

血小板-白细胞聚集体及其在川崎病发病中的研究进展

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[摘要] 活化的血小板会与单核细胞、中性粒细胞、树突状细胞和淋巴细胞等各类白细胞相互作用, 触发细胞间信号转导, 从而导致血栓形成和炎症介质的合成。已在多种血栓性疾病和炎症性疾病中发现血液中血小板-白细胞聚集体水平升高, 该文综述了最新文献, 探讨血小板-白细胞聚集体形成机制、作用、检测方法及其在川崎病发病中的相关作用, 为川崎病发病机制的研究提供了新思路。

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[关键词] 川崎病; 血小板-白细胞聚集体; 抗血小板药物; 冠状动脉扩张

Recent research on platelet-leukocyte aggregates and their role in the pathogenesis of Kawasaki disease

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Abstract: Activated platelets may interact with various types of leukocytes such as monocytes, neutrophils, dendritic cells, and lymphocytes, trigger intercellular signal transduction, and thus lead to thrombosis and synthesis of massive inflammatory mediators. Elevated levels of circulating platelet-leukocyte aggregates have been found in patients with thrombotic or inflammatory diseases. This article reviews the latest research on the formation, function, and detection methods of platelet-leukocyte aggregates and their role in the onset of Kawasaki disease, so as to provide new ideas for studying the pathogenesis of Kawasaki disease.

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Key words: Kawasaki disease; Platelet-leukocyte aggregate; Antiplatelet agent; Coronary artery ectasia

血小板是源自巨核细胞系的无核细胞, 长期以来一直被认为仅负责凝血和纤溶过程。然而, 最近数据表明血小板也是炎症反应中的效应细胞, 是免疫应答的重要组成部分^[1]。血小板储存和释放多种生物活性物质, 如生长因子、细胞因子和趋化因子等, 影响免疫系统的各个组成部分, 从而调节免疫应答和炎症反应。当感染或创伤后, 血小板与活化的内皮细胞相互作用, 进而导致血小板活化^[2], 该过程导致血小板的形状从光滑的椭圆形变为多刺的球形^[3], 功能也随之发生变化, 开始分泌各种生物活性物质, 最终演化为不可逆的活化状态。活化的血小板会与各类白细胞相互作用, 触发细胞间信号

转导, 导致血栓形成和炎症介质的合成^[4]。在多种血栓性疾病和炎症性疾病中发现血液中血小板-白细胞聚集体 (platelet leukocyte aggregates, PLAs) 水平升高^[5-6]。血液循环或局部炎症部位的 PLAs 被认为可能是多种血栓、炎症性疾病的标志物, 可用于评估血栓形成风险和疾病进展情况^[7]。PLAs 在心血管疾病中同样具有重要意义^[8], 已有研究表明川崎病 (Kawasaki disease, KD) 患者中 PLAs 水平显著升高。该文综述了最新文献, 探讨血小板-白细胞聚集体形成机制、作用、检测方法及其在 KD 发病中的相关作用, 为 KD 发病机制的研究提供新的思路。

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1 PLAs 的形成

血小板活化是 PLAs 形成的先决条件，血小板-白细胞的初始结合由血小板 P-选择素（又称 CD62P）和白细胞 P-选择素糖蛋白配体 1（P-selectin glycoprotein ligand-1, PSGL-1）介导（图 1）^[9]。CD62P 是一种黏附分子，血小板是其来源，CD62P 最初位于血小板 α 颗粒膜上，当血小板活化后 CD62P 在血小板质膜上表达，随后 CD62P 通过 PSGL-1 交联血小板和白细胞，而 PSGL-1 在中性粒细胞、单核细胞、树突状细胞、淋巴细胞和内皮细胞的表面表达^[10]。除了与 PSGL-1 结合，CD62P 还能与 S 位点受体激酶（S-locus receptor

kinase, SRK）家族的酪氨酸激酶、磷脂酰肌醇 3 激酶、肌动蛋白和细胞骨架蛋白分子级联激活白细胞，最终诱导 $\beta 2$ 整合素巨噬细胞分化抗原-1（macrophage-1 antigen, Mac-1）的活化^[11]。Mac-1 则进一步与血小板糖蛋白（glycoprotein, GP）I b α （GP I b α ）、血小板 GP II b/III a 相互作用^[12]，后者介导白细胞和血小板之间的相互作用^[13]。当血小板活化后，白细胞分化抗原 40 配体（cluster of differentiation 40 ligand, CD40L）转移到血小板表面，与内皮细胞、单核细胞上白细胞分化抗原 40（cluster of differentiation 40, CD40）作用，从而促进血小板与白细胞的相互作用^[14]。

