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·专家论坛·

血小板:肿瘤诊断与治疗的新兴靶点

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[摘 要] 血小板是肿瘤发生发展过程中的重要参与者,能够通过构建炎性微环境、促进血管生成和介导肿瘤免疫逃逸,直接或间接地影响肿瘤生长和转移进程。随着肿瘤微环境的动态变化,血小板的数量、体积和分子组学也发生相应改变,提示血小板相关的生物标志物具有反映肿瘤负荷演变的巨大潜力。基于血小板对肿瘤发生发展的促进效应,血小板被视为肿瘤生物治疗的重要靶点。靶向抑制血小板功能可以显著控制肿瘤的发生发展并改善患者的预后。此外,血小板对肿瘤组织具有较强的亲和能力。应用靶向血小板或血小板功能模拟的思路研发抗肿瘤靶向制剂以有效地增加纳米药物的肿瘤靶向性和生物相容性,是提高肿瘤靶向治疗效率的新兴策略。本文聚焦于血小板与肿瘤之间的复杂相互作用,在总结作用机制的基础上,对血小板相关的肿瘤标志物和抗肿瘤靶向治疗进行了重点阐述。

[关键词] 血小板;肿瘤诊断;肿瘤治疗;血小板参数;靶向治疗
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Platelets: an emerging target for the diagnosis and therapy of cancer

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[Abstract] Platelets are considered as important participants in the process of tumorigenesis and tumor development, which can directly or indirectly affect the growth and metastasis of tumors by constructing an inflammatory microenvironment, promoting angiogenesis and mediating tumor immune escape. As the tumor microenvironment dynamically changes, the number, volume, and molomics of platelets change accordingly, suggesting that platelet-related biomarkers have great potential to reflect tumor load evolution. Based on the promoting effect of platelets on the process of tumorigenesis and tumor development, platelets are considered as important targets for tumor biotherapy. Targeted inhibition of platelet function can significantly control tumor progression and improve patient outcomes. In addition, platelets have a strong affinity for tumor tissues. Constructing targeted anti-tumor agents with the idea of platelet-targeting or platelet-mimicking can effectively increase the affinity towards tumor tissues and the biocompatibility of nanodrugs, which is an emerging strategy to improve the efficiency of targeted therapy. This paper focuses on the complex interactions between platelets and tumors, summarizing the mechanisms of action and highlighting platelet-related tumor markers and anti-tumor targeted therapies.

[Key words] platelet; tumor diagnosis; tumor therapy; platelet parameter; targeted therapy
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血小板是从巨核细胞上脱离下来的无核细胞组分,能够参与止血过程,促进血管生成,诱导炎症和免疫反应。在肿瘤微环境中,血小板通过释放的细胞因子、血小板微粒(platelet-derived microparticle,PMP)和表面受体与肿瘤细胞、免疫细胞、血管内皮细胞以及基质成分等相互作用,直接或间接地调控肿瘤的发生发展进程,因此被视为肿瘤诊断和治疗的重要靶点。越来越多的研究证明血小板相关的参数具有成为肿瘤标志物的潜力,使无创、动态、全面地监测病情进展成为可能。在肿瘤治疗方面,除了使用抑制血小板功能的药物直接阻断血小板对肿瘤的促进作用外,研发靶向血小板或血小板功能模拟的抗肿瘤纳米药物有望为肿瘤的精准治疗带来重大突破。

1 肿瘤诱导血小板数量和核酸、蛋白组学的变化

肿瘤诱导血小板数量增多的机制尚未完全阐明。血小板第4因子(platelet factor 4,PF4)能够促进巨核细胞和血小板生成,改变肿瘤微环境进而加速肺癌的生长[1]。有研究[2-3]报道,肿瘤或其他细胞来源的血小板生成素、IL-1、IL-3、IL-6、GM-CSF、G-CSF、bFGF和VEGF等具有诱导巨核细胞分化、促进血小板成熟的能力。此外,在肿瘤微环境中凝血过程异常活跃,血小板的大量消耗使血小板生成素代偿性地增多,诱导造血干细胞迅速分化为巨核细胞,进而补充循环中的血小板储存。

