动脉粥样硬化过程中核因子E2相关因子2 对血管平滑肌细胞的调控作用

庄文雯¹, 杨咏琪¹, 李洪亮^{1,2}, 梁景岩^{1,2}

1. 扬州大学医学院, 江苏 扬州 225000

2. 扬州大学转化医学研究院, 江苏 扬州 225000

[摘 要] 动脉粥样硬化是心血管疾病中常见的病理改变。血管平滑肌细胞是斑块细胞和细胞外基质的主要来源,而核因子E2相关因子2(Nrf2)是调控血管平滑肌细胞功能的关键转录因子。在动脉粥样硬化过程中,Nrf2信号通路对血管平滑肌细胞具有以下调控作用:调控血管平滑肌细胞表型向有利于缓解疾病进程的方向转变,抑制血管平滑肌细胞增殖和迁移,降低血脂水平,以及缓解血管平滑肌细胞钙化、衰老和凋亡等过程。本文对现阶段Nrf2在动脉粥样硬化中调控血管平滑肌细胞表型转换、增殖和迁移、脂代谢、钙化、衰老和凋亡等过程的具体机制进行综述,以期为深入理解动脉粥样硬化发生发展的分子机制及寻找治疗靶点提供依据。

[关键词] 动脉粥样硬化;血管平滑肌细胞;核因子E2相关因子2;综述

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Research advance of Nrf2 on atherosclerosis by regulating vascular smooth muscle cell

ZHUANG Wenwen¹, YANG Yongqi¹, LI Hongliang^{1,2}, LIANG Jingyan^{1,2} (1. Medical College, Yangzhou University, Yangzhou 225000, Jiangsu Province, China; 2. Institute of Translational Medicine, Yangzhou University, Yangzhou 225000, Jiangsu Province, China)

Corresponding author: LIANG Jingyan, E-mail: jyliang@yzu.edu.cn, <https://orcid.org/0000-0002-9674-0235>

[Abstract] Atherosclerosis is a common pathological change in cardiovascular disease. Vascular smooth muscle cell is the main source of plaque cell and extracellular matrix, and nuclear factor-erythroid 2-related factor 2 (Nrf2) is a key transcription factor

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第一作者:庄文雯,硕士研究生,主要从事心血管病研究;E-mail:zhuangwenwen_epig@163.com;<https://orcid.org/0000-0003-1172-6512>

通信作者:梁景岩,教授,博士生导师,主要从事心脑血管病研究;E-mail:jyliang@yzu.edu.cn;<https://orcid.org/0000-0002-9674-0235>

regulating the function of vascular smooth muscle cell. In the process of atherosclerosis, Nrf2 signaling pathway has the following regulatory effects on vascular smooth muscle cell: regulating the phenotype of vascular smooth muscle cell to change to the direction conducive to the alleviation of disease progression; inhibiting the proliferation and migration of vascular smooth muscle cell; mitigating the level of blood lipid; alleviating vascular smooth muscle cell calcification, aging and apoptosis process. This article reviews the specific mechanisms of Nrf2 regulating atherosclerosis, such as phenotypic transformation, proliferation and migration, lipid metabolism, calcification, aging and apoptosis in atherosclerosis, in order to provide a basis for understanding the molecular mechanism of atherosclerosis development and finding therapeutic targets.

[**Key words**] Atherosclerosis; Vascular smooth muscle cell; Nuclear factor-erythroid 2-related factor 2; Review

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[**缩略语**] 动脉粥样硬化(atherosclerosis, AS);血管平滑肌细胞(vascular smooth muscle cell, VSMC);核因子E2相关因子(nuclear factor-erythroid 2-related factor, Nrf);血管紧张素Ⅱ(angiotensin Ⅱ, Ang Ⅱ);血红素加氧酶(heme oxygenase, HO);醌氧化还原酶[NAD(P)H quinone dehydrogenase, NQO];NADPH氧化酶(NADPH oxidase, NOX);谷氨酸半胱氨酸连接酶催化亚基(glutamate-cysteine ligase catalytic subunit, GCLC);Kelch样环氧氯丙烷相关蛋白(Kelch-like ECH-associated protein, Keap)

研究发现, AS小鼠模型中VSMC来源的细胞占AS斑块中细胞总数的70%以上^[1]。VSMC主要位于血管壁的中膜, 是构成血管壁的主要成分^[2]。生理状态下, VSMC的增殖、迁移、凋亡等均保持动态平衡, 以维持血管壁的正常形态和功能^[3-5]。当平衡被破坏时, 血管壁发生氧化应激、炎症反应、粥样硬化病变、管腔狭窄等, 是心血管疾病的始动因素^[6]。VSMC在AS所有阶段均发挥重要作用^[7-8]。VSMC具有起源多样、可塑、易克隆等特性^[9-10], 因此VSMC表型易转换为不同细胞类型、出现异常增殖, 从而影响AS的进程。

