

· 新进展 ·

核因子 E2 相关因子 2 对创伤性脑损伤的保护作用机制及其靶向治疗药物研究进展

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【摘要】 创伤性脑损伤 (TBI) 患者的死亡率和致残率相对较高, 为社会和家庭带来极大负担, 因此, 寻找合适的药物治疗TBI对于降低患者死亡率、改善患者预后具有重要意义。核因子E2相关因子2 (Nrf2) 是氧化应激信号通路的主要调节因子, 已被证明在脑损伤等各种中枢神经系统疾病中具有神经保护作用。本文介绍了Nrf2对TBI的保护作用机制, 认为靶向Nrf2治疗TBI具有很大潜力, 并总结了靶向Nrf2治疗TBI的药物研究进展, 以期对TBI治疗药物的研究与开发提供新思路。

【关键词】 脑损伤, 创伤性; 核因子E2相关因子2; 靶向治疗; 综述

【中图分类号】 R 651.15 **【文献标识码】** A DOI: 10.12114/j.issn.1008-5971.2023.00.079

Protective Mechanism of Nrf2 on Traumatic Brain Injury and the Research Progress of Targeted Therapeutic Drugs

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【Abstract】 The mortality and disability rate of patients with traumatic brain injury (TBI) is relatively high, which brings a great burden to society and families. Therefore, it is of great significance to find appropriate drug for TBI to reduce the mortality and improve the prognosis of patients. Nuclear factor erythroid 2-related factor 2 (Nrf2) is the main regulator of oxidative stress signal pathway and has been proved to have neuroprotective effects in various central nervous system diseases such as brain injury. This paper introduces the protective mechanism of Nrf2 on TBI, considers that targeted Nrf2 has great potential in the treatment of TBI, and summarizes the research progress of drugs targeting Nrf2 in the treatment of TBI, in order to provide new ideas for the research and development of TBI therapeutic drugs.

【Key words】 Brain injuries, traumatic; Nuclear factor erythroid 2-related factor 2; Targeted therapy; Review

在全球范围内, 每年超过5 000万人罹患创伤性脑损伤 (traumatic brain injury, TBI), 且TBI是成年人的主要死因之一^[1]。2006—2013年, 中国居民TBI死亡率总体保持相对较高水平, 为12.99/10万~17.06/10万^[2]。调查发现, TBI患者平均住院费用为18 680.7元, 且中、重度TBI患者平均住院费用远高于轻度TBI患者^[3]。即便存活, TBI患者出院后也常会遗留不同程度的躯体功能障碍、认知障碍以及心理障碍^[4]。近年来大量研究深入探讨了TBI的病理过程, 以期发现新的治疗靶点, 且研究显示, TBI后继发性脑损伤的病理基础包括细

胞凋亡、炎症反应和氧化应激^[5-6]。而核因子E2相关因子2 (nuclear factor erythroid 2-related factor 2, Nrf2) 是氧化应激信号通路的主要调节因子, 已被证明在脑损伤等各种中枢神经系统疾病中具有神经保护作用^[7]。本文通过回顾相关文献分析了Nrf2对TBI的保护作用机制, 并综述其靶向治疗药物研究进展, 以期对TBI治疗药物的研究与开发提供新思路。

1 Nrf2概述

Nrf2是一种参与调控细胞氧化应激反应的转录因子, 属于CNC碱性亮氨酸拉链家族^[8]。Nrf2在大部分组织细胞中均表达^[9], 对氧化应激敏感, 可调节多种基因表达, 编码抗氧化酶、解毒因子、抗凋亡蛋白和药物转运蛋白^[10]。生理条件下, Nrf2位于细胞质中, 且保持低水平^[11]。氧化应激反应发生后, Nrf2转移到细胞核内并与抗氧化反应元件 (antioxidant response element, ARE) 结合, 可激活下游基因〔下游基因可以编码抗氧化应激酶^[9], 包括超氧化物歧化酶1 (superoxide dismutase 1, SOD1)、血红素加氧酶1 (heme oxygenase 1, HO-1)、醌氧化还原酶1 (quinone oxidoreductase 1,