血小板具有蛋白质合成能力,并且能够从巨核细胞、肿瘤细胞和周围环境中获取核酸与蛋白质[4]。在肿瘤微环境的刺激下,血小板的mRNA前体资源、RNA剪接和蛋白质翻译过程均被改变。异常的RNA结合蛋白活性、外显子跳跃和选择性剪接以及改变的血小板更新过程可能是导致血小板剪接RNA变化的原因[4-6]。血小板核酸和蛋白质组学的改变与肿瘤的类型、分期等特征紧密相关,为肿瘤标志物的开发奠定了理论基础。

2 血小板调控肿瘤的发生发展进程

2.1 血小板诱导肿瘤发生

长期的细胞损伤和炎症反应能够诱导肿瘤发生。在肝微环境中,血小板是诱导肝细胞再生、肝纤维化和肝细胞癌变的重要因素。血小板释放的PDGF和5-HT作用于肝星状细胞活化和细胞外基质沉积过程,通过诱导TGF-β生成、激活Wnt/β-catenin通路等机制驱动肝纤维化进程,诱导肿瘤发生。在血小板分泌的VEGF、可溶性CD40配体等因子的作用下,肿瘤血管形成,中性粒细胞、巨噬细胞在内的大量炎症细胞在肝内聚集,进一步促进了肝细胞癌的生长和转移。在乙型肝炎、非酒精性脂肪性肝炎等模型中进行抗血小板治疗能够明显抑制炎症细胞在肝内的积累,有效减缓疾病向肝纤维化和肝细胞癌发展的进程,提示抗血小板治疗在炎症相关的肝癌预防中具有巨大潜力[7-9]。相似地,在结直肠癌的发生发展进程中,肠道损伤部位招募血小板浸润,血小板释放血栓素A_2、前列腺素E_2(prostaglandin E_2,PGE_2)、ADP、IL-1β等介质放大炎症反应,进而诱导有促癌作用的环氧合酶-2(cyclooxygenase 2,COX-2)在基质细胞和内皮细胞中过表达。COX-2通过合成PGE_2、诱导EGFR表达上调增强内皮细胞的抗凋亡能力和侵袭特性[10-11],是血小板诱导结直肠癌过程中的关键因子,使用选择性COX-2抑制剂(COX-2 inhibitor,COXIB)抑制COX-2的作用能明显降低结直肠癌的复发风险。

2.2 血小板促进肿瘤的进展

肿瘤细胞通过直接接触或释放介质的方式诱导血小板活化和聚集。被肿瘤“再教育”的血小板可以通过驱动血管生成、促进肿瘤细胞的侵袭与转移、介导免疫逃逸、诱导化疗药物耐药等途径促进肿瘤发生发展进程。血小板诱导肿瘤血管生成和维持血管内皮完整的作用依赖于血小板和PMP释放出的各种生长因子及miRNA等衍生物质的转移。通过分泌TGF-β和与肿瘤细胞直接接触,血小板激活肿瘤细胞的TGF-β/Smad和NF-κB通路进而驱动上皮间质转化(epithelial-mesenchymal transition,EMT)进程,使肿瘤细胞获得更强的侵袭能力和抗凋亡表型[12-13]。血小板源性的MMP、组胺、5-HT、VEGF、HGF、ATP、血小板活化因子等介质参与水解基底膜和削弱血管内皮屏障的过程[14]。在肿瘤定植阶段,血小板招募白细胞协同构建早期转移微环境,并且上调血管内皮细胞的黏附分子增强肿瘤细胞复合物在血管壁上的停滞和外渗。在肿瘤细胞进入血液循环后,血小板对肿瘤细胞的物理覆盖阻碍了血流剪切力的杀伤与免疫细胞的识别,以保证转移细胞的存活。血小板通过抑制NK细胞和CTL的活化与功能、阻碍DC的分化成熟以及诱导Treg细胞的扩增诱导肿瘤细胞发生免疫逃逸,可以推测血小板的免疫抑制作用会在一定程度上削弱免疫治疗的疗效,这为筛选接受免疫治疗的患者、加强输注血小板制品管理、联合应用多途径抗肿瘤治疗策略提出了更高的要求与挑战。此外,血小板与肿瘤患者的获得性耐药相关。通过驱动EMT、促进DNA修复、抑制细胞凋亡、推动细胞周期进程,血小板能够削弱铂类、紫杉醇、5-FU等化疗药物的细胞毒性效应[15-17]。

