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• 综述 •

血管紧张素 II 及其受体 AT1R 与肝纤维化的相关性

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[摘要] 肝纤维化是各种慢性肝损伤修复过程引起的肝脏疾病,以细胞外基质(extracellular matrix, ECM)增生和降解失衡导致过度沉积为特征。血管紧张素 II (angiotensin II, Ang II)是肾素血管紧张素系统(renin-angiotensin system, RAS)中的主要效应成分。越来越多的证据表明,Ang II 及其 1 型受体(angiotensin receptor 1, AT1R)之间的相互作用在对长期肝损伤引起的纤维化中起重要作用,包括促进肝星状细胞(hepatic stellate cell, HSC)的活化、增殖及收缩,诱导人类活化型 HSCs 产生活性氧簇(reactive oxygen species, ROS),促进胶原合成及沉积等。本文就 Ang II 及其受体 AT1R 在肝纤维化的发生、发展及抗纤维化治疗中的作用作一综述。

[关键词] 血管紧张素 II; 血管紧张素受体 1; 肝纤维化; 肝星状细胞; NADPH 氧化酶

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Relation of angiotensin II and its receptor AT1R with liver fibrosis

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[Abstract] Hepatic fibrosis is a common disease caused by wound-healing response to a variety of chronic liver injuries; it is characterized by the imbalance of extracellular matrix synthesis and degradation. Angiotensin II is the major effector of the renin-angiotensin system. Increasing evidence has demonstrated that the interaction of angiotensin II with angiotensin receptor 1 plays an important role in the long-term liver injury-induced liver fibrosis by inducing the activation, proliferation and constriction of hepatic stellate cells, generation of the reactive oxygen species from activated hepatic stellate cells, and the synthesis and accumulation of collagen. In this article we focused on the role of angiotensin II and its receptor 1 in the pathogenesis, development and therapy of liver fibrosis in recent years.

[Key words] angiotensin II; angiotensin receptor 1; hepatic fibrosis; hepatic stellate cells; NADPH oxidase

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肾素血管紧张素系统(renin-angiotensin system, RAS)是机体内一种重要体液调节系统,对维持正常生理功能发挥重要作用。肝纤维化是由肝脏损伤时机体过度修复反应造成肝脏内细胞外基质(extracellular matrix, ECM)的合成与降解失衡所致^[1]。研究发现 Ang II 与肝纤维化的发生、发展有密切联系^[2-3], Ang II 效应阻滞可能成为抗纤维化治疗的一个有效靶点。

1 RAS 及 Ang II

1.1 RAS 的组成 经典的 RAS 由血管紧张素 II (angiotensin II, Ang II)、血管紧张素转换酶(an-

giotensin converting enzyme, ACE)及血管紧张素受体 1(angiotensin receptor 1, AT1R)组成,不仅能够调节控制血管收缩及水电解质的平衡,在炎症、细胞因子分泌、ECM 代谢及细胞增殖等方面也具有十分重要的作用^[4]。近年来, RAS 的另外 1 条作用轴 ACE2-Ang(1-7)-MasR 逐渐被大家所认识,它代表了 ACE-Ang II-AT1R 的主要负性调节机制,在 RAS 中平衡 Ang II 的生物效应。Zhang 等^[5]发现 ACE、ACE2、Ang II、AT1R、Ang(1-7)和 Mas 在四氯化碳(CCl₄)诱导的纤维化大鼠肝脏内的表达均上调,ACE2 将 Ang II 转化为 Ang(1-7)从而减弱 Ang II 对肝脏纤维化的促进作用。

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1.2 Ang II 及其受体 AT1R Ang II 是一个八肽结构, 作为 RAS 系统的主要效应物, 具有广泛的生物学效, 是一种强效的促肝纤维化因子^[4]。肝脏中 RAS 系统的生物作用由一系列的后续酶促反应调控: 肝脏中的血管紧张素原 (angiotensinogen, AGT) 被肾素裂解形成血管紧张素 I (angiotensin I, Ang I), Ang I 继而被 ACE 加工处理生成 Ang II, Ang II 的绝大多数作用主要通过多数细胞质膜上都含有的 G 蛋白偶联受体——AT1R 介导, 形成经典的 ACE-Ang II-AT1R 活性轴。肝脏损伤后, RAS 的一些成分, 包括 ACE、Ang II 及 AT1R 的水平显著增加, 并在肝脏纤维化活跃部位聚集发挥效应^[2]。