Nrf2是一种普遍存在的氧化还原激活的转录因子, 对内源性和外源性氧化刺激具有抵抗作用^[11]。在AS病变中, Nrf2信号通路被激活, 并在VSMC表型转换、增殖和迁移、脂代谢、凋亡等过程中发挥作用, 促进AS的发生发展^[12-13]。由于Nrf2激活程度、VSMC特性及AS的阶段不同, Nrf2对AS的调控具有两面性^[14-15]。本文对Nrf2信号通路在VSMC表型转换、增殖和迁移、钙化、脂代谢、凋亡和衰老等过程中调控VSMC的作用进行阐述, 以期深入了解和早期预防AS形成提供新的思路。

1 Nrf2信号通路与VSMC表型转换

VSMC是血管壁中膜主要的细胞类型, 分为收缩型和合成型两种: 收缩型VSMC在正常血管中占绝大部分; 合成型VSMC增殖迁移快, 是新生内膜的主要组成部分。当发生AS时, 原本静止的VSMC从血管壁中层逐渐进入内膜并形成新生内膜, 而合成型VSMC更易促进脂质的吸收和泡沫细胞的形成^[16]。Pan等^[17]通过单细胞测序发现VSMC在AS过程中转变为一种中间细胞状态, 这种中间细胞称为“SEM”细胞(干细胞、内皮细胞、单核细胞), 具有多能性。VSMC还可分化为巨噬细胞样细胞和纤维软骨细胞样细胞, 并执行各自功能, 在AS进程中发挥重要作用^[17]。

VSMC表型转换受转录因子、胞外刺激、细胞相互作用及表观遗传学等多因素影响^[18]。单细胞RNA测序表明, Nrf2是VSMC细胞转变的关键调控因子, AS患者中Nrf2信号表达异常^[17]。He等^[19]通过体外及体内大鼠腹主动脉缩窄模型实验证明Nrf2被胆碱激活, 其下游蛋白HO-1和NQO-1表达上调, 同时抑制Ang Ⅱ诱导的NOX-1/NOX-2/

NOX-4和线粒体活性氧水平升高,可以延缓VSMC表型向合成型转换所导致的血管重塑。因此,VSMC表型转换似乎是一个(至少部分)可逆的过程,且Nrf2可以调控VSMC表型向有利于缓解AS进程的方向转变。

2 Nrf2信号通路与VSMC增殖和迁移

已有研究证实了Nrf2信号通路与VSMC增生和迁移的关系。VSMC从动脉中膜向内膜迁移并增殖是AS的重要特征之一,VSMC病理性堆积加速了AS斑块形成及破裂,而Nrf2信号通路主要参与抑制VSMC的增殖和迁移^[20-22]。Ko等^[23]发现,Nrf2可以被p38丝裂原激活的蛋白激酶介导的纳米金颗粒激活,继而诱导Nrf2及其下游HO-1蛋白的表达,以此抑制大鼠主动脉VSMC的增殖和迁移。目前有研究报道,20多种植物提取物(姜黄素、白藜芦醇、肉桂醛、青蒿琥酯及夏枯草等)可作为Nrf2表观遗传修饰剂^[9,24-26]。Buglak等^[20]首次在大鼠模型中发现Nrf2可以被肉桂醛激活,导致下游HO-1、超氧化物歧化酶1、GCLC和过氧化物酶1蛋白水平升高,从而抑制新生内膜增生和VSMC迁移。Shawky等^[24]为了研究Nrf2/HO-1信号通路是否可被萝卜硫素激活进而抑制VSMC增殖,通过构建靶向Nrf2基因的小干扰RNA表达载体进而转染人主动脉VSMC以有效抑制Nrf2表达,结果发现下调Nrf2/HO-1信号并不影响萝卜硫素抑制VSMC增殖的过程,而是通过抑制雷帕霉素靶蛋白复合体1的下游靶点(70 000核糖体蛋白S6激酶和真核细胞翻译起始因子4E结合蛋白1)的磷酸化来减弱血小板衍生生长因子诱导的VSMC增殖和迁移。由此可见,利用天然提取小分子药物激活Nrf2及其下游经典通路,抑制VSMC增殖和迁移,可以达到细胞保护的作用,但具体的保护机制尚需进一步研究,后续研究可通过条件性敲除VSMC上的Nrf2基因,以明确其在AS中对VSMC增殖和迁移的靶向调控机制。

