血小板活化在川崎病中的研究进展

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【摘要】川崎病易导致儿童冠状动脉损伤。虽然该病至今原因不明,但近年研究表明血小板活化参与了川崎病的病理过程。现就血小板活化在川崎病中的研究进展做一综述。

【关键词】川崎病;血小板活化;冠状动脉损伤
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Platelet Activation in Pathogenesis of Kawasaki Disease

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【**Abstract**】Kawasaki disease is often complicated by coronary artery lesion in children. Its etiology is still unknown, but recent studies suggest that platelet activation is involved in the pathological process of Kawasaki disease. This article summarizes the research progress of platelet activation in the pathogenesis of Kawasaki disease.

【**Key words**】Kawasaki disease; Platelet activation; Coronary artery lesion

川崎病(Kawasaki disease, KD)是一种急性发热性全身血管炎,多发生于 5 岁以下儿童,主要累及中小动脉,尤其是冠状动脉。虽然 KD 具体机制尚未完全明确,但近年研究表明血小板活化参与 KD 的病理过程。血小板活化可通过多种作用机制参与凝血、血管修复、炎症和免疫反应等过程,引起 KD 时血管内皮组织损害,进而大大增加冠状动脉损伤的发生风险,随着对其活化过程及产物的深入研究,有望发现 KD 药物治疗新靶点以及诊断或病情判断标志物。现就血小板活化在 KD 的研究进展做一综述。

1　血小板活化与冠状动脉损伤

KD 急性期,强烈的炎症反应导致内皮损伤,内皮下胶原暴露并与血小板接触,血小板得以活化[1]。损伤部位聚集的单核细胞可通过产生组织因子促进凝血酶生成而激活血小板。活化后的血小板由圆盘状变为致密的球体,树突延伸,以利于其在损伤部位的沉积。血小板活化过程包括黏附、聚集和释放等步骤,参与或促进 KD 患者冠状动脉血栓形成、闭塞、硬化以及狭窄。炎症与血小板活化密不可分,血管炎症反应导致血小板活化,而血小板活化后其产物又可介导或参与炎症反应过程,从而导致 KD 冠状动脉扩张、动脉瘤甚至疾病后期冠状动脉粥样硬化的发生发展[2-4]。总之,血小板活化在 KD 血管损伤中起着重要作用,是 KD 致冠状动脉损伤的病理基础[5]。

2　血小板活化的相关物质变化

2.1　血小板衍生微粒合成

KD 急性期,血小板活化反应刺激血小板浆膜释放大量血小板衍生微粒(platelet-derived microparticles, PDMPs)[3,6]。PDMPs 表面膜及磷脂结构又可进一步刺激血小板活化。PDMPs 表面表达的 P 选择素和磷脂酰丝氨酸为凝血酶形成提供了结合位点,为血小板的黏附提供底物,是凝血和血小板活化过程中的重要因素[7]。PDMPs 还可通过内源性环氧合酶将来源于内皮细胞的花生四烯酸转化为血栓素 A_2,从而参与 KD 患者内皮细胞活化和炎症放大过程[8-9]。PDMPs 表面携带 PF4、PAF 和 CD40/CD40L 等因子,且与 KD 急性期白介素(IL)-6 和 C 反应蛋白等炎症因子正相关[10-11]。PDMPs 还可与单核细胞相互作用,释放黏附分子、趋化因子及炎症介质(IL-1β、IL-7 和 IL-11),这些物质都在 KD 炎症反应过程中起着重要作用[6-7]。这表明 PDMPs 与 KD 急性期炎症反应密切相关,PDMPs 可作为监测 KD 血小板活化和炎症反应的新

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指标。有研究报道抗血小板治疗可显著降低 PDMPs 水平,但部分 KD 患者使用抗血小板药物 2~3 个月停药后 PDMPs 水平反弹性升高,且持续时间不同[12]。这表明血小板活化可能持续很长时间,且每个 KD 患者血小板活化的持续时间可能是不同的,停止抗血小板治疗的时间应该由每个患者血小板活化各自动态决定,而 PDMPs 有望成为 KD 患者个性化治疗方案的监测指标。

