Hans Journal of Biomedicine 生物医学, 2023, 13(2), 246-254
Published Online April 2023 in Hans. https://www.hanspub.org/journal/hjbm
https://doi.org/10.12677/hjbm.2023.132028

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血小板的研究现状及其影响肝再生的机制

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收稿日期：2023年3月15日；录用日期：2023年4月11日；发布日期：2023年4月19日

摘　要

肝脏是体内重要的代谢器官，具有损伤后独特的再生能力。系统而全面的理解肝脏再生的机制才能找到相应有效的治疗方法。血小板除了在止血以及血栓形成方面发挥作用，同时能够参与炎症反应、肿瘤、组织修复等病理生理事件。近年来的研究结果提示血小板在肝再生中具有重要作用。本文就血小板上述作用以及血小板影响肝再生的作用机制及其研究进展作一综述，希望为相关领域的探索提供基础研究。

关键词

肝再生，血小板，炎症反应，组织修复，肿瘤

The Mechanism and Research Progress of Platelet Affecting Liver Regeneration

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Received: Mar. 15th, 2023; accepted: Apr. 11th, 2023; published: Apr. 19th, 2023

Abstract

The liver is an important metabolic organ in the body and has unique regenerative capacity after injury. A systematic and comprehensive understanding of the mechanism of liver regeneration can lead to effective treatment. Platelets not only play a role in hemostasis and thrombosis, but also participate in pathophysiological events such as inflammatory response, tumor and tissue repair. Recent studies suggest that platelets play an important role in liver regeneration. This article reviews the above effects of platelets and the mechanism and research progress of platelets

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文章引用: 王鹏, 杨宇, 丁隆. 血小板的研究现状及其影响肝再生的机制[J]. 生物医学, 2023, 13(2): 246-254.
DOI: 10.12677/hjbm.2023.132028

affecting liver regeneration, hoping to provide basic research for the exploration of related fields.

Keywords

Liver Regeneration, Platelet, Inflammatory Reaction, Tissue Repair, Tumor

1. 引言

部分肝切除术、肝移植术后，肝脏通过强大的再生能力使其短时间内恢复正常生理功能及体积。然而部分肝切除或肝移植术后发生的肝功能障碍导致的再生失败往往导致严重后果[1]。肝脏再生的过程及其复杂，受机体多系统间的密切调控。血小板在止血过程中的作用已广为人知。此外，血小板涉及肝脏的多种病理过程。本文就血小板与肝再生的影响机制作一简要综述。

2. 肝再生

2.1. 肝祖细胞

肝祖细胞(Hepatic progenitor cell, LPC)是一种卵圆形、具有小的细胞尺寸以及高的核/浆比细胞。Farber 和 Popper 等人于 20 世纪 50 年代中期在 2-乙酰氨基芴(2-AAF，一种肝毒性致癌物)处理的大鼠中观察到位于胆管末端分支的 Hering 管中长出的卵圆细胞[2] [3] [4] [5]。卵圆细胞在体外显示出分化为肝细胞和胆管细胞的能力，被认为是具有双重潜能的前体细胞[6]。卵圆细胞在慢性肝病中被称之为肝祖细胞。同时在慢性肝病中，它们的数量与疾病的严重程度有关[7]。然而，由于缺乏卵圆细胞的特异性标记物以及 2-AAF/PH 模型不适用于小鼠，至今仍缺乏直接的体内证据表明卵圆细胞在任何经典的小鼠损伤模型中都能产生成熟的肝细胞和胆管细胞。

