

中药调控 Nrf2/HO-1 信号通路干预心肌缺血再灌注损伤的研究进展^Δ

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摘要 心肌缺血再灌注损伤(MIRI)是心肌梗死患者进行血运重建时的严重并发症。核转录因子红系2相关因子2(Nrf2)/血红素加氧酶1(HO-1)信号通路在MIRI病理进程中具有重要意义。目前研究发现,中药对缺血再灌注引起的心肌损伤具有很好的效果。本文基于Nrf2/HO-1信号通路总结中药复方和单体干预MIRI的作用机制,发现中药复方(益心方、温阳通脉方、定心方I号方)以及中药单体萜类(银杏内酯、黄芪甲苷、人参皂苷等)、酚类(巴西苏木素、苏木酮A、白藜芦醇等)、醌类(芦荟素、大黄素)等均可通过激活Nrf2/HO-1信号通路,抑制氧化应激、炎症反应等,从而减轻MIRI。

关键词 中药;心肌缺血再灌注损伤;核转录因子红系2相关因子2;血红素加氧酶1;信号通路

Research progress of traditional Chinese medicine in regulating Nrf2/HO-1 signaling pathway to interfere with myocardial ischemia-reperfusion injury

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ABSTRACT Myocardial ischemia-reperfusion injury (MIRI) is a serious complication of revascularization in patients with myocardial infarction. The nuclear factor erythroid 2-related factor 2 (Nrf2)/heme oxygenase-1 (HO-1) signaling pathway plays an important role in the pathological process of MIRI. Currently, research has found that traditional Chinese medicine has a good effect on myocardial injury caused by ischemia-reperfusion. Based on the Nrf2/HO-1 signaling pathway, this article summarizes the action mechanism of traditional Chinese medicine formulas and monomers in intervening with MIRI. It is found that traditional Chinese medicine formulas (Yixin formula, Wenyang tongmai formula, Dingxin formula I), monomers such as terpenoids (ginkgolides, astragaloside IV, ginsenosides), phenols (brazilin, hematoxylin A, resveratrol) and quinones (aloe, emodin) can alleviate MIRI by activating the Nrf2/HO-1 signaling pathway, inhibiting oxidative stress and inflammatory reactions, etc.

KEYWORDS traditional Chinese medicine; myocardial ischemia-reperfusion injury; nuclear factor erythroid 2-related factor 2; heme oxygenase-1; signaling pathway

心肌缺血再灌注损伤(myocardial ischemia-reperfusion injury, MIRI)是心肌梗死患者进行血运重建时的严重并发症^[1]。心肌梗死患者在治疗过程中快速恢复冠状动脉血流和挽救垂死心肌的同时,可能出现心肌梗死面积增大、心律失常、持续的低心室收缩功能、不可逆的心肌细胞死亡等一系列现象,严重危害预后^[2]。MIRI的病理生理机制涉及炎症反应、免疫反应、氧化应激、细胞凋亡、细胞自噬、铁死亡、微血栓形成、细胞内Ca²⁺超负荷等,这些机制加剧了MIRI的形成^[3]。核转录因子红系2相关因子2(nuclear factor erythroid 2-related factor 2, Nrf2)/血红素加氧酶1(heme oxygenase-1, HO-1)信号通路作为氧化应激反应中必不可少的信号通路,

主要参与抗炎、抗氧化、细胞凋亡、细胞自噬、细胞焦亡与铁死亡等过程,是治疗MIRI的重要通路之一^[4]。与心肌缺血性损伤相比,目前MIRI的有效治疗选择很少。基于中药多靶点、多成分、毒副作用小等优势,中药治疗MIRI已逐渐被医学界重视。相关研究也证实,中药对缺血再灌注引起的心肌损伤具有很好的效果^[5]。基于此,本文基于Nrf2/HO-1信号通路探讨中药干预MIRI的研究概况,以期为MIRI的临床治疗提供参考。

1 Nrf2/HO-1信号通路概述

Nrf2是一种内源性抗氧化转录调节因子,在细胞处于应激条件下时发挥着调节细胞周期稳态和保护细胞的作用^[6]。在正常状态下, Kelch样ECH相关蛋白1(Kelch-like ECH-related protein 1, Keap1)和E₃泛素连接酶结合形成蛋白质复合物,该复合物再与Nrf2的Neh2区二聚体结合,经泛素化后,使Nrf2在细胞内始终处于低活性状态^[7]。除此之外,糖原合成酶激酶3(glycogen synthase kinase 3, GSK-3)也可激活Nrf2的Neh6结构域

