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·综述·

富含半胱氨酸的酸性分泌蛋白在原发性开角型青光眼领域的作用机制

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[摘 要] 原发性开角型青光眼(primary open angle glaucoma，POAG)是一种慢性、进行性的视神经病变，其发病机制尚不明确。而眼内敏感区域[如小梁网邻管组织、筛板(lamina cribrosa，LC)等]的细胞外基质代谢异常在其中起关键作用。富含半胱氨酸的酸性分泌蛋白(secreted protein, acidic and rich in cysteine，SPARC)作为一种基质细胞蛋白在眼内广泛分布，具有沟通细胞与细胞外基质信号传递的作用。研究表明SPARC可通过多种途径参与并调控青光眼的发生发展过程，有望成为疾病治疗的新靶点。

[关键词] 富含半胱氨酸的酸性分泌蛋白；基质细胞蛋白；青光眼

Mechanism of secreted protein, acidic and rich in cysteine in primary open angle glaucoma

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Abstract Primary open angle glaucoma (POAG) is one of chronic and progressive optic neuropathies. Its pathogenesis remains to be clarified. The metabolic disturbance of extracellular matrix in some sensitive regions, such as the juxtacanalicular region and lamina cribrosa, may play a key role. Secreted protein, acidic and rich in cysteine (SPARC), as one matricellular protein, is widely distributed inside the eye. It generally allows cells to modulate their attachments with and alter the characteristics of their surrounding extracellular matrix. Research shows that SPARC participates in the development of glaucoma through a variety of ways, and it may, therefore, become a new therapeutic target in the treatment.

Keywords secreted protein acidic and rich in cysteine; matricellular protein; glaucoma

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原发性开角型青光眼(primary open angle glaucoma，POAG)是全球最主要的致盲性眼病之一，其确切的发病机制尚不明确。病理性眼压增高是该病首要的危险因素，长期高眼压最终可导致视功能不可逆性损伤。眼压升高源于房水循环障碍。目前认为小梁网邻管组织(juxtacanalicular connective tissue，JCT)是产生房水流出阻力的主要部位。而JCT细胞外基质(extracellular matrix，ECM)的代谢异常可使房水流出阻力增加，进而导致眼压升高[1]。富含半胱氨酸的酸性分泌蛋白(secreted protein, acidic and rich in cysteine，SPARC)是一种基质细胞蛋白，在人眼内广泛分布，可通过多种途径调控ECM的代谢，与POAG的发生发展密切相关。研究[2]表明：SPARC有望成为青光眼潜在的治疗靶点。

1 SPARC 的概述

SPARC又被称为骨连接素或BM-40，属于基质细胞蛋白家族。后者是一类非结构性分泌糖蛋白，还包括结缔组织生长因子(connective tissue growth factor，CTGF或CCN2)、血栓连接素-1/2(thrombospondin-1/2，TSP-1/2)、肌纤蛋白、细胞黏合素-C/X、骨桥蛋白(osteopontin，OPN)、CCN家族以及富含半胱氨酸酸性分泌型糖蛋白类似物(secreted protein acidic and rich in cysteines like 1，SPARCL1；又称Hevin)等。基质细胞蛋白是沟通细胞与ECM的联系的桥梁[2]。

SPARC最早发现于骨骼[3]，哺乳动物、两栖动物、鸟类SPARC的氨基酸序列同源性超过70%。在ECM中SPARC的表达量一般较高，并在胚胎发生和组织修复中起重要作用[4]。SPARC表达增加见于一些条件性组织异常修复，如肝纤维化[5]、肾基质纤维化[6]、系统性硬化症[7]等。研究[8]表明SPARC能增强纤维连接蛋白介导的ECM积聚。抑制SPARC可减少多种胶原成份[9]和金属蛋白酶组织抑制剂-3(tissue inhibitor of metalloproteinase-3，TIMP-3)[10]的表达。SPARC在人体许多组织和细胞中均可引起金属蛋白酶系统的变化，如在人乳腺癌(MDA-MB-231，BT549)细胞系，SPARC通过抑制TIMP-2和上调MT1-基质金属蛋白酶(matrix metalloproteinase，MMPs)和MMP-14，导致MMP-2升高，进而影响肿瘤细胞的侵袭能力[11]；在单核细胞中，SPARC通过前列腺素合成酶依赖的信号通路上调MMP-1和MMP-9[12]。提示SPARC可促进ECM积聚。