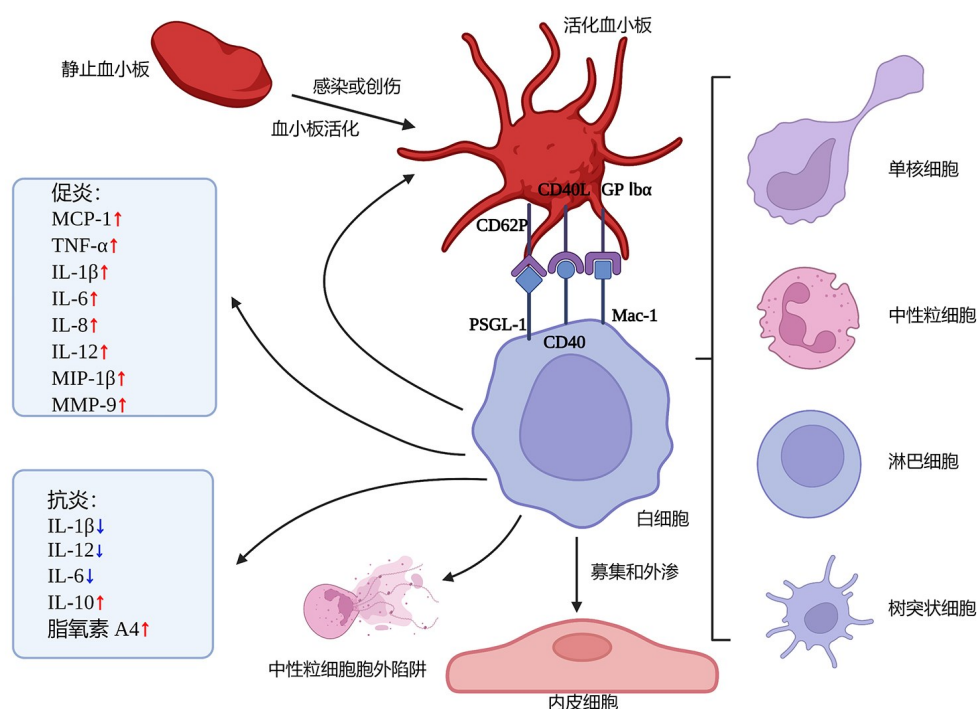


图 1 血小板-白细胞聚集体的形成与作用 [MCP-1] 单核细胞趋化蛋白 1; [TNF- α] 肿瘤坏死因子 α ; [IL] 白细胞介素; [MIP-1 β] 巨噬细胞炎症蛋白 1 β ; [MMP-9] 基质金属蛋白酶 9; [CD62P] P-选择素; [PSGL-1] P-选择素糖蛋白配体 1; [CD40L] 白细胞分化抗原 40 配体; [CD40] 白细胞分化抗原 40; [GP I b α] 糖蛋白 I b α ; [Mac-1] 巨噬细胞分化抗原-1。↑代表升高，↓代表下降。

2 PLAs 的作用

血小板和白细胞的直接相互作用可导致可溶性介质的靶向释放和血小板-白细胞的相互激活^[15]。PLAs 在血栓形成中起重要作用^[16]，其可能通过增加组织因子表达导致纤维蛋白沉积^[17]。血小板-白细胞相互作用促进白细胞募集和外渗至炎症部位^[18]，促进白细胞释放促炎介质、活性氧爆

发、吞噬作用、释放中性粒细胞胞外陷阱（neutrophil extracellular trap, NET）^[19-21]，同时还可以在在某些病理条件下抑制炎症^[1, 22]。在动脉粥样硬化中，血小板与中性粒细胞、单核细胞和树突状细胞的相互作用促进白细胞外渗和泡沫细胞形成，从而加速了动脉粥样硬化的形成。白细胞反过来也可调节血小板，导致血小板破坏增强或产生增加^[23-24]。

