

# 富含半胱氨酸的酸性分泌蛋白在心血管疾病中的研究进展

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**【摘要】** 富含半胱氨酸的酸性分泌蛋白 (SPARC) 为典型的基质细胞蛋白, 参与组织发育和修复, 通过调节细胞黏附、增殖和生长因子信号转导, 以及细胞外基质与细胞的相互作用, 在心肌损伤过程发挥重要作用。该文介绍 SPARC 在高血压、冠状动脉粥样硬化性心脏病、心力衰竭、病毒性心肌炎等心血管疾病中的相关研究进展。

**【关键词】** 富含半胱氨酸的酸性分泌蛋白; 高血压; 冠状动脉粥样硬化性心脏病; 心力衰竭; 心肌炎

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富含半胱氨酸的酸性分泌蛋白 (SPARC) 又称为骨连接素 (osteonectin) 或骨基质 -40 (BM-40), 是典型的基质细胞蛋白, 由 3 个结构域组成<sup>[1]</sup>, 1981 年由 Termine 等<sup>[2]</sup>首次在牛骨中发现。之后的研究发现, 人体内多个器官和组织都可以分泌 SPARC, 如心、脑、胰腺等, 但在脂肪组织中的表达更为明显<sup>[3-4]</sup>。SPARC 在胚胎心脏发育时表达显著升高, 随着器官发育成熟, SPARC 水平逐渐下降, 并在正常心脏中保持相对较低的水平。当心肌受损 (如心肌梗死、心肌纤维化等) 时, SPARC 会再次升高<sup>[5-6]</sup>。近年来研究发现, SPARC 在损伤和伤口愈合<sup>[7-8]</sup>、运动和运动诱导的肌肉变化<sup>[9-10]</sup>、葡萄糖稳态和胰岛素分泌<sup>[11-12]</sup>、代谢和能量平衡<sup>[13-14]</sup>、再生<sup>[15]</sup>、炎症<sup>[16-17]</sup>、癌症<sup>[18-20]</sup>、肥胖和糖尿病<sup>[21]</sup>、脂质代谢<sup>[22]</sup>、心肌修复和纤维化<sup>[6,23]</sup>等中都有重要意义, 而肥胖、糖尿病、脂质代谢、心肌修复和纤维化与心血管疾病均有密切联系。SPARC 在心血管疾病中的作用受到关注。

## 1 SPARC与高血压

高血压是心血管疾病的主要危险因素, 交感神经系统、肾素-血管紧张素-醛固酮系统和免疫系统等在高血压的发展中起重要作用。

李芳等<sup>[24]</sup>临床研究发现, 老年原发性高血压

患者血清中 SPARC 水平显著升高, 且与高血压分级及颈动脉粥样硬化分级呈正相关。李娜等<sup>[25-26]</sup>的研究也证明了 SPARC 在老年原发性高血压患者中升高, 且随着高血压并发症的出现, 其水平呈上升趋势, 并与患者动脉粥样硬化各危险因素相关。其机制可能为 SPARC 参与脂质代谢异常、动脉粥样硬化和慢性炎症进程, 导致血压升高。Toba 等<sup>[27]</sup>研究证明, SPARC 可使肾脏中血小板结合蛋白基序的解聚蛋白样金属蛋白酶 1 (ADAMTS1) 过度表达, 促进高血压相关胶原蛋白沉积, SPARC/ADAMTS1 信号通路被认为是肾素-血管紧张素系统导致高血压肾损伤的机制之一。SPARC 可以预测老年高血压患者动脉粥样硬化程度, 并有可能作为治疗高血压肾病患者肾脏纤维化的新靶点, 但其具体机制有待进一步研究。

## 2 SPARC与冠状动脉粥样硬化性心脏病

我国冠状动脉粥样硬化性心脏病 (冠心病) 患病率及病死率呈逐年快速上升趋势。SPARC 可由脂肪组织分泌, 与肥胖、脂质代谢及糖尿病等多种冠心病危险因素关系密切<sup>[21-22]</sup>。Takahashi 等<sup>[28]</sup>临床研究证明, 冠心病患者血清中 SPARC 水平升高。也有文献证明, SPARC 在动脉粥样硬化血管病变中呈高表达<sup>[29]</sup>。Avolio 等<sup>[5]</sup>研究表明, SPARC 在梗死心肌和慢性缺血心肌中高表达, 并与心肌损伤标志物肌酸激酶同工酶 (CK-MB) 呈正相关。Ragino 等<sup>[30]</sup>研究发现, SPARC 与动脉

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粥样硬化关键标志物显著相关,可作为冠状动脉粥样硬化的新型生物标志物。这些研究结果提示,SPARC 可能在动脉粥样硬化的发生发展中发挥重要作用。

