综 述

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丹参及其单体成分防治肾纤维化的机制研究进展*

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[摘要] 综述丹参及其单体成分防治肾纤维化的机制,丹参及其单体成分能够通过减轻氧化应激、抗炎、抑制上皮-间充质转化、减少细胞凋亡、抑制内质网应激等途径来防治肾脏纤维化。

[关键词] 丹参;单体成分;肾纤维化;作用机制;综述

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Research Progress on the Mechanism of Danshen (Salviae Miltiorrhizae Radix) and Its Monomer Components for the Prevention and Treatment of Renal Fibrosis

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[Abstract] This article reviewed the mechanism of Danshen (Salviae Miltiorrhizae Radix) and its monomer components in preventing and treating renal fibrosis. It is suggested that Danshen (Salviae Miltiorrhizae Radix) and its monomer components can prevent and treat renal fibrosis by alleviating oxidative stress, anti-inflammatory, inhibiting epithelial-mesenchymal transition, reducing cell apoptosis, inhibiting endoplasmic reticulum stress and other ways.

[Keywords] Danshen (Salviae Miltiorrhizae Radix); monomeric components; renal fibrosis; mechanism; review

慢性肾脏病(chronic kidney disease, CKD)是指各种原因引起的肾脏结构和功能障碍>3个月,据统计CKD的全球患病率约升至13.4%[1-2]。肾纤维化(renal fibrosis, RF)作为CKD的主要组织学改变,特征是细胞外基质(extracellular matrix, ECM)的病理性沉积[3]。因RF病理机制复杂,现对其治疗暂无特效药,且临床上西药存在作用靶点单一、药物耐受等限制,而中医药逐渐被用来治疗CKD[4-6]。

丹参为活血化瘀药,有效成分主要为脂溶性丹参酮类和亲水性丹酚酸、丹参素、原儿茶醛等化合物,因其显著的抗炎、抗氧化、抗纤维化、改善循环、保护脏器等功能而被普遍应用于临床[7]。近几年,丹参已成为防治慢性肾脏病的常用中药[8],具有防治肾纤维化的作用。故笔者总结了丹参及其单体成分防治RF的研究进展,以期为深入研究其药理机制提供参考。

1 作用机制

1.1 减轻氧化应激 氧化应激在肾纤维化发生发展中起着关键作用。当炎症刺激或线粒体功能障碍、抗氧化能力下降时,自由基会过多地产生造成肾组织显著损伤[9-10]。

研究[11]发现,丹参可通过增加超氧化物歧化酶(SOD)的活性,阻碍活性氧(ROS)、丙二醛(MDA)等自由基产生来抑制氧化应激,从而减少ECM沉积。谷胱甘肽过氧化物酶(GSH-Px)是一种抗氧化酶。丹参能上调GSH-Px、SOD含量,抑制晚期糖基化终产物(AGEs)和过氧化脂质(LPO)表达,从而对高糖诱导的肾纤维化起到抑制作用[12]。AN L等[13]研究表明,丹参可升高核因子E2相关因子2(Nrf2)转录水平,促进抗氧化蛋白血红素加氧酶-1(HO-1)、醌氧化还原酶1(NQO1)表达,保护肾脏免受氧化应激损伤。

丹酚酸A是丹参水溶性酚酸类成分之一。研究[14]发现,丹

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酚酸A可通过增强AKT/GSK-3β/Nrf2通路信号活性，上调HO-1、SOD、GSH-Px、过氧化氢酶（CAT）的表达，减轻肾纤维化。杨冰等[15]研究表明，丹参多酚酸盐可调控TGF-β1/Smad信号通路，抑制氧化应激，减少下游转录蛋白胶原生成。丝裂原细胞外信号调节激酶（MEK）/胞外信号调节激酶（ERK）活化可调节Nrf2表达，抑制氧化应激[16-17]。丹参素可通过调控MEK/ERK/Nrf2信号通路改善肾损伤，延缓RF进展[18]。

1.2 抗炎 炎症反应通常作为肾纤维化触发因素，可诱导成纤维细胞活化，促进ECM合成，故控制炎症过度刺激对抑制RF具有潜在治疗价值[19-20]。

研究[21-22]表明，丹参酮ⅡA可降低肾脏中肿瘤坏死因子（TNF-α）、巨噬细胞趋化蛋白-1（MCP-1）、趋化因子CXCL-1和$CD68^+$含量，减轻ECM积累。WANG W等[23]研究发现，隐丹参酮能以剂量依赖方式减少巨噬细胞、淋巴细胞浸润，可能机制与抑制NF-κB信号激活有关。

丹酚酸A与丹酚酸B为丹参亲水性成分，具有明显抗炎作用，能减少炎症因子产生，从而有效防治RF进展[24-26]。糖代谢紊乱可诱发炎症反应。丹参多酚酸盐可下调糖尿病肾脏病小鼠TNF-α、IL-1β、IL-6、MCP-1表达水平，抑制炎症反应，显著改善肾纤维化[27]。长链非编码RNA（lnc RNA）9884作为转录后调节因子，可通过与MCP-1结合加重肾脏炎症；原儿茶醛可抑制lnc RNA9884介导的炎症[28]。

