·综述·

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胰岛素样生长因子-Ⅰ(IGF-Ⅰ)在肝硬化预后评估和治疗中的作用

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摘要：胰岛素样生长因子-Ⅰ(IGF-Ⅰ)作为胰岛素样生长因子家族的关键成员，主要在肝脏合成并广泛分布于人体，参与细胞增殖、分化、代谢及凋亡等生理过程。研究表明，IGF-Ⅰ水平与肝硬化严重程度呈负相关，主要通过抑制肝纤维化、促进DNA损伤修复、调控脂质代谢等多种途径影响肝硬化疾病进程。监测IGF-Ⅰ水平有望为改善肝硬化患者预后提供评估指标；刺激IGF-Ⅰ的作用途径或调节其表达水平有望成为肝硬化的治疗新方法。本文综述了IGF-Ⅰ在肝硬化中的研究进展，以期为肝硬化的诊治提供新思路。

关键词：肝硬化；肝纤维化；胰岛素样生长因子Ⅰ；预后

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Role of insulin-like growth factor-Ⅰ in prognostic evaluation and treatment of liver cirrhosis

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Abstract: As a key member of the insulin-like growth factor family, insulin-like growth factor-Ⅰ (IGF-Ⅰ) is mainly synthesized in the liver and is widely distributed in the human body, and it is involved in the physiological processes such as cell proliferation, differentiation, metabolism, and apoptosis. Studies have shown that the level of IGF-Ⅰ is negatively correlated with the severity of liver cirrhosis, and IGF-Ⅰ mainly affects the progression of liver cirrhosis by inhibiting liver fibrosis, promoting DNA damage repair, and regulating lipid metabolism. Monitoring of IGF-Ⅰ level is expected to provide an evaluation indicator for improving the prognosis of patients with liver cirrhosis, and stimulating the action pathway of IGF-Ⅰ or regulating its expression level may become a new method for the treatment of liver cirrhosis. This article reviews the research advances in IGF-Ⅰ in liver cirrhosis, in order to provide new ideas for the diagnosis and treatment of liver cirrhosis.

Key words: Liver Cirrhosis; Hepatic Fibrosis; Insulin-Like Growth Factor Ⅰ; Prognosis

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肝硬化是一种由多种慢性肝病发展而来的严重病理状态，其特征是肝组织的弥漫性纤维化、假小叶形成及肝细胞的再生结节。肝硬化的发病机制十分复杂，涉及多种信号通路之间的串扰、氧化应激、代谢调节和免疫反应[1]。目前，肝硬化已成为全球重要的公共卫生问题[2]，病程复杂且预后较差，常导致患者死亡[3]。然而，针对肝硬化尚无特效药物。研究认为肝纤维化甚至早期肝硬化是可以逆转的，因此，积极探索其发病机制、寻

求肝硬化的临床评估和预后预测手段对于制订个体化治疗方案及预测患者生存具有重要意义。近年来，肝硬化病情评估与预后预测相关生物标志物的研究与应用日益增多，其中，胰岛素样生长因子-Ⅰ（insulin-like growth factor-Ⅰ，IGF-Ⅰ）作为一种重要的胰岛素样生长因子，逐渐引起了研究者的关注。多项研究表明，IGF-Ⅰ水平与肝纤维化进展呈负相关，IGF-Ⅰ水平越低，肝纤维化程度可能越严重[4-6]。因此，IGF-Ⅰ表达水平上调可能使肝硬化患者获益。本文对IGF-Ⅰ在肝硬化发生发展中的作用机制、临床意义及治疗潜力等方面进行综述，旨在为肝硬化的诊治提供新思路。

