTLs的免疫抑制。抗CTLA-4抗体(anti-CTLA-4 antibodies, α CTLA-4)可抑制CTLA-4与其配体的相互作用,活化T细胞使其识别并杀伤肿瘤细胞^[16]。阻断CD47免疫检查点可破坏肿瘤细胞的自我保护机制,提高免疫治疗效果^[17]。第一个实现临床应用的免疫检查点抗体药物是抗CTLA-4分子的单克隆抗体伊匹单抗yervoy(ipilimumab),它在2011年获得美国食品药品监督管理局(Food and Drug Admin-

istration, FDA)批准。2014年, FDA批准了两个抗PD-1单抗Keytruda(pembrolizumab, 派姆单抗)和Opdivo(nivolumab, 纳武单抗)上市, 抗PD-L1单抗Tecentriq(atezolizumab, 阿特珠单抗)在2016年获批上市。尽管免疫检查点阻断疗法已取得很大进展, 其临床应用仍面临重大挑战。首先, 许多肿瘤细胞的免疫原性低导致免疫检查点抑制剂的临床响应率普遍较低。其次, 实体肿瘤普遍存在的免疫抑制微环境也使其疗效受限^[18]。以免疫检查点阻断疗法为基础, 与化疗、靶向治疗和放疗等治疗手段联合可减少肿瘤负荷和增加肿瘤免疫原性, 有望提高响应率, 延长应答时间, 减少不良反应, 改善免疫检查点阻断疗法的疗效并使其适用于更多患者及更广的肿瘤类型。免疫检查点联合疗法的临床研究数量的快速增长充分说明, 联合治疗是免疫检查点阻断疗法的发展趋势(表1)。然而, 这些联合方法仍存在疗效有限、肿瘤渗透性差、靶向性差等局限。因此, 针对免疫检查点阻断疗法的传统联合治疗方法急需改善, 基于纳米递药系统的免疫检查点联合策略有望增强免疫治疗药物的肿瘤渗透性、改善其体内代谢行为从而提高临床响应率并降低毒副作用。

纳米递药系统既可直接递送免疫检查点抑制剂, 也可共递送多种药物, 实现免疫检查点阻断疗法与其他疗法的联合使用。基于纳米递药系统的免疫检查点联合治疗策略在提高疗效以及降低毒副作用等方面都有明显优势: (i) 载药纳米粒可利用肿瘤的增强渗透和滞留(enhanced permeability and retention, EPR)效应实现肿瘤组织被动靶向并高效蓄积^[38,39]; (ii) 利用纳米粒表面修饰肿瘤特异性配体或其他靶标分子使药物主动靶向到肿瘤组织, 提高其体内递送效率^[40]; (iii) 肿瘤微环境响应型纳米递药系统可增强肿瘤渗透, 触发药物定点释放, 高效的药物控释系统有望减少 α PDL1等抗体药物与正常组织相关受体结合, 增强免疫检查点抑制剂疗效, 降低免疫检查点阻断疗法的毒副作用; (iv) 通过表面聚乙二醇(polyethylene glycol, PEG)化修饰减少药物免疫系统清除^[16,41]; (v) 纳米递药系统可递送免疫治疗药物与化疗药物或者光敏剂等免疫调节剂以实现免疫治疗与化学治疗以及光动力治疗等联合治疗, 提高免疫检查点阻断疗法的响应率^[42], 增强疗效并减小毒副作用。

近年来, 科研人员发展了一系列基于纳米递药系统的肿瘤免疫检查点联合治疗策略, 利用纳米递药系

表 1 处于临床研究阶段的代表性免疫检查点联合治疗策略

Table 1 Representative immune checkpoint combination therapeutic strategies in clinical studies