3　血小板为肿瘤标志物研究开辟新道路

3.1　血小板相关的参数

血小板计数较易获得。高血小板计数与肺癌、胃癌、结直肠癌、乳腺癌、卵巢癌和胰腺癌等多种恶性肿瘤的不良预后相关[18]。平均血小板体积(mean platelet volume, MPV)和血小板分布宽度(platelet distribution width, PDW)是两个提示血小板活化程度和反应性的重要指标。MPV反映血小板的平均大小。与小血小板相比,大血小板具有更大的表面积和蛋白质含量,普遍认为具有更强的促凝潜能和反应性[19]。肿瘤患者的血小板更新变快,MPV水平因体积较大的年轻血小板生成增多而增高。然而随着炎症和血栓事件诱导大体积血小板的过度耗竭,MPV水平可能较前下降,这种动态变化规律无疑为解读指标的临床价值增加了难度。MPV被期待具有预测肿瘤患者血栓事件风险和生存预后的能力,但尚未得出一致性结论[20-23],需要更多大样本、设计严谨的研究进一步探索。PDW反映血小板体积的分布情况,是血小板活性的替代指标和炎症指标。在乳腺癌、咽喉癌、胆囊癌、食管癌和肝细胞癌的研究中,高PDW与患者的不良预后相关[24-27]。但对于早期结直肠癌、早期胃癌和非小细胞肺癌患者,高PDW可能是患者更好的预后标志[28-30]。

炎症促进肿瘤发生发展,由中性粒细胞、血小板、单核细胞等促炎细胞共同介导。淋巴细胞参与抑制肿瘤进展和免疫调控过程。肿瘤患者常伴有淋巴细胞减少症,反映抗肿瘤免疫效应不足。血小板/淋巴细胞比率(platelet lymphocyte ratio, PLR)是反映炎症的新兴指标,高PLR水平与结直肠癌、肝细胞癌、胃食管癌、卵巢癌、宫颈癌、乳腺癌、非小细胞肺癌和胰腺癌患者的不良预后相关[31-37],但PLR对小细胞肺癌患者生存的预测价值尚存在争议[37-38]。系统免疫炎症指数(systemic immune-inflammation index, SII)是整合中性粒细胞、血小板和淋巴细胞三者作用而产生的新指标,能够综合反映体内的炎症与免疫情况,体现出优于其他炎症指标的预测能力,是提示结直肠癌、胃癌、肝细胞癌、胰腺癌、乳腺癌、妇科肿瘤、泌尿系统肿瘤和肺癌患者不良预后的因素[39-49]。一项在普通社区人群中进行的包括8 024例的前瞻性队列研究[50]揭示,在调整年龄、性别、社会经济水平、吸烟、BMI和糖尿病等潜在混杂因素后,伴有高基线SII的人群患实体瘤的风险增加30%。这种预测能力在随访时间延长时仍然存在。SII具有成为长期预测肿瘤发生风险的独立指标的巨大潜力。将单核细胞计数与SII的乘积定义为泛免疫炎症值(pan-immune-inflammation value, PIV),PIV反映多种免疫细胞表现出的总体作用,被视为预测抗肿瘤治疗效果、监测原发性耐药以及筛选治疗获益人群的重要预测指标。在进行免疫治疗或靶向治疗的乳腺癌、结直肠癌和肺癌患者中,高PIV水平与更差的生存预后相关[51-54]。