2.2 CD62p 释放

CD62p 亦称 P 选择素,是一种颗粒膜糖蛋白,可作为反映血小板活化和功能的指标[13]。血小板活化时,CD62p 在血小板表面大量分泌并介导血小板与其他细胞的作用[14],如其可与白细胞上的 P 选择素糖蛋白配体-1 结合,使白细胞的黏附作用增加,以发挥促炎作用[15]。血小板通过 CD62p 与 P 选择素糖蛋白配体-1 相互作用的方式调节白细胞的募集,从而达到调控血小板与白细胞结合的效果[4]。CD62p 可通过参与肌成纤维细胞的产生过程,诱导心肌纤维化[16]。CD62p 可发挥促凝活性[17-18],对 KD 血栓形成发挥重要作用。CD62p 诱导白细胞黏附并进入血管内膜,通过激活单核细胞分泌趋化因子引起血管平滑肌细胞的增殖[19],促进细胞外基质在血管损伤处的聚集,进而促进动脉粥样硬化的发生。有研究显示,在小鼠模型中,CD62p 的缺乏可延迟或减少小鼠动脉粥样硬化病变的形成[20],这进一步表明 CD62p 参与动脉粥样硬化病变的发生和进展。因此,抑制 CD62p 或阻止血小板活化的药物可能成为减少 KD 后期动脉粥样硬化病变发生和预防急性心血管事件的重要措施。

2.3 胱冬肽酶原激活物 1 合成

胱冬肽酶原激活物 1(procaspase activating compound-1,PAC-1)是一种单克隆抗体,可识别 GPⅡb/Ⅲa 复合物在活化血小板上的构象变化。血小板活化时,PAC-1 与纤维蛋白原的亲和力迅速增加,并介导血小板的聚集[21]。PAC-1 的形成是血小板活化过程的关键步骤,亦是各种途径引起血小板聚集的最终通路[22]。近年研究表明 PAC-1 可通过抑制血管内皮生长因子/血管内皮生长因子受体(VEGF/VEGFR)通路来调控血管形成和再生[23]。血管内皮生长因子信号通路在调节血管生成中起着至关重要的作用,其中最重要的 VEGFR2 可通过激活局部黏着斑激酶和丝氨酸/苏氨酸激酶等多种细胞信号中间体来介导 VEGF 信号通路[24]。VEGF/VEGFR 通路激活可促进内皮细胞的生长,促进新生血管的形成[25]。而 PAC-1 通过抑制 VEGFR2 激酶的活性来抑制 VEGF/VEGFR 通路的激活,从而负向调控血管的形成,参与冠状动脉病变发生过程。因此监测血小板 PAC-1 表达水平有助于评估 KD 患儿病程的进展,预测冠状动脉损害。

2.4 血小板 Toll 样受体 4 通路激活

血小板上表达的 Toll 样受体家族(Toll-like-receptor,TLRs)是病原体相关的识别受体,是对外来生物启动天然免疫反应的关键调节因子。在 KD 的急性期,TLR4 活性上调,识别炎症信号,触发血小板功能反应[26]。细胞外信号调节激酶,磷酸肌醇特异性磷脂酶 C 通过 TLR4 经典信号传导途径活化血小板,介导趋化因子,如调节正常 T 细胞表达和分泌的活化因子(regulated upon activation normal T cell expressed and secreted factor,RANTES)的聚集和释放[27]。RANTES 参与白细胞趋化和单核细胞向血管壁的募集过程,最终导致动脉粥样硬化的发生[28]。另一方面,TLR4 可诱导核因子 κB(NF-κB)活化,这也是其在血小板活化中最为重要的作用之一[29-30]。NF-κB 是炎症和血栓反应的重要调节因子,可通过非基因组的方式调节动脉粥样硬化的形成[31]。在 KD 急性期,TLR4 通过髓样分化因子(MyD88)依赖的信号途径,与其形成受体复合物并激活 NF-κB,引起促炎因子的合成和释放,继而导致血管炎性损伤[32-33]。

2.5 血小板 miR-223 异常表达

微小 RNA(microRNA,miRNA)是一种调节基因表达的非编码小 RNA,miRNA 通过调控关键信号分子影响血管平滑肌细胞的增殖、迁移和凋亡[34]。miR-223 作为血小板内表达幅度最高的 miRNA,在血小板活化时显著表达并转移至血管平滑肌细胞中[35]。miR-223 通过抑制血小板衍生生长因子受体 β 的表达抑制血管平滑肌细胞去分化,从而抑制动脉粥样硬化和动脉瘤的发展过程[36]。近年来发现 miR-223 的异常表达与 KD 密切相关[37-38],与轻微或无冠状动脉病变的 KD 患者相比较,具有显著冠状动脉病变的 KD 患者血小板中的 miR-223 值明显减低。在 miR-223 基因敲除的小鼠中,冠状动脉病变的发生概率显著增加,而无论给予小鼠 miR-223 模拟物还是带有 miR-223 的血小板,都能显著减轻冠状动脉病变的进展[39]。说明 miR-223 表达与 KD 冠状动脉病变严重程度负相关,miR-223 可能对 KD 中冠状动脉病变的形成具有保护作用,可作为判断 KD 冠状动脉损伤严重程度的指标,有成为 KD 冠状动脉病变治疗靶点的可能。