免疫检查点阻断疗法	联合策略	适应症	参考文献
免疫检查点抑制剂联合治疗			
Nivolumab(抗PD-1抗体)	Ipilimumab(抗CTLA-4抗体)	黑色素瘤	[19]
MEDI0680(抗PD-1抗体)	Durvalumab(抗PD-L1抗体)	晚期恶性肿瘤	[20]
抗PD-1抗体	抗CD47抗体	黑色素瘤	[21]
免疫检查点抑制剂与分子靶向药物联用			
Nivolumab(抗PD-1抗体)	Sunitinib/Pazopanib(受体酪氨酸激酶抑制剂)	转移性肾细胞癌	[22]
Pidilizumab(抗PD-1抗体)	Rituximab(抗CD20嵌合抗体)	滤泡淋巴瘤	[23]
Tremelimumab(抗CTLA-4抗体)	抗雄激素	前列腺癌	[24]
免疫检查点抑制剂与肿瘤疫苗联用			
MDX-010(抗CTLA-4抗体)	肿瘤表位肽疫苗	黑色素瘤	[25]
Ipilimumab(抗CTLA-4抗体)	糖蛋白100(gp100)	转移性黑色素瘤	[26]
Ipilimumab(抗CTLA-4抗体)	GM-CSF基因修饰疫苗(GVAX)	胰腺癌	[27]
免疫检查点抑制剂与化疗药物联用			
Ipilimumab(抗CTLA-4抗体)	紫杉醇+卡铂	转移性前列腺癌、非小细胞肺癌	[28,29]
Pembrolizumab(抗PD-1抗体)	培美曲塞+卡铂	非小细胞肺癌	[30]
PD-L1 mAb(局部PD-L1 trap)	奥沙利铂	结直肠癌	[31]
免疫检查点抑制剂与放射疗法联用			
Ipilimumab(抗CTLA-4抗体)	放疗	黑色素瘤	[32]
Pembrolizumab(抗PD-1抗体)	放疗	晚期非小细胞肺癌	[33]
免疫检查点抑制剂与细胞治疗联用			
Nivolumab(抗PD-1抗体)	肿瘤浸润淋巴细胞治疗	晚期非小细胞肺癌	[34]
免疫检查点抑制剂与溶瘤病毒联用			
Pembrolizumab(抗PD-1抗体)	T-vec疱疹病毒	黑色素瘤	[35]
Ipilimumab(抗CTLA-4抗体)	T-vec疱疹病毒	黑色素瘤	[36]
Pembrolizumab(抗PD-1抗体)	Enadenotucirev溶瘤腺病毒疗法	转移癌或晚期癌	[37]

统, 共递送多种免疫调节剂, 联合化疗或光动力等疗法, 显著提高肿瘤治疗效果。本文初步总结了国内外同行及本团队在基于纳米递药系统的肿瘤免疫检查点联合治疗改善肿瘤疗效方面的研究进展, 并对其发展趋势和临床转化前景进行了探讨与展望。

1 基于纳米递药系统的PD-L1免疫检查点联合治疗

PD-L1也称为表面抗原分化簇274(cluster of differentiation 274, CD274)或B7同源体(B7 homolog 1, B7-H1)。由于PD-L1在上皮细胞、间充质干细胞等正常组织和细胞表面也有表达, 所以 α PDL1在正常组织中的

分布可导致免疫耐受不平衡、免疫应答过度活化, 从而引起自身免疫性副作用, 损伤正常组织和脏器^[11,43]。为了避免这种在靶标但不在肿瘤(on-target but off-tumor)的结合, 研究人员尝试将 α PDL1整合到纳米粒中进行系统全身递送或局部递送^[44], 该方法有望减少 α PDL1的毒副作用, 改善对原位肿瘤的治疗效果^[45]。相比正常组织而言, 肿瘤组织会过表达基质金属蛋白酶-2(matrix metalloproteinase-2, MMP-2)^[46]。基于实体肿瘤的酶环境特征, Wang等人^[42]开发了肿瘤微环境激活型 α PDL1纳米粒以克服免疫检查点阻断疗法中的免疫耐受, 从而防止肿瘤复发和抑制肿瘤转移。研究人员首先利用MMP-2响应肽片段将PEG和儿茶酚二聚体偶联, 然后再将MMP-2响应型PEG化儿茶酚二聚体与