此外也有一些文献提出 LPC 可能来源与胆管上皮细胞(Biliary epithelial cells, BEC)。Wang [8]等人表明位于中央静脉周围的 Axin2 + 肝细胞具有干细胞样特征。当肝部分切除后被激活，并且可以向肝小叶的中心区域延伸以取代受损细胞，在那里它们的代谢特征被区域微环境重新编辑[9]。Schaub 等人发现，门静脉周围的部分肝细胞可以直接分化为胆管细胞，这一过程与 Notch 和转化生长因子 β (transforming growth factor-β, TGF-β)信号传递有关[10]。Li [11] [12]等人发现，在门静脉和胆管末端分支附近存在一种混合型肝细胞，具有肝细胞核因子 4a (HNF4a)阳性表达的肝细胞和 BECs 的混合表型。这些杂交肝细胞可以在肝脏受损后成为肝细胞和 BEC，在不增加癌症发病率的条件下重新填充受损的肝小叶。Lin [13]等人发现，以端粒酶表达为标志的肝细胞稀疏分布在肝小叶的不同位置。这些细胞已被证明是正常肝脏稳态和损伤诱导肝再生的主要肝细胞来源。综上所述，肝细胞具有高度复制能力及可塑性，为探索更多的 LPC 来源提供可能。

2.2. 肝细胞增殖

部分肝切除或活体肝移植术后，肝脏的实质细胞会率先增殖，与此同时，有丝分裂信号在诱导肝内其他类型细胞增殖方面也起到了促进作用。如 BEC，Sox 9 是胆管细胞功能的一个重要转录因子，BECs 向肝细胞转化同时失去其原有的 Sox9 的表达。应用细胞角蛋白 19 (CK19)作为示踪标记，证实了 BEC 是

肝损伤期间肝细胞再生的重要来源[14]。肝窦内皮细胞(liver sinusoidal endothelial cell, LSEC)，LSEC 形成肝窦的开窗壁，是一个调控和测量肝实质与血液之间分子和细胞运输的控制点。其具有调节血管张力、炎症和血栓形成等功能。同时肝再生需要 LSEC 增加肝细胞生长因子(hepatocyte growth factor, HGF)的表达[15] [16] [17]和 LSEC 的增殖[18] [19] [20]。肝星状细胞(hepatic stellate cell，HSC)，HSC 是一种主要的间充质细胞类型，约占肝脏非实质细胞的 1/3，它们位于肝窦内皮细胞层和肝细胞之间的 Disse 窦周隙内。Disse 间隙内含有结缔组织基质，为维持 HSC 的分化功能提供细胞支持和信号，并允许溶质和生长因子的畅通运输[21] [22]。HSC 产生一系列生长因子和细胞因子，这些因子已被证明可以驱动肝脏再生。HSC 产生的一个关键因子是 HGF。HGF 在肝再生的启动中起重要作用，HSC 持续合成 HGF，作为一种无生物活性的单链多肽，大量储存在细胞外基质(Extracellular matrix, ECM)中。其受体酪氨酸激酶(Cellular-mesenchymal epithelial transition factor, c-Met)在肝细胞、胆管细胞和内皮细胞中表达，在损伤后早期激活其受体，并作为肝细胞直接有丝分裂原促进肝再生。TGF-β 是一种多功能细胞因子，由 HSC 产生，在肝脏中存在三种不同的 TGF-β 亚型，它们都与同一个受体结合，并且存在于所有的肝细胞类型中，具有广泛的稳态和再生作用[23]。此外，肝细胞的增殖还受到各种细胞因子、转录激活因子等的共同调控，如肿瘤坏死因子 α (tumor necrosis factor-α, TNF-α)、表皮生长因子(epidermal growth factor, EGF)、和白细胞介素 6 (interleukin-6, IL-6)等细胞因子。信号传导及转录激活蛋白 3 (signal transducer and activator of transcription 3, STAT3)、核因子 κB(nuclear factor-κB, NF-κB)等转录激活因子，细胞外信号调节激酶(extracellular signal regulated kinase, ERK)、磷脂酰肌醇 3-激酶(phosphatidylin-ositol-3-kinase, PI3K)等蛋白激酶参与对肝细胞再生过程[24] [25] [26]。