### 3 SPARC与心力衰竭

心力衰竭是各种心血管疾病的终末阶段,心室重构是心力衰竭主要的病理生理机制。SPARC 可促使心肌细胞外基质改变、胶原蛋白沉着和纤维化发生,在心室重构中起重要作用。

基质金属蛋白酶(MMP)家族中 MMP-2 和 MMP-9 的活性升高与心脏重构和心力衰竭有关<sup>[31]</sup>,而 SPARC 可增加 MMP-2 和 MMP-9 的表达水平和活性<sup>[32]</sup>。Riley 等<sup>[33]</sup>研究证明,在心肌纤维化时,骨髓源性细胞高表达 SPARC,可促进心脏纤维化、心肌硬度增加和心脏巨噬细胞增加。微小 RNA(miRNA)-29b 被认为是心肌纤维化的重要调节因子,动物研究表明,miR-29b-3p 可通过诱导 SPARC 和调节转化生长因子(TGF)- $\beta$ 1/Smad3 通路,在心力衰竭的发生发展中起重要作用<sup>[34]</sup>。SPARC 还可通过调节细胞外基质(ECM)介导的心肌纤维化、巨噬细胞驱动的炎症反应和脂肪酸代谢,直接或间接影响急性心肌梗死后的心肌重构<sup>[6]</sup>。因此,SPARC 可通过参与心肌纤维化、心室重构等影响心力衰竭的发生发展。

Schellings 等<sup>[23]</sup>在动物研究中发现,心肌梗死发生后,SPARC 高表达可增加细胞外基质中成纤维细胞数量,从而引起瘢痕修复和心肌重构。Xia 等<sup>[35]</sup>研究发现,在小鼠心肌梗死模型中,心脏调节性 T(Treg)细胞高表达的 SPARC 可增加心肌梗死区胶原蛋白含量并促进胶原成熟,对心肌梗死后的心脏完整性起到保护作用。这些动物实验说明心肌梗死后 SPARC 高表达可降低心脏破裂、急性心力衰竭等急性并发症的发生率。SPARC 对心脏的保护作用提示该蛋白在预防心肌梗死后心脏扩张和功能障碍方面具有潜在治疗意义。

有临床研究表明,SPARC 与慢性心力衰竭相关死亡、全因死亡及因慢性心力衰竭复发住院的风险增加相关,SPARC 联合 N 末端脑钠肽前体(NT-proBNP)在预测缺血性心力衰竭患者死亡率和住院率方面有极高的敏感性和特异性<sup>[36]</sup>。也有研究发现,冠心病患者 SPARC 水平升高,可预测中至重度心力衰竭患者的心血管不良事件结局<sup>[37]</sup>。因此,SPARC 对心功能恶化有一定的预测作用。

### 4 SPARC与病毒性心肌炎

病毒性心肌炎是一种致命的炎症性心脏病,是扩张型心肌病、(急性)心力衰竭和心源性猝死的主要病因之一。许多病毒都可引起病毒性心肌炎,包括柯萨奇 B 病毒(CVB)、肠病毒、巨细胞病毒等。对于病毒性心肌炎相关心力衰竭患者,心脏活组织检查发现感染最多的是 CVB。到目前为止,关于病毒性心肌炎新治疗策略的研究和开发主要集中在炎症、心肌细胞退变和纤维化等方面<sup>[38]</sup>,只有少数研究涉及到病毒感染对心肌细胞功能的直接影响。

Rienks 等<sup>[39]</sup>研究证实,在 CVB3 感染的心肌炎小鼠模型中,SPARC 可通过修复和保护内皮糖萼层以及改善内皮屏障功能影响炎症和血管通透性,起到预防不良心脏炎症和降低死亡率的效果。在病毒感染期间,尽管野生型小鼠和 SPARC 基因敲除小鼠的心率相似,但野生型小鼠与 SPARC 基因敲除小鼠的 QTc 间期有明显差异。Deckx 等<sup>[40]</sup>也在临床研究中证明,在病毒性心肌炎发生时,SPARC 水平升高可以使左室短轴缩短率和心脏射血分数增加。

SPARC 不仅能够参与修复因病毒感染而受损的心肌细胞,还能通过影响心肌细胞收缩改善心功能。这些研究表明 SPARC 可以作为病毒性心肌炎治疗的新靶点。

### 5 小结

外周循环中的 SPARC 具有多种生物学作用,与冠心病的多种传统危险因素及心血管疾病的发生发展关系密切。随着研究的不断深入,SPARC 将为心血管疾病早期诊断和治疗提供新的思路 and 策略。

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