·综述·

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促血小板生成素调控慢性肝病患者血小板的作用及其临床应用

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【摘要】 慢性肝病患者常有血小板减少，其发生机制复杂且尚未被阐明。随着近年来对慢性肝病合并血小板减少的研究深入，研究者们意识到慢性肝病患者的血小板减少不仅与脾功能亢进有关，而且促血小板生成素在其中也起到一定程度的调控作用，文章提出“肝源性促血小板生成素中心的肠 - 肝调控网络机制”的可能性，就促血小板生成素调控血小板的作用、慢性肝病患者血小板的生物学功能、促血小板生成素在慢性肝病和肝硬化的诊断，以及促血小板生成素与促血小板生成素受体激动剂在慢性肝病血小板减少的治疗应用等方面的研究进展进行综述，为基础及临床相关研究提供新的思路。

【关键词】 促血小板生成素；慢性肝病；肝硬化；血小板；促血小板生成素受体激动剂

Recent advance of pathogenesis of TPO in thrombocytes and its clinical use in patients with chronic liver disease

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【Abstract】 Patients with chronic liver disease frequently exhibit thrombocytopenia, the etiology of which is intricate and not yet fully understood. As research into the association between chronic liver disease and thrombocytopenia has progressed in recent years, investigators have recognized that the thrombocytopenia in these patients is not solely attributed to splenic hyperfunction but is also modulated to a certain extent by thrombopoietin (TPO). The article posits the possibility of a “liver-derived thrombopoietin-centered gut-liver regulatory network mechanism”, providing a comprehensive review of the role of TPO in platelet regulation, the biological functions of platelets in patients with chronic liver disease, the diagnostic implications of TPO in chronic liver disease and cirrhosis, and the therapeutic applications of TPO and TPO receptor agonists in the treatment of thrombocytopenia in chronic liver disease. This review offers novel insights for both basic science and clinical research.

【Key words】 Thrombopoietin; Chronic liver disease; Cirrhosis; Platelet; Thrombopoietin receptor agonists

血小板减少是慢性肝病患者最常见的并发症[1-2]。慢性肝病患者的血小板减少发生率尚未确定，进展期肝纤维化或肝硬化患者血小板减少发生率为 15%~78%[3-4]，其中 14% 的患者合并重度血小板减少[5]。脾功能亢进一直被认为是慢性肝病中血小板减少的主要决定因素[2, 6]。近年多项慢性肝病并发血小板减少的研究证实，促血小板生成素（thrombopoietin，TPO）在血小板代谢中起重要作用。本文就 TPO 在此方面的研究进展进行综述，以加深临床医师对其认识。

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1 TPO 调控血小板的作用

TPO 又称巨核细胞生长发育因子（megakaryocyte growth development factor，MGDF），是调节巨核细胞 / 血小板生长的特异性生长因子，由 1958 年 Kelemen 等[7]首次提出并将其命名为“thrombopoietin”，但直至 1994 年 TPO 才被纯化及克隆出来，而后由于其对巨核细胞和血小板生成的重要作用为人们所熟知[8-9]。TPO 是一种糖蛋白激素，由位于染色体 3 长臂 q26.3-27 的基因编码，包含 2 个结构域：氨基末端和羧基末端[10]。氨基末端与 EPO 同源，并可与 C-Mpl 受体结合[11]。

越来越多的证据显示，机体 TPO 有着更为复杂的网络调节作用。人 TPO mRNA 在成人肝脏、肾脏及骨髓均有表达；然而，外周血循环中 60% 以上的 TPO 是由肝脏产生[12-14]。肝脏生成与分泌 TPO 能力与血浆血小板数量存在交互作用，这就是传统的“血小板调控学说”[15]。机体出现血小板减少时，骨髓基质细胞中特异性 mRNA 显著增加[16]。而在炎症状态下，体内 TPO 水平升高，主要是由白介素 -6（interleukin-6，IL-6）介导调控引起[17]。IL-6 可刺激体内肝细胞 TPO mRNA 的表达，并通过 Janus 激酶 1/ 信号传导和转录激活蛋白 3（Janus kinase 1/signal transducer and activator of transcription 3，JAK1/STAT3）信号通路识别去唾液酸化的血小板，介导血小板的代谢。近年来提出一种新的交互作用假说，衰老的去唾液酸化的血小板可通过肝脏 Ashwell-Morell 受体（Ashwell- Morell receptor，AMR）清除，也可通过 JAK2/STAT3 通路，调控体内肝脏 TPO mRNA 水平[18]。此外，血小板表面分子糖蛋白Ⅰbα（glycoprotein Ⅰbα，GPⅠbα）参与调控肝脏 TPO 生成[19]。如果 GPIbα 缺失，导致肝脏 TPO mRNA 转录和产生障碍。如果肝脏 TPO 的生成障碍，将影响血小板的数量与功能。由此，本文笔者提出“肝源性 TPO 中心的肠 - 肝调控网络机制”的可能性，即慢性肝病患者可能由于肠道微生态改变或细菌移位作用，肝脏内 1 型辅助性 T 细胞与 2 型辅助性 T 细胞（T helper cell 1/T helper cell 2，Th1/Th2）出现免疫失衡，导致 IL-1、IL-6 等炎症因子水平升高，介导肝源性 TPO 产生，而 TPO 可能通过 JAK 相关通路或作用于受体活化巨核细胞，来调控血小板的产生，同时去唾液酸化血小板又反过来调控 TPO。因此，TPO 很可能在调控肝脏炎症的发生与发展中起着重要作用，但是其作用机制有待于深入研究。