1 IGF-Ⅰ概述

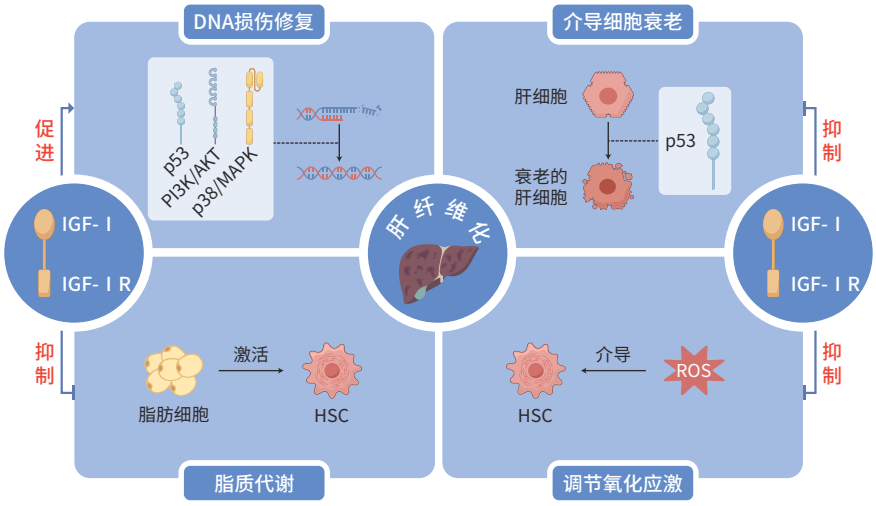
IGF-Ⅰ是一种由70个氨基酸组成的单链多肽，其分子结构与胰岛素相似，约48%的氨基酸序列与胰岛素相同，属于胰岛素样生长因子家族。IGF-Ⅰ约90%由肝脏细胞合成和分泌[7-8]，在人体内广泛分布，参与细胞增殖、分化、代谢及抑制细胞凋亡等多种生理过程[8-11]。其中，生长素释放肽-生长激素-胰岛素样生长因子-Ⅰ轴（GHRH-GH-IGF-Ⅰ轴）在调节肝脏活动中扮演着关键角色，主要通过复杂的信号通路影响肝脏的代谢、生长、免疫和纤维化等关键生理病理过程。作为GH-IGF-Ⅰ轴的上游调节因子，GHRH在中枢神经系统与外周靶器官中均有广泛表达，通过激活生长激素促分泌素受体1a，精细调控GH与IGF-Ⅰ的分泌与功能[12]。在GH的刺激下，肝脏合成并释放IGF-Ⅰ，后者通过其受体（IGF-ⅠR）在循环系统中以IGF/IGFBP-3复合体的形式循环，积极参与肝脏代谢的调节，促进能量代谢的高效进行[13]。IGF-Ⅰ的表达和活性受到GHRH/GH信号通路的调节[14]，同时，IGF-Ⅰ可以反向抑制GH分泌，在平衡GH和IGF-Ⅰ分泌中发挥重要作用[15]。此外，GH-IGF-Ⅰ轴可调控肝脏脂质合成的增加，从而维持脂质代谢的稳态[16-17]。

2 IGF-Ⅰ在肝纤维化中的作用机制

在肝组织中，IGF-Ⅰ及其受体IGF-ⅠR对于维系肝脏正常生理功能具有不可或缺的作用。IGF-Ⅰ/IGF-ⅠR信号传导体系通过激活下游信号通路（如PI3K/AKT和MAPK/ERK），深刻影响着肝细胞生长（刺激DNA合成和细胞增殖）、代谢活动（调节糖原合成与分解、脂肪酸合成及胆固醇代谢）及损伤后修复（促进肝细胞再生、抑制凋亡并加速损伤恢复）等多个方面，是维持肝脏稳态和功能的关键调节因子[18-19]。IGF-Ⅰ对肝纤维化过程具有显著抑制效应，其机制涵盖以下多个方面（图1）。

2.1 IGF-Ⅰ/IGF-ⅠR在DNA损伤修复中的促进作用

据报道，DNA损伤激活的非编码RNA（noncoding RNA activated by DNA damage，NORAD）进一步调控肝纤维化进程，并强调DNA损伤在肝纤维化中的核心作用[20]。从肝纤维化早期到晚期，细胞周期与DNA损伤相关基因表达发生显著变化，提示DNA修复机制在纤维化不同阶段具有不同作用[21]。诸多研究发现，肝细胞内DNA氧化损伤是肝纤维化过程中的关键事件，促进DNA修复成为减缓肝纤维化的潜在策略[22-23]。研究表明，IGF-Ⅰ通过PI3K/AKT及p38/MAPK通路促进DNA修复，同时与p53通路交互作用，共同调控细胞周期与肝纤维化过



注：HSC，肝星状细胞。

图1 IGF-Ⅰ/IGF-ⅠR在肝纤维化中的作用机制

Figure 1 The mechanism of IGF-Ⅰ/IGF-ⅠR in liver fibrosis

程[24-27]。可见，DNA损伤修复在肝纤维化进程中扮演关键角色，而IGF-Ⅰ/IGF-ⅠR系统通过多途径调控DNA修复，进而影响肝纤维化的发生与发展。

2.2 IGF-Ⅰ/IGF-ⅠR通过介导细胞衰老参与肝纤维化 研究表明，IGF-Ⅰ可通过延长作用时间，抑制核内p53与早老素的结合，有效改善肝脏的脂肪变性和纤维化状态，进而缓解氧化应激诱发的肝细胞早衰[28]。值得注意的是，p53的表达上调与肝纤维化密切相关，而IGF-Ⅰ则具有抑制p53核内转位的能力，并在其表达增加时缓解肝细胞的衰老过程[29]。