肿瘤患者通常伴有恶病质、静脉血栓栓塞症、副肿瘤综合征等并发症,提示用单一指标难以描述肿瘤患者的全身状态。将炎症、免疫以及营养等方面的多种标志物组合,形成具有综合评估能力的评分系统并进行肿瘤学相关研究已成为发掘血液学标志物潜能研究的最新趋势。血红蛋白、白蛋白、淋巴细胞和血小板评分由血小板计数、淋巴细胞计数、血红蛋白和白蛋白四个指标组成,是反映炎症和营养状态的新参数,在关于咽癌、食管癌、非小细胞肺癌、胰腺癌、胃癌、结直肠癌和泌尿系统肿瘤的研究中被认为是廉价的预后标志物[55-63]。肝细胞癌是炎症相关的肿瘤之一,其发生发展受血小板的驱动调节。天冬氨酸氨基转移酶/血小板比率指数(aspartate aminotransferase-platelet ratio index, APRI)最初被用来衡量丙型肝炎患者的肝纤维化和肝硬化情况[64],随后也用于评估乙型肝炎等肝病患者的纤维化程度和发生肝细胞癌的风险。APRI水平升高被认为与肝细胞癌患者的肿瘤复发和较差预后相关[65-67]。在伴有肝转移的结直肠癌患者中,新辅助化疗联合肝病灶切除术可显著改善患者的预后[68],但化疗相关的肝损伤对患者的术后恢复存在负面影响。近期一项研究[69]将APRI和白蛋白-胆红素(albumin-bilirubin, ALBI)分级联合并构建风险分层系统,高危组的患者发生不良临床结局和化疗相关肝损伤事件的比率更高,提示APRI+ALBI组合能通过术前风险分层协助选择手术时机。此外,LEE等[70]报道了血小板-白蛋白-胆红素(platelet-albumin-bilirubin, PALBI)对接受不同类型治疗和不同病因来源的肝细胞癌患者OS的预测价值,证明PALBI对姑息性治疗患者具有更好的预后评估能力,提示PALBI可以作为现有肝功能储备评分模型的补充以提高风险评估系统的预测效力。

3.2　血小板相关的蛋白质和RNA标志物

血小板的蛋白质和核酸谱在肿瘤患者和健康人群中表现不同,在不同分期或类型的肿瘤患者中表现也不同,从中寻找与肿瘤特异性相关的蛋白质和RNA分子进行分析,可以很好地了解肿瘤的进展情况和基因特征。与健康对照组相比,结直肠癌患者体内血小板中的PDGF含量增加60%,VEGF和PF4丰度上升到原来的2倍左右[71]。早期肺癌和胰头癌患者接

受手术治疗后,水平异常的85种血小板蛋白质中有81种恢复正常表达范围,支持血小板的蛋白质组学随肿瘤负荷变化而改变的假设[72];这种潜力在其他肿瘤的相关实验中同样被证实[73-74]。近期有研究[75]报道,非小细胞肺癌细胞通过纤连蛋白、整合素α5β1和血小板膜糖蛋白(glycoprotein,GP)Ⅰbα依赖的方式将PD-L1蛋白转运到血小板表面,认为通过分析血小板的PD-L1表达情况能够推测肿瘤细胞的PD-L1负荷,是预测患者免疫治疗疗效的潜在生物标志物。相似地,应用RNA测序、微阵列分析和qPCR等方法分析血小板的RNA谱,可以寻找提示肿瘤发生发展的特异性RNA序列[76]。这些RNA分子的异常表达对肿瘤的诊断、进展和患者预后具有一定的判断能力。BEST等[77]将RNA测序与具备自我学习能力的算法平台相结合寻找最佳的RNA标志物组合,进一步提高了研究效率。他们分别以96%和71%的准确率从健康人群中分辨出肿瘤患者以及判定6种肿瘤来源。在血小板中还能检测到肿瘤细胞来源的突变分子信息,连续监测相应指标将有助于判断靶向治疗的受益人群、患者预后以及获得性耐药时机[5,78]。与健康对照组相比,肿瘤患者血小板的miRNA和lncRNA谱表现异常,从中选取随肿瘤进展发生特异性变化的RNA与其他生物标志物联合或许可以提高对早期肿瘤的诊断效率[79-80]。