3 展望

虽然已发现活化的血小板可通过多种途径同时参与 KD 的血管病理损害、组织改变,并释放出有关活性物质,仍需进一步深入研究血小板活化在 KD 病程中的具体作用机制,探索 KD 早期诊断、预后的新型标志

物以及新的治疗药物作用靶点，将对减少 KD 患儿心血管病变的发生具有重要的意义。

参 考 文 献

[1] Freedman JE. Molecular regulation of platelet-dependent thrombosis[J]. Circulation, 2005, 112(17): 2725-2734.

[2] Levi M, van der Poll T, Büller HR. Bidirectional relation between inflammation and coagulation[J]. Circulation, 2004, 109(22): 2698-2704.

[3] Tamir A, Sorrentino S, Motahedeh S, et al. The macromolecular architecture of platelet-derived microparticles[J]. J Struct Biol, 2016, 193(3): 181-187.

[4] Rossaint J, Margraf A, Zarbock A. Role of platelets in leukocyte recruitment and resolution of inflammation[J]. Front Immunol, 2018, 9: 2712.

[5] McCrindle BW, Rowley AH, Newburger JW, et al. Diagnosis, treatment, and long-term management of Kawasaki disease: a scientific statement for health professionals from the American Heart Association[J]. Circulation, 2017, 135(17): e927-e999.

[6] Jin J, Wang J, Lu Y, et al. Platelet-derived microparticles: a new index of monitoring platelet activation and inflammation in Kawasaki disease[J]. Indian J Pediatr, 2019, 86(3): 250-255.

[7] Nomura S. Function and clinical significance of platelet-derived microparticles[J]. Int J Hematol, 2001, 74(4): 397-404.

[8] Pfister SL. Role of platelet microparticles in the production of thromboxane by rabbit pulmonary artery[J]. Hypertension, 2004, 43(2): 428-433.

[9] Rossaint J, Kühne K, Skupski J, et al. Directed transport of neutrophil-derived extracellular vesicles enables platelet-mediated innate immune response[J]. Nat Commun, 2016, 7: 13464.

[10] Arora K, Guleria S, Jindal AK, et al. Platelets in Kawasaki disease: is this only a numbers game or something beyond?[J]. Genes Dis, 2020, 7(1): 62-66.

[11] Kim HJ, Choi E, Lim YJ, et al. The usefulness of platelet-derived microparticle as biomarker of antiplatelet therapy in Kawasaki disease[J]. J Korean Med Sci, 2017, 32(7): 1147-1153.

[12] Yahata T, Suzuki C, Yoshioka A, et al. Platelet activation dynamics evaluated using platelet-derived microparticles in Kawasaki disease[J]. Circ J, 2014, 78(1): 188-193.

[13] Lu Q, Malinauskas RA. Comparison of two platelet activation markers using flow cytometry after in vitro shear stress exposure of whole human blood[J]. Artif Organs, 2011, 35(2): 137-144.

[14] Tong S, Wang H, Zhang T, et al. Accumulation of CD62P during storage of apheresis platelet concentrates and the role of CD62P in transfusion-related acute lung injury[J]. Mol Med Rep, 2015, 12(5): 7777-7781.

[15] Dole VS, Bergmeie RW, Patten IS, et al. PSGL-1 regulates platelet P-selectin-mediated endothelial activation and shedding of P-selectin from activated platelets[J]. Thromb Haemost, 2007, 98(4): 806-812.

[16] Liu G, Liang B, Song X, et al. P-selectin increases angiotensin Ⅱ-induced cardiac inflammation and fibrosis via platelet activation[J]. Mol Med Rep, 2016, 13(6): 5021-5028.

[17] Tuan HTM, Hock LS, Abdullah ZW. Haemostatic parameters, platelet activation markers, and platelet indices among regular plateletpheresis donors[J]. J Taibah Univ Med Sci, 2018, 13(2): 180-187.

[18] St John AE, Newton JC, Martin EJ, et al. Platelets retain inducible alpha granule secretion by P-selectin expression but exhibit mechanical dysfunction during trauma-induced coagulopathy[J]. J Thromb Haemost, 2019, 17(5): 771-781.

[19] Burger PC, Wagner DD. Platelet P-selectin facilitates atherosclerotic lesion development[J]. Blood, 2003, 101(7): 2661-2666.