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从而促进其磷酸化^[8]。在应激状态和活性氧(reactive oxygen species, ROS)累积时,由于Keap1中IVR结构域对氧化还原反应敏感的半胱氨酸残基(Cys151/273/288)被修饰,导致其构象发生改变和底物接头蛋白活性受损,从而与Nrf2解离,使过量合成的Nrf2移位至细胞核,进而与Maf蛋白或c-Jun蛋白形成异源二聚体,并启动抗氧化反应元件(antioxidant response element, ARE)基因的转录^[9]。HO-1是与ARE基因相关的抗氧化酶之一^[9],主要参与血红素的降解过程^[10],可催化血红素分解产生一氧化碳(CO)、Fe²⁺和胆绿素,从而抑制细胞脂质过氧化和氧自由基的生成^[11]。当受到缺血、缺氧等刺激时,Nrf2将激活HO-1表达,从而发挥显著的抗氧化作用。

2 MIRI中Nrf2/HO-1信号通路的作用

MIRI引起的氧化应激是因为ROS大量产生导致机体抗氧化系统如超氧化物歧化酶(superoxide dismutase, SOD)、谷胱甘肽过氧化物酶(glutathione peroxidase, GSH-Px)和过氧化氢酶(catalase, CAT)等无法维持氧化与抗氧化状态的平衡造成的;Nrf2/HO-1信号通路可促进SOD、GSH-Px、CAT生成,减少ROS产生,进而发挥抗MIRI氧化应激的作用^[12]。

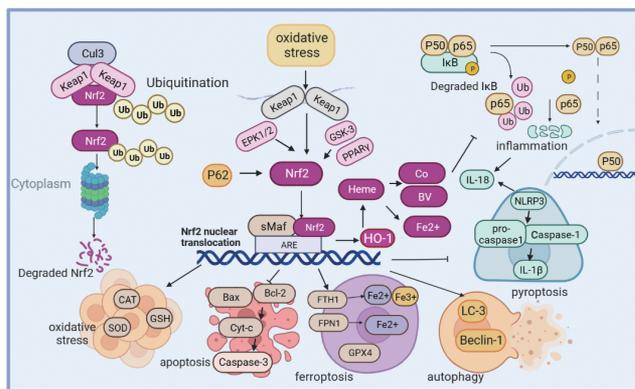
MIRI中的铁死亡是由于再灌注阶段线粒体呼吸增强,使ROS过量产生,引发独特的铁依赖性非凋亡细胞死亡^[13]。活化的Nrf2不仅可以通过重组人铁蛋白重链1(FTH1)氧化Fe²⁺,还可以通过调控膜铁转运蛋白1(ferroportin 1, FPN1)的表达来调节进出细胞的Fe²⁺;另外,HO-1可以通过分解血红素产生Fe²⁺来调控铁代谢^[14]。因此,激活Nrf2/HO-1信号通路可调节铁代谢和增加谷胱甘肽过氧化物酶4(glutathione peroxidase-4, GPX4)的表达,进而减轻MIRI中的铁死亡^[15]。

再灌注阶段产生的过度自噬可导致细胞死亡,自噬关键蛋白泛素结合蛋白62(p62)和Keap1竞争与Nrf2结合,形成p62-Keap1-Nrf2正反馈轴,进而持续激活Nrf2^[16]。有研究发现,在Nrf2、HO-1表达减少的同时,B细胞淋巴瘤2(B-cell lymphoma-2, Bcl-2)相互作用中心卷曲螺旋蛋白1(Bcl-2-interacting myosin-like coiled-coil protein 1, Beclin1)、微管相关蛋白1轻链3(microtubule-associated protein 1 light chain 3, LC3)也表达降低,而Beclin1主要通过激活磷脂酰肌醇3-激酶(phosphoinositide 3-kinase, PI3K)促进自噬体形成,LC3的LC3-I形式则可与磷脂酰乙醇胺共价连接插入到自噬体的双层膜中形成LC3-II^[17]。因此,激活Nrf2/HO-1信号通路可调节细胞自噬,进而改善MIRI。

机体发生MIRI时,大量激酶信号被氧化剂转导,使核因子κB(nuclear factor-κB, NF-κB)抑制蛋白(inhibitor of NF-κB, IκB)发生磷酸化和p50/p65异二聚体结构解离,导致NF-κB发生核移位,进一步产生炎症反应^[18];而HO-1的终产物(胆绿素和CO)可阻止NF-κB的核移位,进而抑制炎症反应的发生。除此之外,激活Nrf2/

HO-1信号通路可升高Bcl-2活性和降低Bcl-2相关X蛋白(Bcl-2 associated X protein, Bax)活性,从而抑制心肌细胞凋亡^[19]。激活Nrf2/HO-1信号通路还可抑制NF-κB和NOD样受体热蛋白结构域蛋白3(NOD-like receptor thermal protein domain associated protein 3, NLRP3)活性,从而减轻细胞焦亡的发生^[20]。

