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可溶性生长刺激表达基因 2 蛋白与高血压左心室肥大的关系

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【摘要】 可溶性生长刺激表达基因2蛋白(sST2)是白介素1受体家族成员,与心肌纤维化密切相关,而心肌纤维化是高血压左心室肥大(LVH)的重要组成部分。近年研究发现,sST2在高血压LVH发生发展中发挥着重要作用。本文通过分析sST2与高血压LVH的关系发现,sST2是高血压LVH的生物标志物,其主要通过心肌纤维化导致高血压LVH。

【关键词】 高血压;左心室肥大;可溶性生长刺激表达基因2蛋白;综述

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Relationship between Soluble Suppression of Tumorigenicity 2 and Hypertensive Left Ventricular Hypertrophy

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【Abstract】 Soluble suppression of tumorigenicity 2 (sST2) is a member of the interleukin-1 receptor family and is closely related to myocardial fibrosis, which is an important component of hypertensive left ventricular hypertrophy (LVH). Recent studies have found that sST2 plays an important role in the development of hypertensive LVH. In this paper, by analyzing the relationship between sST2 and hypertensive LVH, it is found that sST2 is a biomarker of hypertensive LVH, which mainly leads to hypertensive LVH through myocardial fibrosis.

【Key words】 Hypertension; Left ventricular hypertrophy; Soluble suppression of tumorigenicity 2; Review

原发性高血压是一种常见的心血管疾病,而动脉血压长期持续升高会改变心脏结构和功能^[1]。原发性高血压的早期表现有左心室肥大(left ventricular hypertrophy, LVH)和舒张功能障碍^[2],其中LVH可能导致心肌细胞和间质结构改变,从而导致电生理异常;此外,LVH还能导致心肌缺血、心脏自主神经功能改变,进而引起心肌电活动异常,最终导致心律失常^[2]。因此,高血压LVH被认为是心力衰竭、心肌梗死、心律失常、心源性猝死的危险因素^[3]。生长刺激表达基因2蛋白(suppression of tumorigenicity 2, ST2)是IL-1受体家族成员,是机械应激的生物标志物,在暴露于生物机械应力的心肌细胞和成纤维细胞中上调^[4]。可溶性生长刺激表达基因2蛋白(soluble suppression of tumorigenicity 2, sST2)是ST2的亚型,其可参与免疫调节和炎症反应,并可作为心脏成纤维细胞和心肌细胞之间信号转导的重要媒介^[5]。研究表明,IL-33/ST2信号传导通路是促进心室重构的主要途径^[6-8]。国外一项前瞻性研究表明,sST2水平>28.5 μg/L的高血压患者不良心血管事件发生风险更高^[9]。本文通过分析sST2与高血压LVH的关系发现,sST2是高血压LVH的生物标志物,并总

结了其通过心肌纤维化导致高血压LVH的机制。

1 高血压LVH的发病机制

高血压LVH的发病机制非常复杂,涉及血流动力学改变、神经和内分泌因素、氧化应激和炎症反应、细胞凋亡、细胞内钙超载、基因转录和遗传因素等,其中以神经和内分泌因素为主,肾素-血管紧张素-醛固酮系统平衡在LVH发生发展中发挥着至关重要的作用,即血管紧张素(angiotensin, Ang)Ⅱ可引起血管收缩、血压升高,继而造成心肌细胞代偿性肥大,局部AngⅡ作用于血管紧张素Ⅱ受体1可引起心肌纤维化,促进LVH;而血管紧张素转换酶2可通过促进Ang-(1-7)合成而激活Mas受体,进而使血管舒张,抑制心肌纤维化与心肌细胞增殖,从而抑制LVH^[10]。