2 SPARC 在眼内的分布

SPARC广泛分布于眼组织中。研究[13-15]已证实：角膜内皮细胞、视网膜色素上皮细胞、晶体内皮细胞可生成SPARC；同样也产生于小梁组织和睫状体平滑肌细胞[16-17]。在房水和玻璃体液中也可检测到含量较高的SPARC[13]。利用免疫荧光染色可发现SPARC分布于整个小梁JCT区域。SPARC的表达量可作为许多病理过程的标志物。在角膜损伤修复中，角膜成纤维细胞SPARC表达增加[18]；保持适度的SPARC对维持晶体透明可起至关重要的作用[19]；而白内障患者晶体上皮细胞SPARC表达增加[20]；在增生性玻璃体视网膜病变(proliferative vitreoretinopathy，PVR)的视网膜前膜和后膜上均可发现SPARC，其可能是PVR级联反应中的一个重要启动剂[21]。同时有研究[22]比较年龄相关性黄斑变性患者与其年龄配对的正常人的视网膜色素上皮细胞，发现前者视网膜色素上皮细胞中SPARC的含量显著增加。

3 SPARC 对眼压的影响

SPARC的表达与眼压关系密切。Haddadin等[23]发现：在中央角膜厚度相同的情况下，SPARC基因敲除小鼠眼压最低，基因杂合小鼠的眼压位于中间，而野生型小鼠眼压最高；与野生型小鼠相比，SPARC基因敲除小鼠眼压降低15%~20%，提示SPARC可显著影响房水外流模式。Chatterjee等[24]的实验结果与之类似，他们比较了不同基质细胞蛋白基因敲除小鼠的眼压与中央角膜厚度的关系，发现SPARC基因敲除小鼠的眼压下降15.1%，并在一定范围内不受中央角膜厚度变化的影响。而在体外眼前节灌注模型[25]中，SPARC过度表达会导致眼压升高。上述研究表明SPARC的表达与眼压呈正相关，并对眼压起高效的调控作用。

4 SPARC 对于小梁网的作用

SPARC是小梁网细胞上高度表达的基因之一。Wei等[26]发现：在体外培养的人小梁细胞中加入SPARC特异性siRNA后，I型和III型胶原产量增多，纤维连接蛋白产量减少。Swaminathan等[27]发现敲除SPARC的小鼠小梁网JCT区域胶原纤维直径会减少。Oh等[25]通过建立体外灌注模型，发现小梁网SPARC上调后，不但引起眼压升高，而且JCT的ECM成份发生了改变，造成I型、IV型胶原及纤维连接蛋白含量增加，而对VI型胶原及层黏连蛋白的表达无影响；而在体外培养的小梁细胞中，上调SPARC使I型、IV型和VI型胶原、纤维连接蛋白以及层黏连蛋白的均分泌增多，其中以IV型胶原增多最为明显。提示SPARC参与调控眼内ECM的合成，其过表达会造成ECM的异常沉积，堵塞小梁网，阻碍房水流出。SPARC还可能作为一个保护性伴侣稳定ECM的蛋白质，以免其被降解[27]。

5 SPARC 与 MMPs 的关系

ECM的数量与MMPs的降解平衡有关。MMPs是一类细胞外蛋白水解酶，通过调节ECM的降解与合成之间的平衡以调控眼压。SPARC与MMPs的关系较为复杂。小梁网过度表达的SPARC会导致MMP-9蛋白水平降低及TIMP-1蛋白水平升高，相似的结果在髓母细胞瘤细胞中也有发现[28]。过度表达的SPARC对MMP-7和VEGF起抑制作用[29]。SPARC还可阻止MMPs介导的胶原I和IV降解[30]。但Oh等[25]研究发现：在体外培养的小梁细胞中，过度表达SPARC只会减少MMP-9的表达，而对MMP-1和MMP-2的活性无影响，并会增加TIMP和血浆纤溶酶原激活抑制因子-1(plasminogen activator inhibitor l，PAI-1)的合成；TIMP和PAI-1均可发挥抑制MMPs的作用。因此，正常表达和过度表达的SPARC对MMPs的影响不应简单地限定为促进或抑制，对ECM来说也并非单纯量的改变，还可能会有质的变化[25]。