PLAs可诱导多种促炎因子表达增加^[25-26],如单核细胞趋化蛋白1、肿瘤坏死因子 α (tumor necrosis factor- α , TNF- α)、白细胞介素 (interleukin, IL)-1 β 、IL-6、IL-8、IL-12、巨噬细胞炎症蛋白1 β 、干扰素 α 等。然而,PLAs还具有负反馈机制,抑制局部炎症^[27]。血小板与单核细胞的相互作用会推动单核细胞向抗炎表型发展,降低促炎因子IL-1 β 、IL-12和IL-6水平,提高IL-10水平^[28]。而血小板与中性粒细胞的相互作用也可导致抗炎作用,PLAs促进脂氧素A4的产生,从而下调中性粒细胞的黏附和渗出^[29]。

3 PLAs的分类

不同的白细胞亚群可以与血小板相互作用形成PLAs,从而产生各种作用^[30]。由于血小板CD62P对不同类型白细胞PSGL-1的亲合力不同^[31],血小板优先结合单核细胞,而与淋巴细胞的亲合力最低。

3.1 血小板-中性粒细胞聚集体

中性粒细胞上的PSGL-1或Mac-1与血小板CD62P的结合会引发中性粒细胞向内皮迁移,通过CD40与血小板衍生的可溶性CD40L结合形成血小板-中性粒细胞聚集体 (platelet neutrophil aggregates, PNAs),是血管内迁移的先决条件^[26]。血小板进一步参与NET的形成,Toll样受体4激活的血小板与中性粒细胞结合,黏附在内皮细胞上,启动了NET形成^[32],导致释放中性粒细胞DNA,从而诱捕细菌。此外,PNAs会导致中性粒细胞脱颗粒和释放IL-1 β 、IL-8、基质金属蛋白酶9 (matrix metalloproteinase-9, MMP-9),还能促进脂多糖诱导的急性肺损伤小鼠模型中髓过氧化物酶的形成^[29],但Cleary等^[33]发现小鼠吸入脂多糖后,阻断PSGL-1、CD62P或耗尽血液中性粒细胞并不能影响肺部血小板的募集。

3.2 血小板-单核细胞聚集体

循环单核细胞根据其CD14和CD16表达可分为3个亚组:(1)经典单核细胞(CD14⁺CD16⁻),高表达与吞噬作用相关的基因并产生活性氧;(2)非经典单核细胞(CD14⁺CD16⁺),在血管巡逻和监视中发挥作用并参与自身免疫性疾病;(3)中间单核细胞(CD14⁺CD16⁺),不仅释放促炎的IL-1 β 和TNF- α ,也和抗炎因子IL-10的产生有关^[34]。血小板优先与CD16⁺单核细胞结合,可能诱

导经典单核细胞向中间单核细胞转换,Hottz等^[35]发现新型冠状病毒感染的危重患者中血小板-单核细胞聚集体 (platelet monocyte aggregates, PMAs)形成增加,同时确定了高CD16和低人类白细胞DR抗原表达的炎性单核细胞亚组与血小板相互作用。

3.3 其他PLAs

血小板和淋巴细胞相互作用的报道相对较少。血小板-淋巴细胞相互作用参与T细胞表型极化,如辅助性T细胞1^[4]和调节性T细胞^[36]。CD62P和淋巴细胞PSGL-1结合可导致CD11a聚集,通过与细胞间黏附分子1结合增强白细胞黏附,支持淋巴细胞向外周淋巴结高内皮小静脉的归巢^[29]。CD40与CD40L相互作用是血小板诱导的适应性免疫反应的重要介质,CD40在成熟B细胞、部分辅助性T细胞和细胞毒性T淋巴细胞上表达^[37]。通过CD40L,血小板可以直接诱导B细胞产生抗体并介导生发中心的形成。

血小板与树突状细胞通过CD62P/PSGL-1及随后的Mac-1相互聚集,启动单核细胞的交叉呈递和树突状细胞分化^[38]。和血小板与其他白细胞亚群的作用类似,血小板也可以减少树突状细胞的活化,如血小板能够抑制树突状细胞的促炎特性,甚至可能诱导其抗炎表型,从而降低对T细胞的启动能力^[39]。

4 PLAs的检测方法

目前流式细胞术和显微镜技术是检测PLAs的主要手段^[7]。这些技术相互补充,不仅用于研究PLAs对白细胞亚群和分子的影响,还可以明确其在组织中的位置、相互作用及功能的动态变化。