光敏剂吲哚菁绿(indocyanine green, ICG)利用共组装技术整合到一个纳米复合物中, 形成MMP-2激活型 α PD-L1药物递送系统(图2A和B). 该药物递送系统的平均流体力学粒径为 (163.4 ± 6.6) nm(图2C), 可在血液循环中保持稳定, 特异性蓄积到肿瘤组织, 然后利用肿瘤MMP-2酶环境触发 α PD-L1释放. ICG介导的光动力疗法(photodynamic therapy, PDT)还可诱导肿瘤细胞发生免疫原性细胞死亡(immunogenic cell death, ICD), 激活钙网蛋白(calreticulin, CRT)由内质网向细胞膜表面外翻, 释放三磷酸腺苷(adenosine triphosphate, ATP)和高迁移率族蛋白B1(high mobility group

box 1, HMGB1)等免疫原性物质, 进而激活T细胞介导的获得性免疫应答^[47], 促进肿瘤内CTLs浸润(图2B), 免疫检查点阻断和PDT共同作用, 能同时激活抗肿瘤免疫效应, 增加免疫原性, 解除免疫抑制, 实现协同增效. 该纳米递药系统介导的联合治疗使80%的4T1三阴性乳腺癌荷瘤小鼠生存期超过70天(图2D和E). 上述研究表明, α PD-L1结合PDT通过纳米递药系统递送后的抗肿瘤效果显著提高. 这种纳米粒制备简单, 可同时激活免疫应答并解除PD-L1免疫检查点的免疫抑制作用, 有望应用于其他免疫检查点抑制剂的高效递送, 改善免疫检查点阻断疗法的疗效.

图 2 设计在肿瘤微环境中局部激活T细胞的纳米粒^[42]. A: MMP-2 响应型S-αPD-L1/ICG@NP的制备过程; B: S-αPD-L1/ICG@NP介导的免疫检查点阻断与PDT联合治疗示意图; C: S-αPD-L1/ICG@NP透射电子显微镜图像(标尺: 200 nm); D和E: 不同处理下4T1荷瘤BALB/c小鼠的平均肿瘤生长曲线($n=5$) (网络版彩图)

Figure 2 Tumor microenvironment-activatable nanoparticles for local activation of T cells^[42]. A: Preparation of MMP-2-labile S-αPD-L1/ICG@NP; B: schematic illustration for combination ICB and PDT therapy with S-αPD-L1/ICG@NP; C: transmission electron microscope (TEM) images of S-αPD-L1/ICG@NP (Scale bars=200 nm); D and E: tumor growth curves of 4T1 tumor in BALB/c mice with different treatments ($n=5$) (color online)

除了基于单克隆抗体的免疫检查点阻断疗法, RNA干扰技术可高效特异沉默目标基因的转录, 已在恶性肿瘤等重大疾病治疗中表现出巨大潜力。但小干扰RNA(small interfering RNA, siRNA)药物体内稳定性差、易降解且不易入胞, 需要利用载体进行递送。纳米递药系统可有效提高siRNA药物的体内稳定性, 实现特定组织或细胞的靶向递送。利用纳米递药系统递送靶向肿瘤细胞PD-L1靶点的siRNA有望特异性沉默肿瘤细胞PD-L1的表达, 解除PD-L1/PD-1通路介导的肿瘤免疫抑制, 实现高效肿瘤免疫治疗。

Wang等人^[48]将酸敏感阳离子胶束、光敏剂和siRNA整合成一种多功能复合胶束(图3A), 实现PDT和免疫检查点阻断疗法高效联合治疗。研究人员首先将具有酸响应功能的两嵌段共聚物与光敏剂脱镁叶绿酸盐A(pheophorbide A, PPa)偶联成PDPA-PPa, 再采用纳米沉淀法与两亲性多聚阳离子OEI-C14共组装成阳离子胶束PDPA-OEI-C14-PPa(POP)胶束, 最后将该多功能的酸激活胶束与siRNA混合制备成负载siRNA的酸敏感胶束复合物。该胶束复合物在中性生理条件下(pH 7.4)保持稳定, 被细胞内吞后在溶酶体酸性环境下被激活(图3B)。实验结果表明, siRNA介导的PD-L1阻断联合PDT疗法可完全消除B16-F10黑色素瘤(图3C)。相较于单独使用PDT, 其可引起持久的免疫反应, 显著抑制肿瘤生长和复发, 在给药后26天小鼠无瘤率高达75%(图3D), 在C57BL/6小鼠中显著抑制B16-F10肿瘤的肺转移(图3E)。