心肌纤维化(myocardial fibrosis, MF)是高血压LVH的关键特征之一,被认为是心肌胶原纤维过度沉积所致^[11]。MF指心肌间质成纤维细胞增殖、细胞外基质(extracellular matrix, ECM)沉积引起心肌正常组织结构中胶原纤维过量沉积,胶原浓度或胶原容积分数明显增加,各类型胶原比例失调和排列紊乱的一种病理改变,是心脏重构的主要表现之一^[12]。MF主要分为替代性(修复性)MF和间质性(反应性)MF,前者的特征是死亡或凋亡的心肌细胞形成微瘢痕

小病灶,其可发生于心肌梗死或其他原因引起的死亡心肌细胞中;后者的特征是过量胶原纤维弥漫性沉积,会导致左心室收缩、舒张功能障碍,常发生于血流动力学超负荷的心力衰竭或非缺血性心脏病患者,如高血压心脏病、主动脉瓣狭窄、糖尿病心肌病及肥厚型心肌病^[11-12]。

2 sST2的概述

ST2是Toll样/IL-1受体超家族成员之一,其在1989年被首次发现^[13-14]。ST2的主要亚型为sST2和跨膜型ST2(transmembrane growth stimulation expressed gene 2, ST2L),该基因有近端启动子和远端启动子,这两个启动子均能影响基因的转录调控机制及调控sST2、ST2L mRNA的表达,其中mRNA 3'的选择性剪接是导致sST2和ST2L产生差异的原因^[15]。ST2L具有细胞外IgG结构域、细胞内结构域和跨膜结构域,sST2因缺乏细胞内结构域和跨膜结构域而能被检测到^[13],当心肌细胞和成纤维细胞受到生物机械应力时sST2生成增多;此外,心脏大血管(主动脉和冠状动脉)和微血管内皮细胞均是sST2的来源^[16-17]。临床研究证实,心血管疾病患者血清sST2水平始终维持在较高水平,并与患者主要不良心血管事件和全因死亡风险相关^[18]。SCHMITZ等^[19]研究表明,IL-33为ST2的配体。

3 sST2是高血压LVH的生物标志物

目前,高血压LVH的传统生物标志物有NT-proBNP^[20]、IL-6^[21]、超敏心肌肌钙蛋白^[22],新型生物标志物有sST2^[23]、基质金属蛋白酶^[24]、Galectin-3^[25]、生长分化因子^[26]等,其中sST2与NT-proBNP研究较多。研究表明,NT-proBNP可有效评估心脏结构和功能改变^[27]。

与NT-proBNP相比,血清sST2因其特异性低而在包括高血压在内的多种心血管疾病中可被检测到,且其水平受年龄、BMI、肾功能等非心源性因素的影响较小^[28-29]。研究表明,与NT-proBNP相比,sST2对LVH的预测价值更高,提示sST2可能是原发性高血压患者发生LVH的一个重要因素^[30],与杨树涵等^[31]、王正辉^[32]研究结果一致。研究发现,NT-proBNP可有效鉴别高血压患者与高血压心力衰竭患者,但其不能有效鉴别高血压患者是否伴有LVH^[33-34]。国外一项大型前瞻性研究表明,原发性高血压患者左心室质量指数(left ventricular mass index, LVMI)与主要不良心血管事件发生率存在强烈的相关性,如LVMI每增加39 g/m²,患者主要不良心血管事件发生风险将增加40%^[35]。研究指出,在从未接受降压治疗的原发性高血压患者中,NT-proBNP与其LVMI无明显相关性^[36];但有多项研究指出,原发性高血压患者sST2水平与LVMI呈正相关^[37-39],提示sST2对原发性高血压患者伴LVH的筛查价值优于NT-proBNP。FARCAŞ等^[40]研究结果显示,当sST2的最佳截断值为14.04 μg/L时,其诊断LVH的灵敏度、特异度分别为82.1%、53.8%;当sST2的最佳截断值为24.18 μg/L时,其鉴别诊断高血压患者2级舒张功能障碍和正常舒张功能的灵敏度、特异度分别为94.4%、69.1%,提示sST2有助于诊断高血压患者左心室舒张功能障碍。