4.1 流式细胞术

流式细胞术是检测PLAs的首选方法,它是一种快速且灵敏的技术,可以同时分析同一样本中的血小板活化和PLAs的形成^[40],并可对稀有白细胞亚群进行评估。对于基本的PLAs分析,只需要标记血小板特异性抗体和泛白细胞特异性抗体^[41],前向散射光和侧向散射光可以基本区分中性粒细胞、单核细胞和淋巴细胞。当需要更准确地区分各白细胞亚群时,常需加入特异性抗体^[7],如CD66b (人)或Ly6G (小鼠)标记中性粒细胞,CD14、CD16、CD64 (人)或CD115、Ly6C (小鼠)标记单核细胞,CD3、CD4、CD8 (小鼠和人)

标记T细胞, CD19(人)或CD19、B220(小鼠)标记B细胞, CD56(人)或NK1.1(小鼠)标记NK细胞。

4.2 显微镜技术测量组织内的静态和动态PLAs

对冷冻或石蜡包埋的组织切片行组织化学和免疫荧光检测可提供有关血小板募集和PLAs在众多组织器官微环境中的位置信息^[7]。当与共聚焦或电子显微镜相结合时, 可提供高分辨率的图像以定位PLAs的位置。然而, 组织切片只能提供静态终点分析, 并不能完全模拟复杂的动态行为。随着体内成像技术(如活体显微镜)的发展, 现在可以长时间追踪活体动物体内不同器官中的细胞^[7, 42], 这有利于分析血小板和白细胞之间动态的相互作用, 如持续时间和行为变化^[43]。

4.3 微流控检测

微流控检测是另一种基于显微镜的实时研究血小板-白细胞相互作用的方法^[44]。分离的细胞或全血通过涂有固定化蛋白质或细胞的腔室进行灌注, 从而可以精确控制细胞输入。类似于活体免疫荧光成像, PLAs可以通过细胞跟踪器或特异性抗体实现可视化。微流控检测虽然不如体内成像技术那么接近生理, 但当条件明确的情况下, 它能够低成本地实时分析血小板-白细胞的相互作用。

5 抗血小板药物对PLAs的影响

常用的抗血小板治疗包括环氧化酶(cyclooxygenase, COX)抑制剂阿司匹林和二磷酸腺苷受体P2Y₁₂抑制剂如氯吡格雷、普拉格雷和替格瑞洛等。阿司匹林和P2Y₁₂抑制剂均能减弱血小板与白细胞的相互作用, 不仅影响血小板聚集和血栓形成, 还能调节白细胞募集和效应功能, 使抗血小板药物能够作用于多种疾病^[45-46]。

5.1 阿司匹林

阿司匹林通过抑制COX-1和COX-2来阻止前列腺素的合成, 从而抑制血小板生成血栓素A₂(thromboxane A₂, TxA₂), 而TxA₂是血小板活化的重要介质^[47]。低剂量阿司匹林可大幅减弱血小板中的COX-1酶活性^[48], 而高剂量阿司匹林通过干扰其他细胞中构建型COX-1和诱导型COX-2的表达发挥抗炎作用^[49]。抑制TxA₂合成会阻断CD40L释放, 从而减少血小板诱导的活性氧生成和趋化因子CXCL7释放, 以及血小板介导的单核细

胞和中性粒细胞的活化、募集、黏附和渗出^[29, 50]。

5.2 P2Y₁₂抑制剂

在血小板活化过程中, P2Y₁₂信号是其中一个重要的自分泌和旁分泌反馈回路, 在血小板活化放大中具有核心作用^[51]。氯吡格雷可提高内皮一氧化氮的生物利用度并抑制血小板活化、血小板脱颗粒、PLAs形成、炎症细胞因子和组织因子的表达, 在内毒素血症中发挥重要作用^[52]。与阿司匹林相比, 氯吡格雷在减少动脉粥样硬化性血管疾病中PLAs的形成方面更有效^[53]。有研究显示, 在接受经皮冠状动脉介入治疗的患者中, 普拉格雷对降低二磷酸腺苷刺激的血小板-白细胞的相互作用强于氯吡格雷^[54]。替格瑞洛是一类新型抗血小板药物, 可有效抑制血小板P2Y₁₂受体, 并通过抑制平衡型核苷转运体1抑制细胞对腺苷的摄取^[55]。由于替格瑞洛对血小板P2Y₁₂受体和平衡型核苷转运体1的双重抑制, 替格瑞洛对炎症的影响可能是复杂的。在肺炎患者中, 替格瑞洛减少了PLAs的形成及IL-6的表达, 接受替格瑞洛治疗后, 患者肺功能获得了改善, 降低了氧依赖^[56]。

