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血管内皮生长因子 A 在肾脏发育及肾脏疾病中的作用

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[摘要] 肾脏血管系统对于正常肾功能的维持非常重要, 血管内皮生长因子 A (vascular endothelial growth factor-A, VEGF-A) 与肾脏血管系统的发育和多种肾脏疾病密切相关。研究表明, 肾组织中 VEGF-A 表达下调可引起肾髓质微血管密度降低, 造成肾组织局部缺氧, 反馈性导致促红细胞生成素增多, 造成红细胞增多症; 而 VEGF-A 过表达则可导致肾脏纤维化、肾囊肿形成, 促进肾脏疾病进展。因此, 调控 VEGF-A 的表达可能影响肾脏疾病的发生与发展。本文对 VEGF-A 在肾脏血管系统发育和肾脏疾病中的作用进行综述, 为肾脏疾病提供新的治疗策略。

[关键词] 血管内皮生长因子 A; 肾脏血管系统; 肾疾病

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Role of vascular endothelial growth factor-A in kidney development and kidney diseases

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[Abstract] The renal vascular system is vital for maintaining the normal function of kidney, and vascular endothelial growth factor-A (VEGF-A) participates in the development of renal vascular system and is associated with various kidney diseases. Studies have demonstrated that down-expression of renal VEGF-A can result in reduction of microvascular density in medulla kidney, regional hypoxia, and polycythemia, and further lead to increased haemopoietin. The overexpression of VEGF-A can cause renal fibrosis and cyst formation, promoting the progress of kidney disease. Therefore, regulation of VEGF-A expression may influence the occurrence and development of kidney diseases. This review summarized the role of VEGF-A in the renal vascular system and kidney diseases, hoping to provide new therapeutic strategies for kidney diseases.

[Key words] vascular endothelial growth factor-A; renal vascular system; kidney diseases

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肾脏内部复杂的血管系统是其发挥正常功能的关键。肾小管上皮细胞分泌的血管内皮生长因子 A (vascular endothelial growth factor-A, VEGF-A) 参与生成肾髓质微血管系统。研究表明, VEGF-A 的缺失可导致肾小管周围毛细血管 (peritubular capillary, PTC) 稀疏, 氧分压下降, 进而反馈性诱导 VEGF-A、促红细胞生成素 (erythropoietin, EPO) 及一氧化氮合酶 (nitric oxide synthase, NOS) 等产生增多, 最终导致红细胞增多症^[1-2]。本文以常染色体显性多囊肾病 (autosomal dominant polycystic kidney disease, ADPKD)、糖尿病肾病 (diabetic nephropathy, DN) 和慢性肾脏病 (chronic kidney

disease, CKD) 中肾组织 VEGF-A 的变化及其与疾病进展的关系为重点, 对 VEGF-A 在肾脏血管系统发育和肾病中的作用进行综述。

1 VEGF-A 对肾脏的影响

利用多西环素条件敲除小鼠肾小管细胞中的 VEGF-A 基因, 可降低肾脏 VEGF-A 的表达^[1]。肾小管分泌 VEGF-A 对于维持肾脏大小和肾脏微血管形成等非常重要。其分泌主要存在两种形式: 自分泌 VEGF-A 促进肾小管上皮细胞增殖, 维持肾小管正常生长状态; 旁分泌 VEGF-A 维持肾小管周围毛细血管的生成和分布。肾小管上皮细胞内

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VEGF-A 合成减少将引起肾脏局部缺氧,但过表达也会促进纤维化和囊肿形成。

1.1 促进新生血管形成,维持正常的肾脏形态 VEGF-A是调节肾脏血管形成的主要因子,并在肾脏足细胞和小管上皮细胞中广泛表达。VEGF-A影响血管的生成、迁移、增生、渗透性并维持血管张力^[3],其需要通过结合相应受体发挥生物学效应。目前发现 VEGF-A 的受体主要为血管内皮生长因子受体 (vascular endothelial growth factor receptor, VEGFR)-1 和 VEGFR-2,一般在肾小管周围毛细血管内皮细胞中表达^[4]。肾小管 VEGF-A 的表达减少可使肾髓质毛细血管稀疏、氧转运能力下降,进而造成缺氧环境。此时,低氧诱导因子 (hypoxia inducible factor-1 α , HIF-1 α)上调 EPO 基因的表达,加速 EPO 的产生,刺激血管内皮细胞增殖,HIF-1 α 还能引起 VEGF-A 和 NOS 表达增多,这些因子在肾小管周围毛细血管网的增生和形态的维持中也具有重要作用,因此新生血管形成增多^[5-7]。Dimke 等^[1]选择性敲除小鼠肾小管 VEGF-A 基因,发现基因敲除小鼠的肾脏体积较野生型小鼠减小,说明肾小管产生的 VEGF-A 对于维持肾脏正常形态同样非常重要。