由此可知,Nrf2/HO-1信号通路可通过抑制心肌细胞氧化应激、铁死亡、炎症反应、焦亡和凋亡,以及调控自噬来减轻MIRI的病理进程。Nrf2/HO-1信号通路在MIRI中的作用机制如图1所示。



↓:促进;⊥:抑制。

图1 Nrf2/HO-1信号通路在MIRI中的作用机制

3 中药激活Nrf2/HO-1信号通路对MIRI的作用

中药复方及单体可通过抑制氧化应激、减轻炎症反应、减少细胞凋亡和调控细胞自噬来有效改善MIRI对机体造成的损伤。笔者具体从中药复方和单体方面总结中药通过Nrf2/HO-1信号通路MIRI的作用。

3.1 中药复方激活Nrf2/HO-1信号通路防治MIRI

益心方以黄芩、川芎共为君药,具有温通阳气、活血祛瘀的功效,对气虚血瘀不稳定型心绞痛具有很好的疗效。相关研究发现,益心方可通过特异性上调沉默信息调节因子1(silent information regulator 1, SIRT1)激活Nrf2/HO-1信号通路,降低大鼠的心肌细胞凋亡率,进而改善MIRI氧化应激损伤^[21]。温阳通脉方由胸痹经典方枳实薤白桂枝汤加减而来,具有温通阳气、活血化痰的作用。研究显示,温阳通脉方可通过激活Nrf2/HO-1信号通路,增强SOD活性,降低ROS、低氧诱导因子α水平,从而减轻心肌氧化应激损伤,减少心肌细胞凋亡,进而改善MIRI^[22]。定心方I号方以苦参、黄连为主药,具有清心安神、益气活血、祛瘀化痰的功效。研究表明,定心方I号方可通过减少GSK-3的生成激活Nrf2/HO-1信号通路,从而减少大鼠心肌细胞凋亡,进而减轻MIRI^[23]。益气养阴方以黄芪、太子参共为君药,具有益气、养阴、活血的功效,主治气阴两虚型心绞痛。研究表明,益气养阴方可通过磷酸化细胞外调节蛋白激酶1/2(extracellular regulated protein kinases 1/2, ERK1/2),激活Nrf2/HO-1信号通路,从而发挥抗氧化应激和抑制细胞凋亡

的作用,进而减轻MIRI合并糖尿病模型大鼠的心肌损伤^[24]。通脉养心方综合炙甘草汤和生脉散的组方理念,用于治疗冠心病心绞痛。研究发现,该方可增强过氧化物酶体增殖物激活受体 γ 的表达,促使Nrf2/HO-1信号通路发挥抗氧化作用,且能下调Toll样受体4和NF- κ B蛋白表达,进而改善MIRI^[25]。益脉颗粒由四君子汤加减而来,具有益气健脾、化痰祛瘀的功效。研究发现,益脉颗粒可以激活Nrf2/HO-1信号通路,下调肿瘤坏死因子 α (tumor necrosis factor- α , TNF- α)、白细胞介素6(interleukin-6, IL-6)、IL-1 β 、Bax、胱天蛋白酶3(Caspase-3)水平,抑制氧化应激和细胞凋亡,从而改善高脂合并MIRI模型大鼠的心肌损伤^[26]。

3.2 中药单体激活Nrf2/HO-1信号通路干预MIRI

3.2.1 萜类

Chen等^[27]研究发现,经银杏内酯干预后,MIRI模型大鼠心脏组织中HO-1、Nrf2和Bcl-2蛋白表达增加,Bax表达减少,血清中肌钙蛋白T和促炎因子IL-6、IL-1 β 、TNF- α 水平降低,这表明银杏内酯可通过激活Nrf2/HO-1信号通路改善MIRI模型大鼠的氧化应激、炎症反应。李泽华等^[28]研究发现,经黄芪甲苷干预后,心肌细胞H9c2中Nrf2、HO-1蛋白表达增加,Caspase-3、剪切型Caspase-3蛋白表达减少,这表明黄芪甲苷可通过激活Nrf2/HO-1信号通路减少细胞凋亡,进而改善MIRI。Sun等^[29]研究发现,人参皂苷Rb₃可诱导心肌细胞H9c2中蛋白激酶RNA样内质网激酶(protein kinase RNA-like endoplasmic reticulum kinase, PERK)发生磷酸化,并升高Nrf2、HO-1蛋白表达水平,降低ROS、Bax表达水平,这表明人参皂苷Rb₃可通过激活PERK/Nrf2/HO-1信号通路,减少MIRI引起的氧化应激和细胞凋亡。Yao等^[30]研究发现,人参皂苷可通过调节Keap1的活性激活Nrf2/HO-1信号通路,从而降低心肌细胞中促凋亡蛋白Caspase-3、Bax水平,进而减轻MIRI。