6 KD中PLAs的作用

KD患儿常常表现为血小板增多, 体内血小板活化, 表现出异型黏附性, 可与白细胞、红细胞聚集, 多个临床研究发现血小板增多、活化患者更易合并冠状动脉损伤^[57-58]。KD中循环因子诱导血小板聚集和5-羟色胺释放, 导致血小板增多, 而血小板衍生的血管活性物质会增加血管通透性并促进免疫复合物在组织中的进一步沉积, 其中血小板衍生微粒可能会直接刺激中性粒细胞、单核细胞和血管内皮细胞, 从而导致组织因子的表达并增加血栓形成的风险。使用阿司匹林后KD患者的血小板衍生微粒水平显著下降, 当停用阿司匹林后其水平会再次上升^[57]。

目前PLAs在KD发病中的研究较少, 仅有几个单中心临床研究报告了PLAs可能与KD及其冠状动脉损伤有关。Ueno等^[59]研究了KD患者中PNAs水平, 发现KD患儿中PNAs水平明显高于细菌感染患者和正常志愿者, 且冠状动脉异常患者的PNAs水平显著高于无冠状动脉异常者, 同时发现与单独使用静脉注射免疫球蛋白(intravenous immunoglobulin, IVIG)治疗相比, 接受IVIG联合泼尼松龙治疗的患者PNAs显著降低。Vignesh

等^[60]研究了KD患者中PMAs水平,发现与同年龄同性别的发热和健康对照组相比,KD儿童队列中PMAs比例显著升高。KD中PLAs增高的机制尚不明确,据推测当血小板活化后其表面CD62P表达升高,与白细胞上的PSGL-1结合导致PLAs的初始聚集,其后通过CD40L/CD40、Mac-1/GP I b α 等相互作用,导致PLAs的进一步增加。PLAs形成后介导TNF- α 、IL-6、MMP-9等介质的靶向释放和白细胞-血小板的相互激活,白细胞大量迁移并在血管内皮细胞中聚集,进一步导致KD患者的冠状动脉扩张。已有研究表明,KD患儿CD62P的表达升高^[58]。Arora等^[57]研究发现,与正常人相比,KD患儿的可溶性CD40L水平较高。

7 抗血小板药物在KD中的应用

抗血小板药物在KD治疗期间占据极其重要的作用,荟萃分析表明IVIG联合阿司匹林能最大程度地防止KD后发生冠状动脉异常^[61],但大剂量阿司匹林在冠状动脉保护方面并不优于低剂量阿司匹林^[62],甚至最近的一项大型荟萃分析发现急性期应用低剂量阿司匹林的患者较大剂量阿司匹林,冠状动脉损伤概率更低^[63]。目前对中型及以上冠状动脉瘤(Z值 ≥ 5),建议应用阿司匹林联合氯吡格雷等抗血小板,多项研究已证实氯吡格雷联合阿司匹林对KD合并冠状动脉瘤患儿的抗血栓治疗安全有效^[64-65]。Zhang等^[66]报道了在阿司匹林基础上加用氯吡格雷能更有效地降低炎症因子IL-2受体和IL-10,并建议在血小板持续升高时应更早加用氯吡格雷。成人中应用氯吡格雷存在部分抵抗现象,北京的一项前瞻性单中心研究证实了携带CYP2C19功能缺失等位基因、低水平高密度脂蛋白和高水平低密度脂蛋白是我国KD患儿氯吡格雷抵抗的独立危险因素^[67]。

8 小结

近来研究表明,血小板不仅在止血、血栓形成中起作用,其在炎症和免疫应答中也发挥了重要作用,通过与白细胞的相互作用,血小板可以重新编程免疫网络,在多种疾病中调节炎症和免疫反应,包括KD。已有少量研究表明KD中存在血小板活化及PLAs的形成,但鉴于PLAs作用的复杂性,后续仍需更多的研究,以明确PLAs在KD发病及其冠状动脉损伤中的具体作用,这可能成

为KD研究的新方向。

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