2 基于纳米递药系统的PD-1免疫检查点联合治疗

PD-1也称为分化簇279(cluster of differentiation 279, CD279), 是T细胞上一种重要的免疫抑制分子, 与配体PD-L1结合抑制肿瘤免疫应答, 导致肿瘤免疫逃逸。为有效阻断PD-1介导的免疫抑制, Gu课题组^[49]报道了一种表面包载有PD-1受体的细胞膜衍生的PD-1纳米囊泡(PD-1 nanovesicles, PD-1 NVs), 其可结合吡啶胺2,3-双加氧化酶1(indoleamine 2,3-dioxygenase 1, IDO-1)的抑制剂1-甲基色氨酸(1-methyl-tryptophan, 1-MT)协同阻断免疫耐受通路, 克服肿瘤抑制性微环境(图4A和B)。研究人员将分离的细胞膜连续挤压过滤形成纳米囊泡, 并载入1-MT形成1-MT@PD-1 NVs(图

4A)。体内实验结果表明, IDO-1和PD-1的双重抑制作用增加了肿瘤边缘的CD8⁺ T细胞的密度, 驱动宿主免疫系统消退肿瘤, 显著提高了荷瘤小鼠生存率。该纳米囊泡还可递送其他肿瘤药物, 通过协同作用增强免疫疗效, 具有一定临床转化前景。

此外, Gu课题组^[50]还利用造血干细胞的归巢作用使 α PD1积蓄在骨髓中, 并利用原位血小板活化控制 α PD1的释放, 从而增加 α PD1抗体与T细胞结合, 延长小鼠生存期。Gu课题组^[21]进一步构建了联合递送 α PD1与抗CD47抗体(anti-CD47 antibodies, α CD47)的双响应蛋白复合物以增强疗效。

3 基于纳米递药系统的CTLA-4免疫检查点联合治疗

CTLA-4作为免疫应答中关键的负调控因子^[51], 主要在T细胞上表达, 主要调控T细胞早期阶段的响应强度^[12]。虽然抗CTLA-4抗体是最早被FDA批准的肿瘤免疫检查点抑制剂, 但其免疫应答持续时间短、临床响应率低、毒副作用大等问题严重限制了CTLA-4抑制剂的临床使用。因此, 科学家们发展各种联合治疗策略。Chen等人^[52]制备了结合光敏剂ICG与免疫佐剂Toll样受体(toll-like-receptor, TLR)激动剂的多功能纳米粒, 在光疗法消融肿瘤时可引起与疫苗类似的免疫响应, 与CTLA-4抑制剂结合可激活高效抗肿瘤免疫效应, 抑制肿瘤转移, 延长荷瘤小鼠存活期。基于该多功能纳米粒的原位肿瘤光热消融可发挥类似“肿瘤疫苗”作用, 有望克服抗体肿瘤疫苗的个体性差异, 扩大其临床应用范围。同时该纳米粒具有疗效可观、制备技术简单、成本低廉以及辅料安全性高等优势, 具备一定临床转化潜力。

4 基于纳米递药系统的CD47免疫检查点联合治疗

CD47, 也称整联素关联蛋白(integrin-associated protein, IAP), 在多种恶性肿瘤细胞表面高表达, 作为“别吃我”信号抑制APCs对肿瘤细胞的吞噬作用。CD47抑制剂在某些恶性肿瘤中显示出一定的治疗效果, 然而由于CD47在红细胞表面也有高表达, 所以全身注射的CD47抑制剂易会引起贫血和血小板减少等

图 3 用于PD-L1阻断的酸响应多功能胶束增强光动力肿瘤免疫治疗^[48]。A: 胶束复合物的制备和酸活化过程; B: 复合胶束介导的光动力肿瘤免疫治疗的卡通示意图; C: PDT和PD-L1阻断可抑制肿瘤生长($n=6$); D: 通过PDT和PD-L1阻断诱导的适应性免疫反应预防肿瘤复发($n=8$); E: 通过PD-L1 阻断增强PDT对C57BL/6小鼠的B16-F10黑色素瘤转移的抑制作用 (网络版彩图)

Figure 3 Acid-activatable micelleplexes for PD-L1 blockade and photodynamic cancer immunotherapy^[48]. A: Preparation and characterization of the POP micelleplexes; B: schematic illustration of POP micelleplex-mediated photodynamic immunotherapy of cancer; C: tumor growth inhibition by PDT and PD-L1 KD ($n=6$); D: prevention of tumor recurrence via PDT and PD-L1 blockade-induced adaptive immune response ($n=8$); E: the combination of PD-L1 KD and PDT inhibited the lung metastasis of B16-F10 tumors in C57BL/6 mice (color online)

副作用^[53], 这严重制约了 α CD47的临床转化.