4 血小板相关的靶向抗肿瘤治疗策略

基于血小板促进肿瘤发生发展的作用,直接靶向并抑制血小板功能是可行的肿瘤生物治疗策略。此外,血小板具有对肿瘤组织和血管系统的较强反应性与靶向能力,能够被肿瘤细胞吞噬摄取[81],提示将靶向血小板、血小板仿生思路与纳米药物制备技术联合可以提高抗肿瘤靶向制剂的肿瘤定位能力、生物相容性和局部灌注,被认为是提高抗肿瘤靶向治疗效率的重要研究方向。

4.1 抑制血小板功能药物的应用

阿司匹林是最经典的抗血小板药物之一,能通过不可逆地抑制COX-1、COX-2分别减少下游血栓素A_2和PGE_2的产生,进而削弱血小板聚集过程以及PGE_2的促肿瘤作用。大量临床数据[17,82]报告服用阿司匹林能降低胃肠道、泌尿系统肿瘤及肺癌、乳腺癌等肿瘤的发病率和病死率。然而,阿司匹林控制肿瘤发生与进展的作用机制仍未完全阐明。一些研究[83-84]指出,阿司匹林对抑癌基因、细胞凋亡、炎症代谢以及表观遗传学具有直接调控能力,提示分辨阿司匹林的抗肿瘤作用在多大程度上依赖于血小板抑制,是更好地应用阿司匹林治疗肿瘤的理论基础,长期应用阿司匹林会因COX-1抑制导致血小板聚集持续减少而引发出血事件。COXIB罗非昔布和塞来昔布在结直肠癌、乳腺癌和肺癌等相关研究中显示出了肿瘤控制效应,但是这些药物的心血管毒性阻碍了它们的进一步应用[85]。

血小板表面受体的拮抗剂是另一类抑制血小板功能的药物,主要包括抑制GPⅡb/Ⅲa、P2Y12、GPⅠbα、P-选择素功能的药物。虽然临床前实验证明上述药物能够抑制肿瘤发生或转移,但相关的临床证据尚不充足,并且在应用时需要警惕药物相关的出血并发症。GPⅥ和C型凝集素样受体2是炎症状态下保证血管完整性的关键分子,阻断相应通路均不影响血小板的生成和止血,两者被视为潜在安全的抗肿瘤靶点[86-87]。GPⅥ功能抑制剂revacept通过干扰血小板与肿瘤细胞间GPⅥ-半乳糖凝集素3介导的相互结合,有效地抑制血小板对HT29结直肠癌细胞中COX-2和EMT相关基因表达上调的诱导作用[88]。在另一项研究[89]中,拮抗GPⅥ的作用能够在不影响止血的情况下降低小鼠模型中结直肠癌和乳腺癌细胞的肺转移。靶向GPⅥ和C型凝集素样受体2的血小板功能拮抗药物在临床前实验中显示出减少血栓形成、抑制肿瘤转移、促进肿瘤出血、增加化疗药物疗效的潜力,是改善患者预后和生活质量的理想药物[14,87-90]。此外,PAPA等[91]设计了一种活化、聚集功能缺失的血小板诱饵,通过竞争性地干扰正常血小板与肿瘤细胞间的相互作用抑制肿瘤转移。抑制血小板功能是有前途的靶向抗肿瘤策略,但在临床应用前还应进行进一步的机制探索及临床研究。

4.2 血小板相关的靶向抗肿瘤制剂的研发

4.2.1 以血小板为作用靶点的新型抗肿瘤药物 血小板与肿瘤细胞共定位存在的现象提示,通过靶向GPⅡb/Ⅲa[92]、P-选择素[93]等血小板表面受体,可以将抗肿瘤药物以“搭便车”的方式特异性运送到肿瘤组织或肿瘤微环境中。YAP等[94]首次在体内实验中将GPⅡb/Ⅲa特异性的ScFv与常规造影剂结合,通过靶向活化血小板对肿瘤的分布情况进行了成像检测,提示血小板可以看作是肿瘤细胞的“新型”表面标志物。在此基础上,该团队设计了一种抗体-药物偶联的新型抗肿瘤药物$ScFv_{GP\,II\,b/III\,a}$-MMAE。该药物通过结合GPⅡb/Ⅲa靶向血小板进而定向传递微管抑制药物MMAE杀伤肿瘤细胞,不但降低了化疗药物的毒性作用,而且克服了三阴性乳腺癌因缺少特异性分子靶标而较少受益于靶向抗肿瘤药物的困难[92]。最近开发出的PSN-HSA-PTX-IR780纳米复合物用能够靶向结合血小板表面P-选择素的PSN肽修饰白蛋白颗粒构建给药平台,靶向运送化疗药物紫