1.3 抑制上皮-间充质转化 上皮-间充质转化（EMT）是支撑肾纤维化的主要机制之一[29]。EMT是指上皮细胞失去其结构或功能的极性而转变为间质细胞的过程，可导致黏附性减弱、迁移或侵袭增强[30]。

研究[11,31]表明，丹参可抑制上皮细胞失去其特定的细胞标志物E-钙黏蛋白（E-caderin），阻碍其获得间质细胞或肌纤维细胞的特征，降低纤连蛋白（FN）、α-平滑肌肌动蛋白（α-SMA）表达，阻止EMT，减少ECM合成。锌指蛋白（Snail）在调节EMT过程中也发挥重要作用[32]。研究[33-34]发现，丹参酮Ⅰ与丹参酮Ⅱ可直接下调Snail、α-SMA、FN和波形蛋白表达，并上调E-caderin表达，参与调控EMT；丹参酮Ⅱ可能通过抑制Wnt/β-连环蛋白通路激活，阻碍EMT发生，减轻RF[35]。WANG W等[36]研究显示，隐丹参酮可抑制TGF-β1及其下游Smad3信号磷酸化，逆转单侧输尿管梗阻（UUO）诱导的肾纤维化组织中EMT有关标记物表达。

丹酚酸B可降低EMT相关蛋白FN、α-SMA和TGF-β表达，显著减少ECM沉积，改善肾纤维化[37]。体外实验中，丹酚酸B能呈剂量依赖性下调乙酰肝素（HPSE）、TGF-β1、α-SMA表达，上调多配体蛋白聚糖1（SDC1）、E-cadherin表达，并能通过抑制HPSE/SDC1轴保护肾脏[38]；此外，丹酚酸B还可激活Sirt1介导的自噬对TGF-β1诱导的EMT产生明显抑制效应[37]。孙兰等[39]研究表明，丹酚酸B可抑制PI3K/Akt信号通路抑制高糖诱导的大鼠近端肾小管上皮NRK-52E细胞发生EMT，进而延缓肾纤维化。

1.4 减少细胞凋亡 细胞凋亡与肾纤维化密切相关。当肾实质细胞受损致过多细胞凋亡时，ATP合成不足，促纤维化和炎症因子广泛生成，从而驱动RF[40]。细胞凋亡增强可促使肾纤维化加重[41]。B细胞淋巴瘤2（Bcl-2）家族蛋白中Bcl-2蛋白能抑制细胞凋亡，Bcl-2关联X蛋白（Bax）能促进细胞凋亡，且半胱天冬酶3（Caspase-3）也参与调控细胞凋亡[42]。研究[43]发现，低剂量丹参酮ⅡA可保护肾脏实质细胞，减少细胞凋亡，有助于改善纤维化。丹参素可上调Bcl-2蛋白表达，下调促凋亡因子Bax、Caspasase-3表达，抑制细胞发生凋亡，减缓肾纤维化，其机制可能与抑制TGF-β/Smad3、NF-κB或Wnt/β-catenin信号通路有关[44-45]。丹参乙酸镁是丹参水溶性活性成分。WANG M等[46]研究显示丹参乙酸镁可通过抗细胞凋亡途径保护肾脏，抑制Bax、Caspase-3表达。

1.5 抑制内质网应激 内质网应激是指内质网中错误折叠或未折叠的蛋白质增加及钙离子平衡紊乱时，细胞激活未折叠蛋白反应、内质网超负荷反应等细胞反应过程[47]。干扰内质网应激可减弱肾纤维化，表明内质网应激可能是新的纤维化因子[48-49]。内质网应激能介导细胞凋亡，其主要信号途径有C/EBP同源蛋白（CHOP）、c-Jun氨基末端激酶（JNK）和Caspase信号通路[48]。UUO大鼠模型中内质网应激相关蛋白葡萄糖调节蛋白78（GRP78）、CHOP和Caspase-3的表达显著增加[50]。陈琪等[51]证实，丹参酮ⅡA能够调节慢性肾衰竭大鼠内质网应激相关分子GRP78、CHOP和Caspase-3的表达，抑制细胞凋亡，保护肾脏。丹参酮ⅡA可能通过抑制蛋白激酶R样内质网激酶（PERK）/真核翻译启动因子-2α（eIF2α）/转录激活因子4（ATF4）通路信号传导，下调TGF-β1、GRP78、CHOP表达，减轻内质网应激，减少ECM沉积，从而改善RF[52]。

2 小结及展望

丹参及其单体成分具有防治肾纤维化的作用，其药理机制虽然广泛，但大多数实验结果只在基础研究中得到验证，仅有少部分研究报道含丹参复方制剂的临床疗效[8,53]。丹参及其主要成分的生物利用度不足，限制了其临床应用。因此，后续研究应探索良好的药物载体，提高其溶解度，增强组织靶向性。同时，为确保临床有效性和安全性，未来还需进行严格的大规模随机对照试验和进一步深入研究，促进丹参及其单体成分在临床实践中的应用。

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