肿瘤细胞发生ICD时，会在表面表达“吃我”信号CRT，从核内释放HMGB1并分泌ATP^[54]。已有研究表明，PDT引起的ICD与IDO-1抑制剂联合能增强PDT治疗效果^[55]。

Zhou等人^[18]设计了一种肿瘤胞外酶环境激活的前药囊泡用于联合ICD与 α CD47,既可以解决化学小分子药物引起的ICD诱导不足而无法杀伤肿瘤细胞的

问题, 又可以通过瘤内注射 α CD47降低其毒副作用(图5A)。科研人员首先利用2,3-二甲基马来酸酐(2,3-dimethylmaleic anhydride, DMMA)修饰前药十六烷基奥沙利铂二乙烯胺(hexadecyl-oxaliplatin diethylene amine, HOA)合成酸响应前药HOAD, 接着利用MMP-2响应的聚乙二醇化光敏剂PPa和HOAD构建肿瘤酶及酸性微环境双响应前药囊泡MPV-HOAD(图5A和B)。该囊泡的PEG亲水壳和表面负电荷的存在可有效避免

图 4 用于肿瘤免疫治疗的PD-1阻断细胞囊泡^[49]. A: 装载1-MT的PD-1 NVs的制备示意图; B: PD-L1与PD-1受体相互作用, 耗竭CD8⁺ T细胞, 同时IDO也会抑制CD8⁺ T细胞的活性. MHC-I: 主要组织相容性复合体I类; TCR: T细胞受体; CTLA4: 细胞毒性T淋巴细胞相关蛋白4; C: PD-1 NVs引起的PD-L1阻断使耗尽的CD8⁺ T细胞重新攻击肿瘤细胞, IDO抑制剂1-MT的释放也能使衰竭的CD8⁺ T细胞恢复(网络版彩图)

Figure 4 Cellular vesicles blocking PD-1 for combination cancer immunotherapy^[49]. A: Schematic illustration of 1-MT-loaded PD-1 NVs; B: the overactivation of PD-L1 and IDO-1 in the tumor cells and DCs exhausts CD8⁺ T cells. MHC-I: major histocompatibility complex class I; TCR: T cell receptor; CTLA4: cytotoxic T-lymphocyte associated protein 4; C: PD-L1 blockade by PD-1 NVs and the release of IDO inhibitor 1-MT revert the exhausted CD8⁺ cells to attack tumor cells (color online)

纳米粒的蛋白吸附和网状内皮系统的清除, 因此前药囊泡在血液循环过程中表现出良好稳定性. 到达肿瘤部位后, 通过MMP-2介导的PEG脱壳和微酸环境引发的表面电荷逆转, 可有效地实现肿瘤富集和渗透. 接着, 前药囊泡在激光照射下诱导ROS生成, 促进瞬时药物释放, 触发肿瘤细胞的ICD效应. 前药囊泡介导的ICD效应和 α CD47介导的免疫检查点阻断可发挥抗肿瘤的协同作用(图5B). 实验结果表明, 该纳米粒可有效抑制原位肿瘤和远端肿瘤的生长、抑制肿瘤转移并防止肿瘤复发. 该MMP-2/pH双响应的新型纳米前药囊泡MPV-HOAD将免疫疗法与化疗、光疗结合在一起, 协同促进肿瘤细胞的ICD效应, 提高肿瘤免疫原性, 促进DCs熟化. 此外, 鉴于CD47在多种肿瘤细胞中过表达, 故同时诱导肿瘤细胞ICD效应并特异性阻断CD47有望应用于多种肿瘤的治疗, 为改善癌症化疗免疫治疗提供一种新策略.

除了上述肿瘤微环境刺激型免疫检查点抑制剂纳米递药系统, Gu课题组^[53]提出了一种简单的术后肿瘤

免疫治疗策略, 该策略利用免疫治疗性纤维蛋白凝胶激活机体的先天和适应性免疫应答, 抑制手术后肿瘤复发以及转移扩散. 科研人员首先将预先载有 α CD47的碳酸钙纳米粒嵌入纤维蛋白凝胶内, 碳酸钙可中和手术伤口附近的H⁺离子并释放 α CD47, 解除酸性和炎症性的肿瘤抑制微环境, 诱导肿瘤相关巨噬细胞由M2型(肿瘤免疫抑制, 促进肿瘤增殖)向M1型(肿瘤免疫激活, 抑制肿瘤生长)转化, 激活抗肿瘤免疫反应. 同时 α CD47阻断“别吃我”信号, 增加巨噬细胞对肿瘤细胞的吞噬作用. 这种基于纳米递药系统的纤维蛋白凝胶递送 α CD47可扩大免疫检查点阻断疗法的应用范围, 为免疫联合治疗带来新思路.