综上,sST2可作为诊断高血压LVH的新型生物标志物。

4 sST2通过心肌纤维化导致LVH的机制

4.1 信号通路

4.1.1 IL-33/ST2L信号通路

研究表明,IL-33/ST2L信号通路是促进心肌纤维化的主要途径^[8]。生物力学应力是IL-33/ST2L信号通路的主要诱因,是心脏中主要的机械敏感信号传导系统^[41]。在生物力学应力作用下,受损的心肌细胞首先释放“警报”蛋白细胞因子——IL-33,进而阻止局部心肌细胞死亡和组织损失^[16]。心肌细胞和心脏成纤维细胞在生物力学应力作用下,ST2L和sST2的释放均增加^[42],这种释放增加是由于容量和/或压力超负荷诱导心室肥大中的重要一步^[43]。高水平sST2可作为“诱饵受体”与IL-33结合,并作为IL-33/ST2L信号通路的一种“关闭开关”,从而导致IL-33/ST2L信号通路中断,降低IL-33对心脏的保护作用,并对整体心血管风险产生不利影响^[6]。IL-33的作用是促进细胞存活并防止促凋亡和促纤维化信号之间的传导,尤其是通过激活和募集Th2免疫应答而减少有害的ECM重排^[19,44]。激活的IL-33仅通过ST2L和IL-33复合物发挥生物学效应,而ST2L和IL-33复合物通过髓样分化因子88衔接蛋白、白介素1/4受体相关激酶和TNF受体相关因子6激活细胞内信号传导,从而促进细胞存活,激活NF-κB、丝裂原活化蛋白激酶、细胞外信号调节激酶、p38和c-Jun氨基末端激酶^[7],最终导致Th2相关细胞因子/趋化因子的产生,而这些细胞因子/趋化因子被分泌到细胞外并产生足够的免疫反应,进而抑制炎症反应、心肌纤维化和心室重塑,从而保护心脏;但sST2可作为“诱饵受体”与IL-33结合,从而阻止ST2L/IL-1RAcP二聚体复合物的激活,阻断IL-33/ST2信号通路对心脏组织的保护作用^[19]。SANADA等^[6]研究表明,IL-33激活了心肌细胞和成纤维细胞中的NF-κB通路,但抑制了Ang II和去氧肾上腺素对NF-κB的直接激活作用,从而减轻心肌细胞肥大、心肌纤维化。此外,YIN等^[23]的一项包含472名受试者(166名高血压患者,306名健康对照者)的研究发现,高血压患者sST2水平高于健康对照者(663.84 μg/L比549.05 μg/L, $P<0.001$)、中位IL-33/sST2比值低于健康对照者(0.17 μg/L比0.20 μg/L, $P<0.001$);Pearson相关分析结果显示,血清IL-33与血清sST2呈负相关。

综上,sST2通过阻止IL-33与ST2L结合而中断IL-33/ST2L信号通路,进而抑制心肌纤维化导致的LVH。

4.1.2 NF-κB信号通路

心肌纤维化的关键是心脏成纤维细胞活化及其向肌成纤维细胞转化,从而促进ECM的产生。肌成纤维细胞活化后通过释放促纤维化因子而引起心肌细胞肥大和心脏功能障碍^[45]。NF-κB信号通路可直接调控心肌纤维化相关基因表达,包括纤连蛋白和基质金属蛋白酶^[46];此外,NF-κB磷酸化还可导致心脏成纤维细胞转化为肌成纤维细胞^[47]。神经纤毛蛋白1(neuropilin-1, NRP-1)是一种分子量为130 kDa的跨膜蛋白,是人成纤维细胞激活和促纤维化表型的新型诱导剂,国外研究指出,在压力超负荷大鼠模型中,sST2可上调成人心脏成纤维细胞中的NRP-1表达,且其通过NRP-1介