基金项目: 国家自然科学基金资助项目 (81660327); 广西医疗卫生重点 (培育) 学科课题

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NQO1)、谷胱甘肽过氧化物酶 (glutathione peroxidase, GSH-Px)、谷胱甘肽巯基转移酶 (glutathione S-transferase, GSH-ST)、谷胱甘肽过氧化物酶4 (glutathione peroxidase 4, GPx4) 和谷胱甘肽还原酶 (glutathione reductase, GR) [12-14], 而这些酶可参与调节各种神经系统疾病的氧化应激、炎症反应和细胞凋亡的转录, 还可参与活性氧 (reactive oxygen species, ROS) 的清除和还原型烟酰胺腺嘌呤二核苷酸磷酸 (nicotinamide adenine dinucleotide phosphate, NADPH) 的生成过程 [15]。

2 Nrf2对TBI的保护作用机制

2.1 减轻氧化应激 研究显示, 减轻TBI后的氧化应激是神经保护的一种有效途径 [16]。多项研究已证实, TBI后Nrf2活性升高 [17-19], 其主要通过调节内源性防御机制来抵抗氧化应激 [20]。研究表明, Nrf2/ARE信号通路通过抑制炎症因子、诱导解毒酶表达、维持钙离子稳态而在TBI后继发性脑损伤中发挥重要的神经保护作用 [21]。研究显示, 神经元中的氧化应激可以引起DNA损伤和各种生物分子的降解, 并最终导致神经元凋亡 [22-23]。WU等 [24] 研究显示, Nrf2过表达可抑制小胶质细胞的活跃度, 降低肿瘤坏死因子 α (tumor necrosis factor- α , TNF- α) 和白介素6 (interleukin-6, IL-6) 水平, 从而减轻炎症反应。相反, Nrf2缺失可加剧脑损伤程度, 这与氧化应激、神经炎症, 包括促炎因子和抗炎因子的分泌、外周免疫细胞的募集和脑内胶质细胞的激活、凋亡、泛素化和血脑屏障损伤有关 [25-26]。综上, TBI发生后, Nrf2可以通过抗炎和诱导解毒酶表达来减轻氧化应激。

2.2 促进线粒体生物合成 Nrf2与线粒体的呼吸功能和能量产生有关, Nrf2缺乏时会导致线粒体脂肪酸氧化, 呼吸作用减弱和ATP减少; Nrf2增多时则会增加线粒体膜电位和ATP水平, 提高呼吸速率及氧化磷酸化效率 [27-28]。研究显示, Nrf2通过调节抗氧化系统相关基因的表达来维持线粒体氧化还原动态平衡, 促进线粒体的生物合成 [29]。还有研究表明, 增强线粒体自身的生物合成功能可以改善线粒体的能量代谢, 从而减轻TBI后神经元损伤 [30]。综上, Nrf2可以通过促进线粒体生物合成来减轻TBI发生后的神经损伤。

2.3 减轻内质网应激 研究显示, 抑制磷酸二酯酶4 (phosphodiesterase 4, PDE4) 可激活Nrf2, 减少ROS的产生, 从而减轻缺氧缺血损伤 (oxygen-glucose deprivation, OGD) 所致的神经元内质网应激 [31]。还有研究显示, 阿托伐他汀可通过激活Nrf2而减轻TBI小鼠内质网应激, 从而减少神经元凋亡 [32]。内质网应激会导致TBI发生后的神经元凋亡加重, 而Nrf2可能通过内质网应激信号途径改善TBI所致的继发性脑损伤 [33]。综上, 激活Nrf2可能减轻TBI发生后的内质网应激。

2.4 诱导自噬 在Nrf2基因缺陷小鼠中, 自噬基因表达减少 [34]。研究显示, Nrf2通路的活化能诱导自噬反应 [35]。p62可作为自噬的标志, 其原因是p62被磷酸化后增强了其与Kelch样ECH关联蛋白1 (Kelch-like ECH-associated protein 1, KEAP1) 结合的能力, 而竞争性地抑制了Nrf2与KEAP1的结合, 导致Nrf2与KEAP1解离, 从而促进Nrf2靶基因的表达 [36]。有研究表明, Nrf2能够促进C17.2神经干细胞增殖,