5 总结和展望

肿瘤免疫检查点抑制剂对黑色素瘤等多种肿瘤均有治疗作用, 已成为重要的肿瘤治疗手段. 但其毒副作用大、响应率低、临床应用受限等问题仍亟待解决.

图 5 肿瘤微环境激活的前药囊泡结合免疫原细胞死亡诱导和CD47阻断用于增强肿瘤免疫治疗^[18]. A: 酸和MMP-2双响应前药囊泡的微环境响应原理; B: MPV-HOAD介导的化疗免疫治疗和CD47阻断抑制肿瘤生长、复发和远处转移的机制简图 (网络版彩图)

Figure 5 Combination of immunogenic cell death induction and CD47 blockade enhanced immunotherapy of cancer^[18]. A: Schematic demonstration of the acidity and MMP-2 dual-responsive prodrug vesicles; B: mechanism illustration of MPV-HOAD-mediated chemo-immunotherapy and CD47 blockade to inhibit tumor growth, recurrence, and distant metastasis (color online)

纳米技术、生物学和材料科学的迅速发展推动了纳米递药系统的智能化设计 and 应用^[56], 不仅可提高免疫检查点阻断疗法对肿瘤的治疗效果, 还为免疫治疗联合其他肿瘤治疗手段提供了平台. 利用纳米载体联合免疫检查点阻断治疗与化疗、放疗、光疗等其他疗法, 基于解除免疫抑制微环境和增加肿瘤免疫原性两种策略^[57], 不仅能在一定程度上减小免疫检查点阻断疗法的毒副作用, 还可发挥协同作用, 增强疗效, 甚至扩大肿瘤免疫检查点阻断疗法的适用范围^[58,59]. 因此, 免疫检查点阻断疗法与其他疗法的联合使用是必要的, 也是免疫检查点阻断疗法可能的发展趋势.

尽管基于纳米递药系统的免疫检查点联合治疗具有巨大潜力, 但其临床转化仍存在许多问题. 首先, 对

于免疫调节机制以及肿瘤微环境的研究还不够深入, 而肿瘤异质性也限制了肿瘤免疫治疗的广泛应用. 其次, 纳米递药系统的载体材料安全性至关重要. 此外, 纳米递药系统也会在正常组织分布, 因此优化纳米系统构成、改善其血液稳定性、增加肿瘤部位的蓄积和渗透、促进肿瘤细胞的摄取以及细胞内的可控药物释放也是实现纳米递药系统临床转化的关键所在.

虽然基于纳米递药系统的肿瘤免疫检查点联合治疗面临着诸多挑战, 但挑战即为机遇. 通过免疫检查点作用机制及肿瘤微环境的深入研究, 随着纳米医学的不断发展, 基于纳米递药系统的肿瘤免疫检查点联合治疗的疗效有望进一步提高, 为肿瘤免疫疗法提供新策略.

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Recent advance of nanosized drug delivery systems targeting immune checkpoints for combination cancer immunotherapy

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Immune checkpoint blockade (ICB) therapy has gained increasing attention due to its remarkable therapeutic performance. However, its therapeutic performance was highly impaired by the low immunogenicity of the tumors, insufficient intratumoral infiltration of the T lymphocytes, and the immunosuppressive tumor microenvironment. To address the challenge of current ICB therapy, nanosized drug delivery systems have been extensively exploited to deliver various immune modulators (e.g., chemotherapeutics, photosensitizers, and immune checkpoint inhibitors) for improved ICB therapy. In this review, we provide a brief overview of the recent advance of nanosized drug delivery systems for combination ICB immunotherapy. We also discuss the challenges and provide perspectives for the clinical translation of nanosized drug delivery systems for cancer immunotherapy.

nanosized drug delivery system, immunotherapy, immune checkpoint blockade, combination therapy, tumor microenvironment

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