6 SPARC 与 TGF-β 的关系

TGF-β是调节小梁ECM合成及参与POAG发病的重要细胞因子。POAG患者房水中TGF-β2表达明显增加，且可进一步造成ECM的异常沉积[31-32]。TGF-β2信号通路还可诱导小梁细胞骨架合成增多，促进细胞收缩，使细胞张力增大，造成房水流出阻力升高[33]。POAG患者房水内TGF-β2的增高可使SPARC蛋白表达量明显上调[34]。反之，SPARC也会影响TGF-β的表达。研究[35-36]表明：在SPARC基因敲除的细胞中，TGF-β1的mRNA表达下降；在添加外源性SPARC后，TGF-β1的mRNA水平恢复正常。Swaminathan等[27]发现：向正常C57BL6/SVl29wT小鼠眼内注射含TGF-β2的腺病毒后，胶原蛋白IV，纤维连接蛋白，PAI-1，CTGF，SPARC的表达均上调，这些物质均可造成ECM异常沉积，堵塞房水流出通路；而在敲除SPARC基因的小鼠眼内，TGF-β2只能诱导PAI-1和CTGF表达，敲除SPARC通过限制胶原蛋白IV和纤连蛋白的表达，可显著降低TGF-β2的作用。提示SPARC参与TGF-β2的升眼压作用。Kang等[37]通过进一步研究发现：在人小梁细胞中，TFG-β2可通过Smad2/3和P38通路导致SPARC上调，表明SPARC可能是TGF-β2的下游调控点，并在其作用通路中发挥关键作用。

7 SPARC对人 Tenon's囊成纤维细胞的作用

人Tenon's囊成纤维细胞(human tenon's capsule fibroblast，HTF)是结膜下瘢痕形成的主要细胞，也是导致青光眼滤过手术失败的主要细胞。目前研究[38]认为：滤过术后，成纤维细胞的大量增殖与凋亡抑制、细胞外基质合成与降解失衡、部分细胞因子的大量产生，三者密切关联并构成病理性瘢痕形成的生物学基础。HTF细胞大量增殖及分泌大量的细胞外基质，可促进滤过道瘢痕的形成[39]。Fuchshofer等[40]发现：用TGF-β1处理后，HTF细胞在mRNA和蛋白水平SPARC表达均增多；经SPARC处理后的HTF细胞，其细胞胶原基质收缩，细胞增殖增加。Seet等[41]通过敲除HTF细胞SPARC基因，发现HTF细胞SPARC表达降低，并且伤口修复和纤维化过程中的重要指标，如collagen I，MMP-2，MMP-9，MMP-14，IL-8，MCP-1和TGF-β2等表达降低，骨胶原收缩能力降低；同时，在SPARC敲除的HTF细胞中，TGF-β2

作用刺激下的HTF细胞无法显著增加骨胶原I、纤连蛋白的表达。

8 SPARC 的其他作用

除上述作用外，SPARC在眼内的某些作用可能也参与到青光眼的发病机制。研究[42]证实：青光眼患者的虹膜SPARC表达显著增加，可改变虹膜的生物力学特性，并可能在青光眼的进展中发挥一定的作用。此外，Hernandez等[43]指出POAG患者的筛板(lamina cribrosa，LC)发生了纤维化和机械性损伤。研究[44]证实LC和小梁组织具有相似的生物化学性质。LC区域ECM的代谢异常也是青光眼发病机制中的重要环节，而SPARC在调节LC区域的ECM中同样起关键作用[45]。

9 结语

目前，SPARC已成为青光眼发病机制研究中的热点。其确切作用机制，尤其是上游调控通路机制仍不明确。但随着相关研究的深入，SPARC未来在青光眼领域将会有广阔的应用前景。

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