2 TPO 对慢性肝病及肝硬化的诊断价值

TPO 主要由肝细胞分泌，肝脏可直接影响血清 TPO 水平，但目前关于外周血清 TPO 水平与慢性肝病轻重之间的关联尚不明确。TPO 水平与外周血小板计数变化相关，在急性肝病患者中 TPO 水平接近正常甚至升高，而在慢性肝病患者中血清 TPO 水平显著降低[2, 5, 20]。终末期肝病致 TPO 生成减少，继而导致血小板减少。移植健康的肝脏 TPO 生成增多，使得血小板数量恢复正常[21]，但有学者对 110 例肝移植前肝病患者的血清 TPO 水平与血小板数量之间相关性进行评估，并未发现存在相关性[22]。

此外，有研究显示肝硬化并发血小板减少患者的血清 TPO 水平与脾脏的大小、凝血酶原时间（prothrombin time，PT）呈负相关，与肝功能指标如谷丙转氨酶、胆红素等无相关性[21, 23]；但也有研究显示，慢性肝病及肝硬化患者体内血清 TPO 水平与血浆白蛋白水平、PT 呈正相关[24-25]。肝移植术后患者体内 TPO 水平升高，将显著增加其术后肝功能不全的发生风险[20, 26]。慢性肝病患者血清 TPO 水平与肝功能和残余肝功能的检查（如氨基比林呼气试验和吲哚菁绿滞留试验）结果呈负相关[24, 27-28]。

肝病患者肝纤维化程度与体内 TPO 水平有关[29]。李琴等[30]对 71 例肝硬化患者进行研究，结果显示血清 TPO 水平与 Child-Pugh 分级呈负相关。Wolber 等[31]也发现，在儿童慢性肝衰竭中，失代偿性肝硬化患儿的肝脏组织中 TPO mRNA 表达水平明显低于代偿性肝硬化患儿。另有学者报道，肝硬化患者的肝组织 TPO mRNA 表达水平降低[32]。此外，慢性丙型肝炎病毒感染患者经过干扰素 -α 治疗后，体内 TPO 水平随之升高[33]。

上述研究说明，慢性肝病患者体内 TPO 水平与肝功能和肝纤维化之间有一定的相关性，TOP 在将来有可能成为肝功能和肝纤维化的检测指标。

3 TPO 及其受体激动剂在慢性肝病方面的治疗价值

对慢性肝病血小板减少患者的治疗一直是一

个具有挑战性的问题。由于慢性肝病患者后期需要干预治疗，而严重血小板减少症引起患者出血风险增加，如延误治疗则影响患者预后，导致该类患者疗效较差[27, 34]。目前对于慢性肝病伴重度血小板减少症患者，血小板输注是主要的治疗方法[1]。但输注血小板预防出血仍存在争议，且血小板输注受供应的限制，可能出现获得性降低和不良反应，患者获益也不明确，均使得其在临床使用受限。脾脏切除术、脾动脉栓塞等因手术侵入性和并发症风险高[35-36]，仅在临床特定患者中使用。尽管有研究表明，经颈静脉肝内门体静脉分流术可升高血小板水平[37]，但该治疗对血小板数量和慢性肝病并发症也未显示明显获益，对于控制食管静脉曲张出血或治疗难治性腹水有一定的疗效[38]。

TPO 作为慢性肝病血小板减少的主要机制之一，可以驱动巨核细胞和血小板生成的细胞因子，在从干细胞到多能祖细胞、未成熟和成熟的巨核细胞，再到血小板的形成和释放的所有阶段均发挥作用[1]。随着研究的深入，其在慢性肝病血小板减少患者中的可用性备受期待。