鉴于许多Nrf2药理激活剂正在进行临床试验,且这种激活缺乏特异性,未来的研究还需完善Nrf2靶向调控机制(如识别细胞特异性的Nrf2靶基因),以寻找特异、安全和生物利用度高且可口服的小分子Nrf2激活剂。尽管已有多项研究证实Nrf2信号通路可以抑制VSMC增殖和迁移,但考虑到Nrf2信号通路的复杂性以及与其他信号通路的

交联作用^[3,27-28],具体机制有待于更多的研究进一步证实。

3 Nrf2信号通路与VSMC钙化

动脉钙化是心血管疾病的常见并发症,通常发生在动脉的内膜和中膜,而动脉中膜钙化是AS进程的主要危险因素^[29]。血管钙化的关键细胞类型是VSMC^[28],因此了解调节血管钙化的VSMC内通路可能有助于开发可行的治疗新方法。正常生理情况下,Nrf2被胞浆蛋白Keap1锚定在细胞质中,而Keap1作为泛素连接酶3依赖性E3泛素连接酶复合物的作用底物,能够促使Nrf2发生泛素化且被蛋白酶体快速降解^[30-31]。发生氧化应激等刺激时,Nrf2从Keap1中解离且快速转移至细胞核,激活其下游相关调控蛋白及抗氧化因子^[32-33]。Xu等^[34]研究发现,Nrf2可因Keap1糖基化而快速降解,抑制VSMC自噬,从而促进高磷酸盐诱导的VSMC钙化,导致AS等心血管疾病恶化。在AS中,一方面,自噬具有保护作用,通过降解VSMC中受损的细胞内物质促进斑块稳定;另一方面,过度刺激自噬导致AS发生过程中VSMC自噬性死亡^[35]。因此,自噬的形成在不同条件下具有不同的含义,运用靶细胞自噬的方法治疗血管性疾病时应综合考虑。Aghagolzadeh等^[36]采用循环钙蛋白颗粒诱导VSMC钙化模型,并采用高通量测序技术证实硫化氢可激活经典通路Keap1/Nrf2/NQO-1,从而减弱VSMC的钙化程度。Wei等^[29]通过体外高磷诱导氧化应激和VSMC钙化模型实验,证明特丁基对苯二酚可激活非经典通路Keap1/Nrf2/P62,降低VSMC的活性氧水平和钙沉积。综上所述,动脉钙化不是一个被动过程,是主要由VSMC钙化驱动的主动过程,而Nrf2的激活可以抑制VSMC的钙化。因此,了解Nrf2调节VSMC钙化的机制,可为识别AS新的治疗靶点提供帮助。

4 Nrf2信号通路与VSMC脂代谢

AS形成过程中,VSMC转换为巨噬细胞表型时可承担巨噬细胞的功能^[37]。分化的VSMC表达多种脂肪酸和胆固醇摄取受体,执行捕获脂肪酸和胆固醇功能,使细胞质充满脂滴,从而形成VSMC型泡沫细胞。He等^[38]通过体内外实验发现,青蒿琥酯可激活非经典通路KLF2/Nrf2/TCF7L2,促使VSMC转换为巨噬细胞表型,上调脂

蛋白脂肪酶的表达,从而抑制AS。该研究首次发现青蒿琥酯可激活Nrf2信号通路,从而降低载脂蛋白E基因敲除小鼠血清甘油三酯水平,为其治疗AS提供了实验依据^[38]。综上,推测降血脂药物除了通过Nrf2经典通路达到降血脂效果外,也可能通过Nrf2非经典通路发挥协同作用。

5 Nrf2信号通路与VSMC衰老和凋亡

VSMC衰老和凋亡是AS病变终末期特征之一,并受炎症因子、活性氧类物质、低密度脂蛋白等体内多种因素的调控。Maltese等^[39]发现,Nrf2由抗衰老基因*klotho*激活,并上调其下游HO-1、GCLC和过氧化物酶1蛋白表达水平,继而缓解人动脉VSMC的衰老和凋亡进程。因此,靶向*klotho*激活的Nrf2信号通路可作为一种治疗VSMC功能障碍和心血管衰老的新策略。Zhou等^[40]首次揭示肠促胰岛素类似物4抗VSMC衰老的机制,除了激活Nrf2/HO-1/NQO-1经典通路,还通过促进Nrf2与cAMP反应元件结合蛋白的相互作用进而增加Nrf2乙酰化抑制Ang II诱导的VSMC衰老。因此,Nrf2信号通路可被多种因子激活进而缓解VSMC的凋亡和衰老。