2 Ang II /AT1R 在肝纤维化中的作用

2.1 Ang II /AT1R 与 HSCs 肝星状细胞 (hepatic stellate cells, HSCs) 的激活在肝纤维化中起关键作用, 活化的 HSCs 是 ECM 的主要来源。在正常肝脏中, 静息态 HSCs 中的 RAS 成分水平很低, 也不能分泌 Ang II, 肝脏损伤时 HSCs 激活, 活化的 HSCs 表达 ACE 和 AT1R 并产生 Ang II^[6]。活化的 HSCs 是肝纤维化的主要效应细胞, Ang II 能够剂量依赖性地促进活化型 HSCs 增殖、DNA 合成及细胞收缩, 诱导 HSCs 产生一系列的促纤维化反应, 包括加速细胞增殖、迁移, 合成 I 型和 III 型胶原等 ECM 成分及促纤维化因子转化生长因子 β (Transforming growth factor β 1, TGF- β) 的表达^[7-8]。经 Ang II 处理后的 HSC-LI90 细胞内, α 平滑肌肌动蛋白 (smooth muscle actin α , α -SMA)、胶质纤维酸性蛋白 (glial fibrillary acidic protein, GFAP) 和 I 型胶原这些 HSCs 活化的特异性标志物的表达明显上调^[9]。

此外, Ang II 还可以与内皮因子 1 (endothelin-1, ET-1) 共同调节 HSCs 引起肝纤维化。Ang II 与 AT1R 结合后能够通过磷脂酰肌醇-3-激酶 (Phosphatidylinositol-3-kinase, PI3K)/Akt 信号通路增加 ET-1 的表达水平, 而 ET-1/ET 受体 A 轴能够调节 Ang II 对 HSCs 向肌成纤维样细胞 (myofibroblast-like cells, MFB) 的转化^[10]。Okamoto 等^[9] 研究认为, 肝内胆管癌 (intrahepatic cholangiocarcinoma, ICC) 组织中高水平的 Ang II 还可以通过 Ang

II /AT1R 轴促进癌组织中的 ICC 细胞和 HSCs 活化和增殖, 使得这两种细胞之间产生协同作用加速间质纤维化及肿瘤进展, 引起了 ICC 的高度恶性。

2.2 Ang II /AT1R 与 NADPH 氧化酶 NADPH 氧化酶 (nicotinamide adenine dinucleotide phosphate oxidase, NADPH oxidase, NOX) 介导的氧化应激是肝纤维化的重要调节器, Ang II 的促纤维化效应正需要 NADPH 氧化酶及其产生的活性氧簇 (reactive oxygen species, ROS) 来实现^[11]。研究发现, NOX 亚基 *p47phox* 基因缺失小鼠实验性肝损伤及肝纤维化程度比正常野生型小鼠明显要低, 同时从 *p47phox* 基因缺失小鼠体内分离的 HSCs 对 Ang II 刺激反应也更迟钝^[11]。Ang II 能够诱导静息和活化型 HSCs 内细胞外信号调节激酶 1/2 (extracellular signal-regulate kinases 1/2, ERK1/2) 磷酸化, 并通过 NOX 增加活化型 HSC 内 ROS 的产生^[8]。随后, Aoyama 等^[12] 研究表明 Ang II 刺激增加 HSC 内 ROS 的产生后, 肝脏内胶原蛋白的沉积增加, HSCs 内 TIMP-1、胶原蛋白 1a 及 NOX4 的 mRNA 表达水平上调, 而它的这些促纤维化效应都依赖于 NOX1。有研究人员指出, Ang II 刺激是通过非吞噬型 NOX 诱导产生氧化应激而促进肝脏纤维化发生的, 他们研究发现丙肝患者, 口服洛沙坦治疗后体内主要的非吞噬型 NOX (NOXO-1、NOXA-1 和 Rac1) 明显降低, 同时 I 型和 IV 型前胶原, 这两个纤维化肝脏中主要的胞外蛋白的表达也明显减少^[13]。