2.3 IGF-Ⅰ/IGF-ⅠR在氧化应激介导的肝纤维化中的多重调节作用 众多研究指出，氧化应激在肝纤维化发病机制中起关键作用。该应激状态源自活性氧（ROS）的累积，无论是ROS的过量生成还是抗氧化剂的缺乏，均能诱发氧化应激及损伤。ROS来源多种多样，包括NADPH氧化酶（NADPH oxidase，NOX）家族酶、一氧化氮合酶、黄嘌呤氧化酶和细胞色素P450等多种酶类。值得注意的是，在肝组织中，尤其是在HSC内，NOX的表达水平显著上调，这直接导致ROS的大量产生，并在HSC中触发多种促纤维化反应[30-34]。

在CCl_4诱导的肝纤维化模型中，肝细胞经历加剧的氧化应激与早衰，同时血浆中IGF-Ⅰ浓度显著降低。然而，IGF-Ⅰ的过表达可阻断p53-早老素信号通路，显著缓解肝细胞的氧化应激与早衰状态，进而改善肝脂肪变性和肝纤维化[35-37]。同时，IGF-Ⅰ通过与其受体IGF-ⅠR结合，能够触发PI3K/AKT信号通路的活化，这一过程对于保护细胞免受氧化应激损害、线粒体功能紊乱以及细胞凋亡具有关键作用[38-39]。有研究指出，IGF-Ⅰ通过MAPK/ERK1/2而非p38 MAPK通路，保护细胞免受氧化损伤，进而有助于肝纤维化的改善[40]。部分研究还发现IGF-Ⅰ通过解偶联蛋白3UCP3减少线粒体膜电位，从而降低ROS水平，可能在肝纤维化中发挥保护作用[41-43]。此外，在经H_2O_2处理的诱导多能干细胞中，作为氧化应激调控因子的microRNA-1的表达呈现上调趋势，而IGF-Ⅰ则能够下调其表达，进而缓解氧化应激所引发的损伤[44-45]。由此可见，IGF-Ⅰ通过作用于多种信号通路，在细胞与组织氧化应激的调控中发挥着重要作用，这进一步彰显了其在肝纤维化治疗中的潜在价值。值得注意的是，IGF-Ⅰ在特定条件下亦可促进氧化应激，如在脂肪细胞中刺激ROS生成，或降低肝细胞抗氧化酶活性[46]。因此，IGF-Ⅰ在肝纤维化中的作用具有双重性，需根据具体条件进行评估与调控。

2.4 IGF-Ⅰ对脂质代谢的调控作用 IGF-Ⅰ在脂质代谢中同样发挥着重要作用。在IGF-Ⅰ缺陷小鼠中，脂质代谢相关酶的表达水平显著下降，导致血脂异常，表明IGF-Ⅰ与脂质代谢之间存在紧密联系[47]。在间充质干细胞中，IGF-Ⅰ通过AKT/mTOR/PPAR-γ通路促进脂肪生成分化，而在肌腱干细胞中，IGF-Ⅰ激活p-CREB，与BMP2激活的pSmad协同作用，上调PPAR-γ的表达，进而增强肌腱干细胞的脂肪生成分化能力。因此，IGF-1可能与脂质代谢相关，通过PPAR抑制HSC激活，这可能是IGF-Ⅰ通过脂质代谢介导肝纤维化的潜在途径[48-49]。IGF-Ⅰ在脂质代谢中的作用具有双重性。除了已知的抗脂肪分解作用外，IGF-Ⅰ还能在饥饿条件下激活脂肪组织中的脂肪酸β氧化，促进能量消耗[15,50]。这一发现更新了以往对IGF-Ⅰ功能的认知，并提示IGF-Ⅰ在脂质代谢调控中的复杂性。此外，GH作为IGF-Ⅰ的重要上游调控因子，在脂质代谢和肝纤维化中也发挥着重要作用。GH通过刺激IGF-Ⅰ的合成与分泌，间接调控脂质代谢和HSC活化。

综上所述，IGF-Ⅰ通过复杂的信号通路和脂质代谢途径，在肝纤维化进程中发挥着重要调控作用。深入理解IGF-Ⅰ与脂质代谢、HSC活化之间的相互作用机制，对于开发肝纤维化治疗新策略具有重要意义。

2.5 IGF-Ⅰ在多元代谢途径中的调控角色 IGF-Ⅰ广泛参与葡萄糖、谷氨酰胺等代谢途径的调控，能够促进葡萄糖被细胞摄取并加以利用，这对于机体能量平衡的维持至关重要。研究显示，IGF-Ⅰ还具备调节谷氨酰胺代谢相关酶（例如谷氨酸脱氢酶）活性的功能，进而对谷氨酰胺的代谢过程产生影响。通过一系列对葡萄糖和谷氨酰胺代谢途径的调控，IGF-Ⅰ确保了细胞获得必要的能量与营养供给，进而促进细胞的生长与增殖。值得注意的是，这些代谢活动与肝纤维化的病理演变之间存在着密切的联系。因此，IGF-Ⅰ通过精确调控这些代谢通路，间接地影响肝纤维化的发展进程[51-52]。