6 结 语

作为动脉重要的组成部分,VSMC与AS的发生发展关系密切。无论是主动脉还是冠状动脉的VSMC,Nrf2信号通路均广泛参与其表型转换、增殖、迁移、钙化、凋亡和衰老过程。目前,AS中Nrf2信号通路对VSMC的调控研究显示,VSMC中Nrf2信号通路对缓解AS进程起到积极作用。Nrf2对AS的影响也有消极作用,这可能由于Nrf2调控具有细胞特异性。所以目前的研究尚需深入,以阐释Nrf2信号对VSMC的各项功能调控及在AS发展过程中的具体分子机制。未来应整合谱系追踪技术、单细胞基因组学和人类遗传学等研究方法,识别VSMC特异性的Nrf2靶基因;同时应结合临床患者具体病情及体内外实验,以寻找相对标准且符合人类疾病进程的动物模型,促进动物模型向临床的转化,充分利用Nrf2信号通路调控VSMC功能向有利于缓解疾病进程的方向转变,为靶向治疗AS提供新思路。

临床上减少AS斑块多集中于控制血脂及抗炎,但AS是一种长期发展的疾病,而运用降脂抗

炎药治疗AS的具体分子机制并未明确且治疗效果不确定。利用VSMC可发生表型转换的特点,诱导其向有益于缓解AS进程的细胞表型转换,可以达到预防并减少AS斑块破裂及血栓形成的风险。因而今后可更多聚焦于能够激活Nrf2信号通路和调控VSMC表型转换、增殖迁移、钙化、脂代谢、凋亡衰老的天然或内源性药物、纳米靶向药物、外泌体-Nrf2以及基于微RNA的基因疗法等,为控制AS斑块提供帮助。

利益冲突 所有作者均声明不存在利益冲突

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· 学术动态 ·

沈承勇研究员团队揭示小片段DNA重复序列异常扩增疾病多肽聚集体清除机制

染色质基因组内小片段DNA重复序列异常扩增(又称微卫星重复扩增)常常导致一系列神经或肌肉疾病,如脊髓小脑共济失调症、亨廷顿舞蹈症、肌萎缩侧索硬化(ALS)、额颞叶痴呆(FTD)等,多数表现为运动障碍。其中ALS/FTD患者C9ORF72基因内含子存在大量异常重复的GGGGCC序列,是目前最常见的致病因素。C9ORF72基因突变导致疾病的病理机制之一是由于内含子区域的GGGGCC重复片段能够不依赖ATG启动子进行翻译,生成毒性二肽重复蛋白。其中多聚甘氨酸-丙氨酸(poly-GA)在神经元内倾向形成蛋白聚集体,与神经退行性疾病的蛋白异常聚集特征非常类似,提示poly-GA聚集体可能是患者神经元长期退行病变过程中的主要致病因素。目前poly-GA聚集体的体内清除机制并不清楚。

2021年5月15日,浙江大学沈承勇研究员与中国科学院生物与化学交叉研究中心的王文元研究员团队合作在《神经元》(*Neuron*)发表题为“UBQLN2-HSP70 axis reduces poly-Gly-Ala aggregates and alleviates behavioral defects in the C9ORF72 animal model”的研究论文(<https://pubmed.ncbi.nlm.nih.gov/33991504/>),揭示了UBQLN2-HSP70联合清除poly-GA聚集体并缓解小鼠发病的作用机制,为ALS/FTD和其他微卫星重复疾病提供新的治疗靶点。

研究发现,患者体内poly-GA聚集体能够招募ALS/FTD的另一个致病因子UBQLN2,后者促进poly-GA聚集体的清除,体内外减少其神经毒性。分子伴侣蛋白HSP70存在于GA聚集体中,其中HSP70的泛素化能够帮助UBQLN2识别不能泛素化的底物,从而促进UBQLN2-HSP70-GA复合物的形成和poly-GA的清除。打破UBQLN2与HSP70的结合或突变体减弱UBQLN2与HSP70的结合将抑制poly-GA聚集体的清除。在相对安全浓度下,通过坦螺旋霉素提高HSP70表达量,可以有效清除患者神经元的poly-GA聚集体。且小鼠发病后给药可有效缓解小鼠的运动障碍。该研究有助于深入了解不同致病因子协同作用导致ALS/FTD的发病新机制,为干预治疗提供新的思路;对研究其他微卫星重复序列疾病和神经退行性疾病的致病机制也有一定的借鉴意义。

张克兢博士、王爱莲和钟可可硕士为论文共同第一作者。研究工作获得了国家重点研发计划、国家自然科学基金、浙江省自然科学基金等资助。