3. 血小板

血小板来源于骨髓中成熟的巨核细胞，其内包含具有多种分泌功能的颗粒，如 α 颗粒、致密颗粒、溶酶体等。目前研究比较清楚的是血小板的止血作用[27] [28]。此外，最近的研究表明血小板至少参与机体炎症反应、调节免疫应答、肿瘤形成和转移、组织修复、肝再生等多种病理生理过程[29] [30] [31]。

3.1. 血小板与炎症反应

血小板能够通过表达 Toll 样受体(Toll-like receptors, TLRs)识别病原体[32]，释放储存在其颗粒内的各种细胞因子、趋化因子和生长因子[33]，并在其表面表达细胞黏附分子，从而与血管和免疫细胞相互作用，主要是中性粒细胞和单核细胞[34]。血小板有多种类型的颗粒，根据其密度和含量进行分类。其中 α 颗粒最为丰富，占据血小板体积的 1/10 [35]，而致密颗粒较小，具有高电子密度的特点[36]。血小板活化后，致密颗粒和 α 颗粒的膜与质膜融合，释放出血小板膜上的分子内容物或暴露颗粒内实体。血小板在血管损伤修复、血管生成和炎症反应中的作用主要与 α 颗粒的分泌有关。来源于 α 颗粒内的分子包括 P -选择素和 CD40L (一种跨膜蛋白，主要表达于活化的 T 细胞和血小板上)。它们有助于血小板与其他细胞的黏附。当血小板被激活时，这些分子转移到膜上，支持与内皮细胞和炎症细胞如单核细胞和中性粒细胞的相互作用[37]。这种相互作用的结果是白细胞的激活，白细胞反过来又表达或释放其他化合物，进一步放大炎症和免疫反应。此外，除了粘附分子外，α 颗粒还含有如血小板因子 4 (Platlet factor 4, PF4)和基质衍生因子等细胞因子和趋化因子，这些细胞因子和趋化因子激活内皮细胞，驱动额外的白细胞募集、激活和迁移到炎症部位。

此外，血小板与肝脏的多种病理过程有关，包括炎症状态和再生。虽然血小板调节肝脏稳态的确切分子机制仍然难以捉摸，当肝脏部分切除出现缺血性损伤后，血小板会被吸附到肝脏，然而血小板在肝脏聚集的机制仍需进一步研究。血清素作为血小板的衍生物，似乎与肝再生密切相关，其是一种有效的

促分裂剂，有助于血小板活化[38]。血清素在肠道中合成，可以被血小板吸收，并储存在 α 颗粒中，超过95%的循环血清素储存在血小板中，因此当需要再生反应时，血小板可能是将血清素运输到肝脏的理想载体。

3.2. 血小板与肿瘤

血小板在肿瘤细胞生长和转移中发挥作用。这有助于肿瘤细胞的生长及其在恶性肿瘤进展和存活中的后续作用。血小板 α 颗粒内含多种生长因子和细胞因子，其与肿瘤的生长和转移密切相关。血小板活化时，大量的促有丝分裂蛋白、血管生成蛋白和生长因子被释放到肿瘤微环境中，进而促进肿瘤细胞生长。同时，血小板能够促进肿瘤细胞与血管内皮相互粘附，形成一种受保护微环境，避免肿瘤细胞被机体免疫细胞溶解[39]。此外，肿瘤细胞释放可溶性介质，如 ADP [39] [40]、血栓素 A2 (ThromboxaneA2, TXA2) [41] [42]或高迁移率族蛋白 1 (High mobility group box-1 protein, HMGB1)。其与血小板 Toll 样受体 4 (Toll-like receptor 4, TLR4)结合，从而引发局部血小板活化，进一步加强了血小板与肿瘤细胞之间的稳定状态[43]。血小板活化后释放溶血磷脂酸(Lysophosphatidic acid, LPA)，其可以增强肿瘤细胞的血管通透性和侵袭性，进而促进了肿瘤细胞的生长和转移[44]。部分肿瘤细胞可以在其细胞膜上表达组织因子(TF)，最终经过凝血级联反应形成凝血酶进一步引起血小板活化[45]。