3.2.2 酚类

Qi等^[31]研究发现,巴西苏木素可增强缺氧/复氧后心肌细胞中SOD、Nrf2、GPX的活性,减少心肌细胞中ROS、丙二醛(malondialdehyde, MDA)含量;同时,Nrf2的磷酸化和转录活性的增强可通过蛋白激酶C(protein kinase C, PKC)抑制剂处理而消除,这说明巴西苏木素可激活PKC/Nrf2/HO-1信号通路,减轻MIRI。Shi等^[32]研究发现,苏木酮A可升高MIRI模型大鼠Nrf2蛋白的磷酸化水平和SOD、GSH-Px活性,降低ROS、MDA水平;同时,Nrf2蛋白的磷酸化可被PKC或PI3K抑制剂消除,这表明苏木酮A可通过PKC或PI3K途径调节Nrf2/HO-1信号通路,进而改善MIRI。Xu等^[33]研究发现,白藜芦醇协同AMP活化蛋白激酶(AMP-activated protein kinase, AMPK)抑制剂可抑制MIRI模型大鼠心肌组织中AMPK、磷酸化AMPK、Nrf2和HO-1蛋白表达,促进p38蛋白表达以及氧化应激指标回升,这表明白藜芦醇

可通过激活AMPK/p38/Nrf2/HO-1信号通路减轻大鼠MIRI。顾民华^[34]研究发现,斯皮诺素可降低MIRI模型大鼠心肌组织中过氧化物酶体增殖物激活受体 γ 辅助因子1 α (peroxisome proliferator-activated receptor γ coactivator-1 α , PGC-1 α)、Nrf2、HO-1和SOD的mRNA表达水平以及p62蛋白表达水平,升高LC3B表达水平,这表明斯皮诺素可通过激活PGC-1 α /Nrf2/HO-1信号通路促进细胞自噬,减轻细胞凋亡,进而改善MIRI。

3.2.3 醌类

Sun等^[35]研究发现,芦荟素可增强心肌细胞中Nrf2、HO-1、SOD、Bcl-2的活性,减轻ROS、MDA、Bax的活性,降低促炎因子TNF- α 、IL-6、IL-1 β 的水平,这说明芦荟素可通过激活Nrf2/HO-1信号通路减弱MIRI导致的氧化应激、炎症反应和细胞凋亡。崔勤涛等^[36]研究发现,大黄素可通过激活Nrf2/ARE/HO-1信号通路,保护MIRI模型大鼠心脏功能。Zeng等^[37]研究发现,二氢丹参酮I可通过激活蛋白激酶B/Nrf2/HO-1信号通路,发挥抗氧化应激作用,进而减轻MIRI。

3.2.4 其他类

牛少辉等^[38]研究发现,西红花苷可通过激活SIRT1/Nrf2/HO-1信号通路,升高MIRI模型大鼠血清和心肌组织中SOD的活性,进而减轻MIRI氧化应激。姚琪等^[39]研究发现,虾青素可升高MIRI模型大鼠血清中MDA水平和心肌组织中Nrf2、HO-1、醌氧化还原酶(NADH quinone oxidoreductase 1, NQO1)的表达水平,降低GSH-Px水平,这说明虾青素可通过激活Nrf2/HO-1/NQO1信号通路,减轻MIRI氧化应激。Cheng等^[40]研究发现,毛冬青苷A可修饰Keap1的Cys77和Cys434残基,促进Nrf2移位至细胞核,升高小鼠心肌细胞中HO-1、NQO1蛋白表达水平,从而减轻MIRI。

4 结语

MIRI是一种治疗心血管疾病时产生的并发症,严重影响着患者的预后。Nrf2/HO-1信号通路在MIRI病理进程中具有重要意义。本研究基于Nrf2/HO-1信号通路探讨中药干预MIRI的研究概况,发现中药复方(益心方、温阳通脉方、定心方I号方)以及中药单体萜类(银杏内酯、黄芪甲苷、人参皂苷等)、酚类(巴西苏木素、苏木酮A、白藜芦醇等)、醌类(芦荟素、大黄素)等均可通过激活Nrf2/HO-1信号通路,抑制氧化应激、炎症反应等,从而减轻MIRI。

但是,目前的研究仍存在问题,如建立的MIRI模型并不能完全反映MIRI过程中的病理生理变化,中药的具体作用机制和最佳剂量也仍需进一步探究。另外,中药是否直接作用于Nrf2/HO-1信号通路的相关靶点来发挥抗MIRI的作用也有待深层次研究。

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