1.2 VEGF-A 过表达导致肾脏纤维化和囊肿形成 Hakroush 等^[8]研究发现,上调肾小管 VEGF-A 的表达后肾小管周围毛细血管增生及成纤维细胞增多,致使细胞外基质聚积,最终导致肾间质纤维化。Donderski 等^[9]通过过表达 VEGF-A 引起肾小管间质纤维化,肾功能受损,估算肾小球滤过率 (estimated glomerular filtration rate, eGFR) 下降;而且肾小管出现节段性囊肿,囊肿多集中在近端、远端肾小管和集合管,周围有密集的毛细血管网包围,提示肾小管 VEGF-A 表达增加可能参与了肾囊肿形成。因此,有学者推测肾小管 VEGF-A 的过表达将导致两方面的病理生理改变,即促进肾小管周围毛细血管增生和诱导成纤维细胞增多,使肾小管和毛细血管襻之间的空隙被大量新生基质填充,最终使富含毛细血管网的纤维组织包绕在囊肿周围^[10]。

2 VEGF-A 与 ADPKD

ADPKD 是最为常见的单基因遗传性肾病,其发病率为 1/1 000~1/400,居我国终末期肾衰竭病

因的第四位^[11-12],目前尚无有效的治疗手段。ADPKD 主要的病理特征表现为肾小管上皮细胞异常增殖、双肾多发进行性增大的液性囊泡,最终导致终末期肾病 (end stage renal disease, ESRD) 的发生^[11-12]。有学者在 ADPKD 患者肾组织标本中发现囊肿周围有丰富的毛细血管网形成,并证实 VEGF 为囊肿上皮细胞增殖提供营养并促进囊肿增大;此外,形成的新生血管网形状较正常肾组织也有所不同,呈螺旋状而非线形^[13-14]。

2.1 囊肿衬里细胞高表达 VEGF-A Song 等^[15]研究发现,ADPKD 患者的囊肿衬里上皮细胞能够分泌 VEGF-A,且 VEGF-A 的表达明显高于正常肾小管上皮细胞;VEGF-A 的水平和肾脏囊肿增长的速度相关,较大的囊肿中分泌的 VEGF-A 明显增多。在 ADPKD 发病早期,VEGF-A 表达增多,通过作用于肾小管上皮细胞表面的 VEGFR-1 和 VEGFR-2 而导致肾小管上皮细胞增殖、囊肿扩张、肾脏体积增大;同时 VEGF-A 还作用于肾小管周围毛细血管内皮细胞上的 VEGFR-2,促进新生血管形成,导致囊肿周围包绕丰富的毛细血管网^[14,16];随着疾病进展至 ESRD,囊肿增长速度减慢,VEGF-A 分泌减少,致使囊肿周围毛细血管网萎缩^[17-18]。

2.2 抑制 VEGF-A 表达延缓 ADPKD 进展 Tao 等^[18]利用特异性核酶将杂合型 Han:SPRD 大鼠 VEGFR-1 和 VEGFR-2 mRNA 的表达水平减至基线的 50%,保留 VEGF-A 的部分功能,结果发现囊肿衬里上皮细胞增殖显著下降,囊肿生长速度减缓,肾功能显著提高。Amura 等^[19]使用 VEGFR-2 抑制剂对 *pkd2*(WS25/-) 小鼠进行干预,未发现肾脏囊肿大小及肾功能显著改善。Raina 等^[20]使用特异性抗体结合 VEGF-A,抑制了包括足细胞及肾小管上皮细胞在内的多种肾脏细胞中 VEGF-A 的表达,但结果并未延缓囊肿进展,反而出现肾功能及病理损害加重。上述研究结果表明完全阻断 VEGF-A 功能并不能达到预想的肾脏保护作用,要在一定程度上对肾小管 VEGF-A 的表达进行干预,为治疗 ADPKD 提供新的思路。