凝血酶在转移过程中几乎每一步都起着关键的作用。凝血酶促进肿瘤细胞增殖和肿瘤生长，例如通过激活蛋白酶激活受体-1 (Protease-activated receptors-1, Par-1)和纤维蛋白原[46]。在肿瘤微环境中，凝血酶刺激的纤维细胞和巨噬细胞分泌单核细胞趋化蛋白，促进原瘤性髓系细胞的侵袭[47]。凝血酶对内皮细胞也有一些支持血管生成的作用，例如通过增强血管内皮生长因子(Vascular endothelial growth factor, VEGF)对内皮细胞的有丝分裂活性[48]。此外，凝血酶抑制凋亡并诱导血管前体细胞的增殖和分化[49]。凝血酶刺激后的内皮细胞形态呈圆形，粘附细胞特性消失，促进了肿瘤细胞的跨内皮迁移[50]。

除凝血酶外，Shao [51]揭示了癌黏蛋白在中性粒细胞和血小板中启动相互激活机制。黏蛋白与血小板上的 P-选择素和中性粒细胞上的 L-选择素结合，使两种细胞紧密相连。P-选择素和 L-选择素是一种细胞粘附分子。P-选择素糖蛋白配体-1 (P-selectin glycoprotein ligand 1, PSGL-1)同样是一种黏附分子，被认为是 P-选择素的配体。血小板上的 P-选择素和 PSGL-1 诱导中性粒细胞释放组织蛋白酶 G 诱导血小板活化。

3.3. 血小板与组织修复

血小板 α 颗粒中含有数百种生物活性蛋白，包括以血小板衍生生长因子(Platelet derived growth factor, PDGF)、成纤维细胞生长因子(Fibroblast Growth Factor, FGF)、VEGF、表皮生长因子(Epidermal growth factor, EGF)、TGF-β、胰岛素样生长因子(Insulin-like growth factor)、和 HGF 为代表的广泛的生长因子(GF)。在组织修复过程中，每一种主要的 GF 都参与了特定的生物分子功能，在伤口愈合和毛发再生长中发挥着重要作用。事实上，当 GF 分泌时，它与靶区细胞的跨膜受体结合，产生细胞生长、有丝分裂、趋化、增殖和 ECM 形成，从而促进组织修复[52] [53]。此外，血小板释放因子诱导和控制其他与组织修复密切相关细胞类型的增殖和迁移，如平滑肌细胞(Vascular smooth muscle cell, VSMC) [54]和间充质干细胞(Mesenchymal stem cell, MSC) [55]。损伤组织中的血管生成是组织功能恢复的另一个重要机制，由于血小板激活时释放大量的促血管生成和抗血管生成介质，因此也受到血小板的重要调节。富血小板血浆(Platelet-rich plasma, PRP)是一种自体的全血衍生物，含有超生理浓度的血小板。PRP 的理论优势在于为组织再生提供富含生长因子以及其他细胞因子的局部环境，这已经得到了大量的研究支持。

3.4. 血小板与肝再生

血小板颗粒中含有多种细胞因子，包括 PDGF、VEGF、IGF-1、TGF-β、HGF、EGF 等，这些细胞因子与肝脏的生理活动息息相关[27] [56]。当发生严重肝病的以及合并门静脉高压、脾功能亢进时，血小板数量会相应的下降，此时应外源性输注血小板或使用血小板生成素(Thrombopoietin, TPO)给予治疗。反之，当肝功能出现障碍时，例如肝切除、肝移植、肝硬化以及胆汁淤积等情况下，血小板会在肝内聚集并释放生长因子促进肝细胞再生[57]。

在动物实验中，肝脏部分切除后，血小板对肝脏再生至关重要。引人注意的是，在接受抑制血小板功能药物治疗的小鼠中，或在化疗药物、血小板减少抗体诱导的血小板减少症小鼠中，肝脏部分切除后的肝脏再生明显延迟[58]。相反，在应用血小板生成素受体激动剂或浓缩血小板使血小板数量升高后，肝细胞再生的速度显著提高[59] [60] [61]。