[20] Collins RG, Velji R, Guevara NV, et al. P-Selectin or intercellular adhesion molecule(ICAM)-1 deficiency substantially protects against atherosclerosis in apolipoprotein E-deficient mice[J]. J Exp Med, 2000, 191(1): 189-194.

[21] 郑晨，黎璇，丁粤粤，等. 川崎病患儿血小板表面 PAC-1 表达水平变化及意义[J]. 临床儿科杂志，2019，37(4)：241-244.

[22] Inami N, Nomura S, Kikuchi H, et al. P-selectin and platelet-derived microparticles associated with monocyte activation markers in patients with pulmonary embolism[J]. Clin Appl Thromb Hemost, 2003, 9(4): 309-316.

[23] Wang F, Wang L, Li Y, et al. PAC-1 and its derivative WF-210 Inhibit Angiogenesis by inhibiting VEGF/VEGFR pathway[J]. Eur J Pharmacol, 2018, 821: 29-38.

[24] Jiang L, Ping L, Yan H, et al. Cardiovascular toxicity induced by anti-VEGF/VEGFR agents: a special focus on definitions, diagnoses, mechanisms and management[J]. Expert Opin Drug Metab Toxicol, 2020, 16(9): 823-835.

[25] Zhou Y, Wang S, Zhao J, et al. Correlations of complication with coronary arterial lesion with VEGF, PLT, D-dimer and inflammatory factor in child patients with Kawasaki disease[J]. Eur Rev Med Pharmacol Sci, 2018, 22(16): 5121-5126.

[26] Carnevale R, Sciarretta S, Valenti V, et al. Low-grade endotoxaemia enhances artery thrombus growth via Toll-like receptor 4: implication for myocardial infarction[J]. Eur Heart J, 2020, 41(33): 3156-3165.

[27] Marín Oyarzún CP, Glembotsky AC, Goette NP, et al. Platelet toll-like receptors mediate thromboinflammatory responses in patients with essential thrombocythemia[J]. Front Immunol, 2020, 11: 705.

[28] Koupenova M, Clancy L, Corkrey HA, et al. Circulating platelets as mediators of immunity, inflammation, and thrombosis[J]. Circ Res, 2018, 122(2): 337-351.

[29] Trinchieri G, Sher A. Cooperation of Toll-like receptor signals in innate immune defence[J]. Nat Rev Immunol, 2007, 7(3): 179-190.

[30] Kojok K, El-kadiry AE, Merhi Y. Role of NF-κB in platelet function[J]. Int J Mol Sci, 2019, 20(17): 4185.

[31] Libby P. Inflammation in atherosclerosis[J]. Arterioscler Thromb Vasc Biol, 2012, 32(9): 2045-2051.

[32] Majdi F, Taheri F, SalehI P, et al. Cannabinoids Δ^9-tetrahydrocannabinol and cannabidiol may be effective against methamphetamine induced mitochondrial dysfunction and inflammation by modulation of Toll-like type-4(Toll-like 4) receptors and NF-κB signaling[J]. Med Hypotheses, 2019, 133: 109371.

[33] Wang M, Niu J, Ou L, et al. Zerumbone protects against carbon tetrachloride (CCl4)-induced acute liver injury in mice via inhibiting oxidative stress and the inflammatory response: involving the TLR4/NF-κB/COX-2 pathway[J]. Molecules, 2019, 24(10): 1964.

[34] Tülay Aydın P, Göz M, Kankılıç N, et al. Micro-RNA gene expressions during cardiopulmonary bypass[J]. J Card Surg, 2021, 36(3): 921-927.

[35] Parra-Izquierdo I, McCarty OJT, Aslan JE. Platelet miR-223 delivery rescues vascular cells in Kawasaki disease[J]. Circ Res, 2020, 127(7): 874-876.

[36] Chu M, Wu R, Qin S, et al. Bone marrow-derived microRNA-223 works as an endocrine genetic signal in vascular endothelial cells and participates in vascular injury from Kawasaki disease[J]. J Am Heart Assoc, 2017, 6(2): e004878.

[37] Ning Q, Chen L, Song S, et al. The platelet microRNA profile of Kawasaki disease: identification of novel diagnostic biomarkers[J]. Biomed Res Int, 2020, 2020: 9061568.

[38] Wang B, Wang LN, Cheng FF, et al. MiR-222-3p in platelets serves as a distinguishing marker for early recognition of Kawasaki disease[J]. Front Pediatr, 2019, 7: 237.

[39] Zhang Y, Wang Y, Zhang L, et al. Reduced platelet miR-223 induction in Kawasaki disease leads to severe coronary artery pathology through a miR-223/PDGFRβ vascular smooth muscle cell axis[J]. Circ Res, 2020, 127(7): 855-873.

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