杉醇(paclitaxe, PTX)和光敏剂IR780。IR780通过光热疗法诱导局部组织损伤进一步促进血小板募集与活化,纳米颗粒在光疗作用下明显增强了转移性乳腺癌模型中PTX的蓄积[93]。纳米药物和大分子药物可以通过高通透性和滞留(enhanced permeability and retention, EPR)效应选择性地从脉管系统渗出进入肿瘤组织,但仍会受到血管内皮屏障的阻碍。血小板参与维护血管完整,提示共同递送血小板功能抑制药物和抗肿瘤制剂是增加抗肿瘤药物局部灌注的另一种可行策略。MMP-2响应的聚合物-脂质-肽纳米颗粒在肿瘤微环境中高表达的MMP-2的刺激下释放血小板耗竭抗体R300和化疗药物多柔比星,在不引起出血并发症的情况下增加血管内皮通透性,增强EPR效应,进而提高多柔比星的肿瘤杀伤效率[95]。CAO等[96]将上述两种策略结合构建肿瘤靶向制剂,该团队设计的复合药物以能被MMP-2分解的明胶壳包裹,用能够特异性结合血小板表面蛋白P-选择素的TM33肽修饰,内部承载以浓度依赖性效应抑制胶原和ADP介导的血小板活化的丹参酮ⅡA药物。纳米药物通过靶向P-选择素黏附到活化的血小板表面,在MMP-2的作用下局部释放大量丹参酮ⅡA药物抑制血小板的活化、黏附和聚集活动,扩大内皮缝隙,增加药物在肿瘤组织的渗透。将新型制剂与伊文思蓝和两种不同尺寸的纳米药物分别进行共处理试验,三种分子药物的肿瘤渗透率分别增加3.2、4.0和11.2倍,药物向正常组织的递送未见明显增加,治疗诱导的内皮破坏能够可逆性恢复,提示这种辅助抗肿瘤制剂具有较大的转化潜力。

4.2.2　构建模拟血小板功能的抗肿瘤靶向药物　构建模拟血小板功能的抗肿瘤靶向药物的策略主要包括血小板膜蛋白模拟、血小板膜涂层和血小板工程化等思路。进行“血小板伪装”的新型纳米复合物具有类似血小板的生物学行为,可以增加靶向药物在体内的停留时间和肿瘤摄取量。血小板膜蛋白模拟指在纳米药物表面添加具有血小板膜蛋白功能的物质使靶向制剂具有类似血小板的行为特性。PAN等[97]用两种分别结合GPⅡb/Ⅲa和P-选择素的肽修饰脂质体并装载多柔比星,发现药物复合物具有类似血小板的靶向特性,显著增强对乳腺癌MDA-MB-231细胞的特异性识别能力。用血小板膜覆盖药物表面能使纳米材料不被免疫系统清除,同时使药物对肿瘤和血管组织具有更强的亲和能力。这种设计思路可以同时将多种药物成分靶向运送到肿瘤组织,将化疗与铁死亡[98]、钙超载[99]、线粒体诱导细胞凋亡[100]、光疗[101-102]、放疗[103]和免疫治疗[104]等多种策略联合协同杀伤肿瘤细胞,被视为肿瘤治疗领域新的研究热点。驱动多种药理途径进行抗肿瘤治疗可能有助于减少药物剂量和不良反应,克服肿瘤耐药性,重塑肿瘤微环境以及延长不可切除肿瘤患者的生存时间。例如,用血小板膜包裹二甲双胍和光敏剂IR780构建的纳米药物具有更好的肿瘤靶向性和循环稳定性,内部包含的两种药物能够抑制线粒体呼吸,降低肿瘤的氧气消耗进而改善肿瘤微环境中的缺氧状态,激活并增强光动力效应,逆转抑制性的免疫微环境,杀伤原位和转移部位的肿瘤细胞[101]。索拉非尼和雷公藤甲素的联合疗法可以增强对肝细胞癌的杀伤。由于两者存在生物分布和药代动力学差异,无法控制肿瘤组织中的两药比例。近期一项研究用血小板-肿瘤细胞杂化膜包裹的纳米粒子以10∶1的摩尔比例靶向运送索拉非尼和雷公藤甲素,在减少药物毒性的同时增强对肿瘤细胞的杀伤作用,达到较好的“协同减毒效应”[105]。血小板对运载的药物耐受性好,具有较大的细胞表面积和药物装载量,是构建载药系统的优秀原料。血小板工程化包括将血小板进行药物填充、表面修饰和基因编辑处理。RAO等[106]运用电穿孔方法使血小板装载金纳米棒,该系统能通过反馈性行为增强光热疗法的疗效,抑制头颈部鳞状细胞癌的生长。LI等[107]将肿瘤血管破坏药物vadimezan与共价连接抗PD-L1抗体的工程化血小板结合制造靶向颗粒,通过诱导肿瘤的出血性坏死和驱动血小板募集,以进一步增强免疫检查点抑制剂介导的免疫激活反应和肿瘤杀伤效应,提出了肿瘤生物治疗的新思路。将结合抗PD-L1抗体的血小板与CAR-T细胞疗法相互联合能够通过阻碍T细胞衰竭增强抗肿瘤效应,在黑色素瘤小鼠模型中显示出抑制局部肿瘤复发和远处肿瘤生长的能力[108]。ZHANG等[109]对巨核细胞进行基因编辑以获得表达PD-1和携带环磷酰胺的血小板,这种工程化血小板可以聚集到不完全切除的B16F10黑色素瘤模型的手术切口,通过排斥Treg细胞与防止$CD8^+$ T细胞耗竭阻止肿瘤复发,改善患者的生存。