3 IGF-Ⅰ在肝硬化病程与预后评估中的作用

3.1 IGF-Ⅰ水平与肝功能的关系 研究显示，肝硬化患者血清IGF-Ⅰ水平显著低于健康人群，且随肝功能Child-Pugh分级的增高而进行性下降[53]。此外，动物模型实验表明，IGF-Ⅰ治疗能够显著降低由CCl_4诱导的急性肝损伤小鼠的血清ALT水平，这表明IGF-Ⅰ能够改善肝细胞损伤和肝功能[54]，体现了IGF-Ⅰ对肝功能的保护作用。

3.2 IGF-Ⅰ在肝硬化预后预测中的价值 一项前瞻性研究表明，作为GH的主要效应分子，IGF-Ⅰ水平的变化可反映肝功能减退以及肝纤维化/肝硬化的发展进程，这可能预示着不良的临床结局[55]。此外，进一步队列研究结果支持IGF-Ⅰ是非酒精性脂肪性肝病进展中的关键生物标志物，其水平波动与肝纤维化严重程度密切相关，有望成为预测患者向肝硬化转变的重要评估指标[56]。上述研究表明，IGF-Ⅰ水平在肝硬化病程中至关重要，有助于估计肝功能储备或病理状况以及预测患者预后。一项针对148例肝硬化患者的回顾性研究，根据基线血清IGF-Ⅰ水平将患者分为低、中、高三组，多变量分析表明，低血清IGF-Ⅰ水平是预测病死率[所有患者：风险比(*HR*)=0.967，*P*=0.004；代偿期患者：*HR*=0.927，*P*=0.002]和失代偿进展(*HR*=0.939，*P*<0.001)的独立因素[57]。研究结果强调了IGF-Ⅰ在评估肝硬化患者肝功能储备及预测预后中的重要性，因此，IGF-Ⅰ可作为预测代偿期肝硬化患者失代偿相关事件的一个有用指标，监测血清IGF-Ⅰ水平有助于识别高危患者，以便早期干预，改善预后。另有回顾性研究分析IGF-CTP评分系统对失代偿性肝硬化患者1年病死率的预测能力，并与传统的CTP评分和终末期肝病模型(MELD)评分进行比较，发现IGF-CTP评分的受试者操作特征曲线下面积在预测1年病死率方面显著高于CTP和MELD评分[58]。提示，IGF-CTP评分系统比传统的CTP和MELD评分能更准确地预测失代偿期肝硬化患者的1年病死率，为临床评估失代偿期肝硬化患者的肝功能储备和预测病死率提供了新的、更准确的工具。综上，IGF-Ⅰ水平对肝硬化患者预后具有较高的预测效能，低水平IGF-Ⅰ可能预示着患者预后不良，如更高的并发症发生率、住院率和病死率。因此，IGF-Ⅰ可作为肝硬化患者预后评估的一个重要参考指标。然而，上述研究均为小规模的回顾性研究，可能存在潜在偏倚。因此，在未来需要前瞻性的大规模研究来进一步证实。

4 IGF-Ⅰ在肝硬化治疗中的潜力

基于动物实验与临床数据，IGF系统在肝脏疾病的发生和发展中起着重要作用，特别是IGF-Ⅰ在维持肝脏稳态、调控肝细胞增殖与凋亡平衡，以及干预肝纤维化至肝硬化转变中显示出不可替代的重要性[13,59-60]。在肝硬化实验模型中，IGF-Ⅰ治疗显著可改善肝功能指标，如AST、ALT水平，并有效缓解肠道屏障功能受损[61]。同时，一项针对非酒精性脂肪性肝病/非酒精性脂肪性肝炎患者的研究发现，调控IGF-Ⅰ至生理水平有望改善患者的肝脏状况，降低肝纤维化和肝硬化的风险[62]。

上述研究均表明IGF-Ⅰ对肝脏具有明确的保护作用，具有减轻肝细胞损伤、恢复肝功能的作用，提示IGF-Ⅰ在抗纤维化与抗肝硬化方面的潜力，可能作为治疗肝硬化的新靶点。

5 展望

随着IGF-Ⅰ在肝硬化领域研究的不断深入，未来研究应聚焦于多维度、多层次地分析其在疾病进展各阶段的详细作用机制，并加速其临床转化进程。IGF-Ⅰ联合其他生物标志物的预测效能、GH-IGF-Ⅰ轴在肝脏疾病中的治疗潜力、IGF-Ⅰ的具体作用机制及其治疗反应性和安全性均有待更高质量的临床试验和多中心研究，可能为肝脏疾病的病程进展、治疗及预后评估提供新方向。

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