3 VEGF-A 与 DN

DN 是糖尿病的常见慢性并发症之一,是需要通过透析维持生命的最常见原因之一。目前常用的

延缓DN进程的方法是控制血糖、改善血压和肾脏血流动力学等,但其导致的蛋白尿和ESRD的发生率仍很高^[21]。研究发现,在高糖和缺氧等复杂环境下,转化生长因子 β (transforming growth factor- β , TGF- β)、血小板源性生长因子(platelet-derived growth factor, PDGF)、血管紧张素II等均可上调VEGF的表达^[22],而且VEGF参与了糖尿病微血管病变和血管新生^[23]。此外,临床研究和动物实验证实VEGF的表达与蛋白尿和肾功能的损害程度等呈正相关^[24-25]。Chen等^[26]研究发现,足细胞产生的VEGF通过VEGFR-1和PI3K信号通路促进IV型胶原蛋白合成增多,导致肾小球基底膜增厚、毛细血管通透性增加;通过VEGF单抗阻断其活性后,糖尿病大鼠的尿蛋白排泄等明显减少。Mironidou-Tzouveleki等^[27]通过实验证明抑制VEGF的表达能够改善DN动物的肾脏结构和功能。袁明霞等^[28]使用冬虫夏草后发现DN大鼠VEGF的表达降低,24h尿蛋白排泄和血肌酐的水平显著下降。Tian等^[29]使用非那雄胺抑制DN大鼠VEGF的表达,降低微血管密度,结果发现肾小球的体积等均显著下降,提示通过拮抗VEGF的表达可治疗潜在的糖尿病微血管并发症。以上研究结果表明VEGF的表达水平可能成为DN严重程度的理想评估指标,拮抗VEGF的病理生理作用可为DN的治疗提供新的思路。

4 VEGF-A与CKD

肾脏维持新陈代谢和发挥其正常生理功能均需要内稳态的平衡,而血管生成促进及拮抗双重因素是构成内稳态的重要因素。人类诸多疾病均与内稳态失衡有关,而肾脏内稳态失衡则是CKD发病的重要机制之一。在CKD的抗血管生成环境下,肾小管周围毛细血管内皮细胞凋亡、毛细血管网丢失,导致组织缺氧和氧化应激。

VEGF-A与CKD进展密切相关,VEGF-A缺乏引起毛细血管网稀疏,造成肾脏损伤^[30]。在内稳态失衡状态下,慢性肾损伤可导致血管周围细胞迁移和分化为肌成纤维细胞,使肾小管周围毛细血管内皮细胞失去血管周细胞的支持,从而因失去自身的平衡和完整性而凋亡;凋亡细胞黏附于血管内壁形成微血栓,引起毛细血管闭塞、白细胞溢出,造成

缺氧、炎症反应和血流动力学改变,最终导致更多肾小管周围毛细血管内皮细胞凋亡、血管萎缩,加速了CKD的进展^[31-33]。CKD患者肾脏表达VEGF-A的部位主要在肾小管,足细胞表达相对较少^[34]。CKD早期肾小管周围毛细血管萎缩、VEGF及VEGFR-2的表达减少,能反馈性引起肾小管VEGF的表达增高及肾小管周围毛细血管再生;但随着疾病进展,血小板反应蛋白1、内皮抑素等抗血管生成因子及凋亡相关因子配体(FasL)、白介素1(interleukin-1, IL-1)、肿瘤坏死因子 α (tumor necrosis factor- α , TNF- α)等表达增加,促进肾小管周围毛细血管内皮细胞凋亡,VEGF生理作用逐渐减弱^[35-36]。综上所述,VEGF-A表达减少引起的肾小管周围毛细血管网萎缩既是CKD进展的诱因,也是CKD进展的结果。但VEGF-A在CKD进展的作用目前尚存在争议,有学者认为适当提高VEGF-A的表达水平可减少肾小管周围毛细血管萎缩和肾纤维化,改善肾功能,延缓CKD进展^[37-38];但也有学者认为VEGF-A不能显著改善肾小管周围毛细血管的稀疏状态及CKD患者的预后^[39]。因此,仍需更多实验研究证明该如何合理调控CKD患者中VEGF-A的表达,以实现最终改善CKD患者预后的目的。

5 小结

VEGF-A是目前研究肾脏发育和肾脏疾病进展的热点之一,肾小管VEGF-A的正常表达对肾髓质血管网的形成至关重要;VEGF-A的异常表达则与缺氧、肾间质纤维化、肾囊肿形成密切相关。然而,目前该领域研究尚未形成完整的理论体系,还未明确是否存在其他机制协同参与肾小管VEGF-A构建肾脏髓质微循环系统等。基于VEGF-A及其受体的研究成果未来有望成为治疗肾脏疾病尤其是ADPKD的一种新的策略。

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