导心脏成纤维细胞活化及胶原蛋白和促纤维化分子的积累；而阻断NF- κ B信号通路可恢复NRP-1的表达，改善sST2诱导的促纤维化状态。因此，NF- κ B信号通路可能是调控sST2和NRP-1诱导的肌成纤维细胞活化和胶原蛋白分泌的关键通路^[48]。研究表明，NRP-1可调节血管张力和血压，其表达缺失会导致高血压并加剧心功能障碍^[49]。

综上，sST2与NRP-1在高血压LVH发生发展中具有重要作用，但其具体作用机制尚不清楚。

4.2 氧化应激和炎症反应

氧化应激和炎症反应在高血压LVH中发挥着重要作用^[50]。研究表明，sST2可抑制线粒体融合蛋白1 (mitofusin 1, MFN1) 表达，并促进活性氧 (reactive oxygen species, ROS) 和炎症因子的分泌，从而导致人心脏成纤维细胞发生氧化应激和炎症反应^[51]，促进心肌肥大和心功能障碍。

4.3 细胞衰老

细胞衰老是一种不可逆的细胞周期阻滞状态，与纤维化密切相关^[52]。部分研究表明，细胞衰老可促进心肌纤维化^[53]；但也有研究表明，细胞衰老可减轻心肌、肝脏、肺纤维化^[54]。细胞衰老主要由SIRT1/p53/p21信号通路介导，实验表明，sST2可上调SIRT1 mRNA、蛋白表达水平，下调衰老相关蛋白p16、p21、p53表达水平，而经sST2中和抗体处理的病毒性心肌炎小鼠纤维化指标 (I型胶原、III型胶原和 α -平滑肌肌动蛋白) 明显降低，提示sST2通过抑制细胞衰老而促进胶原沉积，从而加速心肌纤维化^[55-56]。衰老标记蛋白30 (senescence marker protein 30, SMP30) 被认为具有抗衰老作用，研究表明，心脏特异性过度表达SMP30可抑制Ang II诱导的心脏不良重塑和舒张功能障碍，提示SMP30可能成为高血压LVH的防治靶点^[57]。

4.4 肥大细胞

研究表明，肥大细胞可参与高血压LVH的发生发展^[58]。肥大细胞是多功能细胞，具有持续的免疫调节和“哨兵”作用，其可选择性分泌多种促炎细胞因子 (如IL-1 β 、IL-6、干扰素)、抗炎细胞因子 (如：IL-10、IL-13)、促纤维化因子 (转化生长因子 β 、碱性成纤维细胞生长因子) 和抗纤维化因子 (血管内皮生长因子、IL-33、前列腺素D2)^[59-60]。KOTOV等^[61]通过甲苯胺蓝、类胰蛋白酶和c-kit染色评估6月龄 (已确诊高血压和心脏肥大) 和12月龄 (晚期高血压和心脏肥大) 的自发性高血压大鼠肥大细胞数量，结果显示，12月龄自发性高血压大鼠肥大细胞明显增多。鉴于肥大细胞可能产生促纤维化递质和抗纤维化递质作用，故其在组织重塑中的作用尚存在争议^[62]。研究表明，细胞表面的肥大细胞可大量表达IL-33受体sST2^[63-64]。

综上，sST2可能通过肥大细胞而在高血压LVH中发挥重要作用。

5 小结与展望

高血压是心脏病的独立危险因素，该病患者左心室负荷增加可促使心肌细胞、肌成纤维细胞和血管内皮细胞分泌并释放sST2。目前虽有研究表明，sST2可通过IL-33/ST2L信号通路、NF- κ B信号通路及氧化应激、炎症反应、细胞衰老、肥

大细胞等促进心肌纤维化，进而参与高血压LVH，但其高血压LVH发生发展中的机制尚未完全阐明，未来还需要大量研究进一步证实、探索sST2与高血压LVH的关系。

作者贡献：谢云梯进行文章的构思与设计，文献/资料整理，论文撰写、修订；潘兴寿进行文章的可行性分析，负责文章的质量控制及审校，并对文章整体负责、监督管理。

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