2.3 Ang II /AT1R 与肝纤维化 早期研究发现, Ang II 是肝纤维化的一个重要调控介质, Ang II 水平的增加对肝脏炎症、氧化应激及纤维化具有明显促进作用^[3]。非酒精性脂肪肝 (non-alcoholic fatty liver disease, NAFLD) 是常见的致肝脏纤维化的肝损伤之一, 临床研究显示, 在活检证实患有 NAFLD 的高血压患者中, 接受 Ang II 效应抑制剂治疗的患者与不接受 Ang II 效应抑制剂治疗的患者相比, 肝脏纤维化分期前者显著更低, 这提示肝纤维化需要 Ang II 的参与^[14]。研究表明, Ang II /AT1R 刺激能够增加 JAK2 的表达及磷酸化, 磷酸化的 JAK2 随后磷酸化激活下游的 RhoA/Rho 激酶通路和膜突蛋白, 引起 HSC 活化和肝脏纤维化的发生^[15]。

同时, 有观点提出脂多糖 (lipopolysaccharide, LPS) 和 TGF- β 促纤维化效应依赖于 Ang II, Ang

II与它们在肝脏纤维化中发挥协同作用。他们认为,Ang II增加活化HSC内TLR4的表达,通过加强LPS-TLR4信号通路表达下调HSCs细胞膜上TGF- β 1的抑制性受体类似物BAMBI的表达从而促进TGF- β 发挥致纤维化效应^[16]。与此同时,Goto等^[17]研究发现在常染色体隐性多囊肾病/先天性肝纤维化模型大鼠体内ACE-Ang II-AT1R轴成分及下游促纤维化介质TGF- β 的表达均增加,这提示Ang II/AT1R也可能是先天性肝纤维化病情发展中的一个重要调控介质。

3 Ang II/AT1R抑制的抗纤维化效应

鉴于Ang II在肝纤维化中的重要作用,抑制Ang II的生物效应或生成可能将有效减轻肝脏纤维化。研究发现,患有慢性丙肝及高血压的患者接受Ang II阻滞剂治疗后肝纤维化程度明显低于没有接受Ang II阻滞剂的患者^[18]。利用基因沉默技术降低Ang II和AT1R的基因表达后HSC内TGF- β 的mRNA水平及与肝脏内胶原的合成相关的前胶原III、透明质酸、层粘连蛋白的分泌均明显降低^[19-20],并且在AT1R缺失小鼠,JAK2的促HSCs活化及肝纤维化的效应降低^[15]。

越来越多的证据显示,药理性阻滞剂AT1R能有效减弱肝脏纤维化,并且在肝纤维化早期阶段使用效果可能更好^[7,10,21-23]。研究证明,ARB可以抑制HSC的增殖、激活转化为MFB并降低ROS生成^[9,24]。ARB对各种急慢性血吸虫性肝纤维化均具有良好抗纤维化效应,它能显著降低血吸虫性肝纤维化小鼠MMP-2、TGF- β 1和羟脯氨酸的血清和组织表达水平^[22-23]。此外,ARB还能有效阻止非酒精性脂肪肝向肝癌发展^[25]。Koganti等^[26]研究发现甲氧雌二醇就是通过抑制AT1R基因转录下调肝脏上皮细胞内AT1R的水平发挥对机体的保护作用。

综上所述,肝纤维化已经成为一个严重影响人们健康的疾病,但是目前仍未有能够显著逆转或治愈肝纤维化的有效药物。Ang II及其受体AT1R在肝纤维化发生、发展中的重要作用与地位,为我们提供了一个潜在有效治疗靶点。然而值得一提的是,Karimian等^[27]最新研究发现Ang II/AT1R能够对胆酸诱导的肝细胞凋亡发挥保护作用,而药理性抑制AT1R后这种保护作用会被减弱,可能给肝实质细

胞带来损伤。因此,肝纤维化治疗的仍需要我们进一步的探索研究。

4 利益冲突

所有作者声明本文不涉及任何利益冲突。

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