在临床中，部分肝切除术或肝移植后的低血小板计数已被证实是术后肝功能障碍和术后死亡率升高的一个强有力的独立预测因素[62] [63] [64]。同时活体供肝移植受者的肝再生能力能够通过输注血小板进而得到提升[65]。

4. 血小板促进肝再生的机制

第一，血小板直接效应：肝损伤后，血小板会迅速的在肝内聚集[66] [67] [68]，由于去唾液酸化血小板糖蛋白 Iba 和肝细胞 Ashwell-Morell 受体之间的相互作用，肝细胞从循环血中清除老化或功能障碍的血小板[69] [70] [71]。然而有研究表明，在血小板促进的肝再生过程中，肝细胞对血小板的摄取是以不依赖于 Ashwell-Morell 受体的方式进行的[72] [73] [74]。部分肝切除后 1.5 小时内，血小板在人体肝脏中积聚。可以想象，这种快速的血小板积聚导致储存在血小板颗粒中的生长因子分泌，从而增强再生反应。血小板储存 HGF、IGF 和血清素等，这些因子已被证明能够在体外刺激肝细胞增殖[17]。此外，VEGF 储存在血小板中。部分肝切除后，内皮细胞增殖并释放生长因子 HGF 刺激肝细胞增殖，并可能通过刺激新血管生成来直接支持肝再生[75]。第二，血小板与 LSECs 相互作用。LSECs 是血小板与外周血液之间的屏障，促进二者之间的物质交换。在肝细胞再生的过程中，血小板可粘附于免疫细胞和 LSECs [68] [76]进而导致血小板活化促进肝细胞增殖。同时，血小板活化后释放多种细胞因子、生长因子促进 LSECs 增殖。第三，血小板和枯否细胞(Kupffer cell, KC)相互作用。KC 是部分肝切除后多种细胞因子的重要来源。当 KC 细胞耗竭后，小鼠肝部分切除术后肝组织的 TNF-α、IL-6 浓度明显下降，肝再生速度显著降低[77] [78]。部分肝切除后，KC 与血小板相互黏附于肝窦周腔内，进而诱导血小板颗粒的释放。同时，血小板能够促进 KC 细胞释放 TNF-α、IL-6 等细胞因子提高肝再生速率[60] [79]。有研究证实，血小板通过调节 KC 中 IL–6 和 IL–10 (Interleukin-10, IL-6)的表达降低氧化应激反应，进一步保护肝细胞，加速肝再生[80]。此外，血小板内含有大量的编码 RNA (Messenger RNA, mRNA)以及微小 RNA (microRNAs, miRNA)。Kirschbaum 等[72]表明了血小板内 RNA 促进肝再生的机制，血小板通过将其内的 RNA 水平转移到肝实质细胞，经过 mRNA 的翻译或 miRNA 的调控作用于肝细胞，进而促进肝再生。

5. 总结与展望

部分肝切除术、活体肝移植术等外科手术的实施依赖于肝脏强大的再生能力。多数患者肝脏再生进展顺利。然而，在一些患者中肝脏能力下降导致“小肝综合征”。越来越多的证据表明，血小板在再生反应中的重要性，刺激血小板促进肝再生可能对这些患者有益。然而应用血小板促进肝再生的风险也不容忽视。首先，血小板计数的升高可能增加了血栓形成的风险。其次，血小板的输注也导致输血相关的急性肺损伤。另外，血小板能够促进肿瘤生长和转移。因此在应用血小板治疗时，应考虑如何合理的应

用血小板。通常以输注外源性血小板或应用 TPO 来提高血小板数量。同时在临床应用中，血小板的制备和储存成本相对较高。应用血小板治疗时应考虑在围手术期时间窗内何时给予血小板治疗能够尽可能放大有益效果，仍需进一步研究，以期为肝病的治疗提供了新的策略。

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