4.2.3　新型抗肿瘤靶向药物应用的挑战　虽然血小板相关的靶向药物显示出了精准杀伤肿瘤细胞的巨大潜力,但将研究结果进行临床转化仍存在许多困难。首先,血小板在存储时容易发生活化聚集,需要深入探究模拟血小板功能的抗肿瘤靶向药物的药代动力学和理化性质,以保证药物的生产规范与质量稳定;其次,为了推进临床转化进程,应尽量优化提取、分离、提纯、合成技术,简化载药系统的制造难度,充分考虑制备过程中的经济和时间成本;最后,合成的靶向制剂不除外存在未知的长期毒性,需进一步探究纳米药物的生物安全性。

5 结 语

肿瘤细胞和血小板之间存在着复杂的相互作用。一方面,肿瘤与周围环境改变血小板的数量、体积、分子组学和细胞行为,另一方面,血小板和PMP通过构建炎症环境、促进血管生成、介导免疫逃逸和调控信号通路影响肿瘤的发生和进展。血小板同样具有抑制肿瘤细胞增殖的效应[110-111],提示需要结合肿瘤类型、疾病阶段、局部微环境等因素对血小板作用进行综合分析。基于肿瘤细胞和血小板之间的双向作用,血小板被视为肿瘤诊断和治疗方面的潜力巨大的新兴靶点。将血小板相关的标志物与其他肿瘤标志物联合应用,能够完善现有的肿瘤诊断和预后评价体系,具有肿瘤筛查、病情监测和预后判断的巨大潜力。靶向抑制血小板功能是可行的抗肿瘤治疗策略。在构建抗肿瘤纳米药物方面,血小板具有较好的生物相容性、肿瘤靶向性、安全性和载药能力。血小板模拟的靶向制剂使应用化疗、光疗、放疗、钙超载等方法协同杀伤肿瘤细胞成为可能。在临床转化过程中,必须关注血小板相关抗肿瘤药物的出血和脱靶效应等不良反应的风险。想要使肿瘤患者获得最大受益,需要进一步探究血小板与肿瘤间相互作用的分子机制。血小板相关的肿瘤标志物和抗肿瘤靶向药物在肿瘤诊治方面具有广阔的前景,有望为肿瘤的精准治疗带来重大突破。

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