有研究显示，TPO 可通过增加血小板来促进小鼠的肝脏再生[39]。对二甲基亚硝胺诱导的肝硬化大鼠行 70% 肝切除术后，单次静脉注射 TPO 不仅能增加血小板计数，同时肝星状细胞的活化被抑制和肝纤维化面积减少。有研究者选用四氯化碳诱导肝纤维化小鼠模型，每周予腹腔内注射 TPO，5~8 周后小鼠肝纤维化得到改善[40]。此外，超生理质量浓度（>100 ng/mL）的 TPO 可直接启动体外血小板聚集和分泌，说明 TPO 是血小板反应的独立诱导剂[41]。近年来多项研究表明，TPO 除了作用于造血系统外，对心肌细胞、内皮细胞和神经细胞也有保护作用[42-43]，或许 TPO 也可能通过非血小板机制直接作用于肝脏，但需要更多的研究加以证明。

重组人 TPO（recombinant human TPO，rhTPO）氨基酸序列与内源性 TPO 完全一致，但糖基化位点稍有差异[29]。rhTPO 可明显增加血小板数量[44-45]，在血液病患者的临床试验中显示出临床益处，且没有安全性问题，但因可能产生交叉反应性抗体[46]，目前未在临床中广泛使用。

TPO 受体激动剂是刺激血小板生成的药物。它在结构上与内源性 TPO 不同，避免了自身抗体的产生[47]。这些药物已在慢性血小板减少性紫癜患者和慢性肝病患者中进行了多项研究。艾曲波帕（eltrombopag）和罗普司亭（romiplostim）是首先被批准用于治疗血液病血小板减少的二代 TPO 受体激动剂，两者在肝病相关研究中均可有效提升血小板数量[48-49]，但是由于增加门静脉血栓（portal vein thrombosis，PVT）的风险，且绝对获益较小[50-51]，并未在临床广泛应用。最新一代的 TPO 受体激动剂阿伐曲泊帕（avatrombopag）和芦曲泊帕（lusutrombopag）已完成 3 期研究，在美国和欧洲被批准用于治疗接受有创操作的慢性肝病血小板减少患者[52-53]。在全球Ⅲ期 ADAPT-1 和 ADAPT-2 研究结果中，TPO 受体激动剂阿伐曲泊可明显升高血小板水平，降低血小板输注率，且与安慰剂组相比未明显增加不良反应风险，其安全性和有效性在真实世界研究中也得到了证实[54-55]。有关芦曲泊帕的有效性和安全性，也在日本进行的 2 项 L-PLUS-1 和 L-PLUS-2 Ⅲ期研究中得到类似的结果[53, 56]。其中纳入了 96 例重度血小板减少（血小板计数 < 50×10^9/L）患者的随机双盲试验 L-PLUS-1 研究结果显示，与安慰剂组相比，芦曲泊帕组患者的血小板输注率明显下降（20.8% *vs.* 81.5%）。在 L-PLUS-2 研究中，芦曲泊帕组患者的不良事件（包括 PVT）发生率与安慰剂组相比差异无统计学意义，且不良反应多为轻度或中度，主要表现为头痛、腹痛、疲劳和恶心等。一项荟萃分析表明，TPO 受体激动剂明显增加了术前血小板计数 >50×10^9/L 者的比例（72.1% *vs.* 15.6%），降低血小板输注率（22.5% *vs.* 67.8%）和围术期出血率（11.6% *vs.* 15.6%），且未增加血栓形成的风险（2.2% *vs.* 1.8%）[57]。在《2022 年欧洲肝病学会临床实践指南：预防和管理肝硬化患者出血和血栓形成》中，专家建议将 TPO 受体激动剂作为有创操作的慢性肝病血小板减少患者的一线用药[58]。上述研究表明，TPO 受体激动剂用于慢性肝病血小板减少患者可快速、有效地升高血小板计数，减少该类患者在手术或侵入性操作中的出血风险，并且具有可接受的安全性。

4 结语与展望

关于 TPO 在调控慢性肝病患者血小板作用的相关研究取得了一定的进展，笔者基于已有研究针对有关肝脏 TPO 调控作用，提出“肝源性 TPO 中心的肠 - 肝调控网络机制”这一可能性，即 TPO

可能通过JAK相关通路或作用于受体活化巨核细胞，来调控血小板的产生，同时去唾液酸化血小板又反过来调控TPO，但是具体机制尚有待开展相关基础及临床研究进行验证。而且，有关慢性肝病患者肝脏合成TPO能力、TPO与血小板之间的交互作用及具体机制，TPO用于评估肝纤维化程度方面的研究，还有待于进一步深入研究。基于目前已经证实的TPO作用机制开发的TPO受体激动剂，不仅可增加血小板数量，还可能对肝纤维化、肝再生等具有一定的作用，TPO及其新的TPO受体激动剂临床应用将为慢性肝病诊断与治疗开辟广阔的空间。

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