这可能与其升高细胞内的自噬水平有关 [37]。在TBI大鼠模型中, 谷氨酰胺可通过激活Nrf2通路而降低氧化应激反应、促进自噬反应, 从而起到保护神经元的作用 [38]。综上, Nrf2可能通过诱导自噬而在TBI中发挥保护作用。

2.5 抑制铁死亡 在TBI模型中, 铁死亡的分子机制主要涉及铁代谢异常、GSH-Px的活性降低、神经元的脂质过氧化 [39]。而GPx4是铁死亡的标志物, 铁死亡发生时其表达减少 [40]。研究显示, 绝大部分与铁死亡相关的基因均受Nrf2的转录调控, 这些基因包括GR调节基因和GPx4调节基因, 其对GPx4活性的恢复至关重要 [41-43]。因此, Nrf2可能通过抑制铁死亡而在TBI中发挥保护作用 [44]。

3 靶向Nrf2治疗TBI的药物研究进展

MILLER等 [18] 指出, 寻找激活Nrf2的药物对于TBI的治疗具有重要意义。鉴于激活Nrf2可以减轻氧化应激, 抑制神经元凋亡、炎症细胞浸润及炎症因子的产生, 因而近年来靶向Nrf2治疗TBI的基础研究成为研究热点。

3.1 右美托咪定 LI等 [45] 研究显示, 右美托咪定可增加TBI患者Nrf2、HO-1、NQO1表达水平, 抑制炎症因子的产生, 降低NF- κ B以及IL-6水平, 从而减少神经炎症诱导的细胞凋亡。PENG等 [46] 指出, 右美托咪定可以为TBI患者提供更好的术中镇静、镇痛和临床恢复效果, 不良反应可控, 且可抑制氧化应激及炎症反应。

3.2 氯胺酮 LIANG等 [47] 研究发现, 氯胺酮可激活Nrf2, 增加其下游因子包括HO-1和NQO1的表达, 指出氯胺酮可能通过激活Nrf2来减轻TBI后的氧化应激和抑制细胞凋亡, 从而发挥神经保护作用。此外, 氯胺酮与其他镇静剂联合使用对于TBI患者有更好的镇痛和镇静效果, 且常规剂量具有很好的安全性 [48]。

3.3 依达拉奉 (edaravone, EDA) LI等 [49] 采用过氧化氢处理海马神经干细胞及采用外科手术建立体外TBI模型和TBI大鼠模型, 结果显示, EDA预处理后, 神经干细胞凋亡减少, Nrf2被激活; 而经EDA处理的TBI大鼠模型创伤面积缩小, 海马损伤减轻, 记忆和学习能力提高, 且Nrf2被激活。还有研究显示, EDA可以抑制NF- κ B从细胞质转移到细胞核, 上调Nrf2蛋白表达, 即EDA通过抑制NF- κ B介导的炎症反应来激活Nrf2抗氧化途径, 从而在TBI小鼠中发挥神经保护作用, 包括减轻神经功能缺陷、细胞凋亡和结构损伤 [50]。

3.4 姜黄素 姜黄素是一种天然酚类化合物, 并具有抗炎和抗氧化等多种药理作用 [51]。DONG等 [25] 研究发现, 姜黄素可减轻野生型TBI小鼠同侧皮质损伤, 抑制中性粒细胞浸润、小胶质细胞活化及TBI后神经元的凋亡和变性; 然而, Nrf2基因敲除小鼠发生TBI后, 姜黄素的神经保护作用减弱。

3.5 岩藻黄素 岩藻黄素在海藻中含量丰富, 被认为是一种强大的抗氧化剂。ZHANG等 [52] 研究发现, 岩藻黄素在体内和体外均可激活Nrf2和诱导自噬, 然而, 在Nrf2基因缺失的TBI小鼠中, 岩藻黄素未能提供神经保护作用 and 诱导自噬。

3.6 特丁基对苯二酚 (tert-butylhydroquinone, TBHQ) TBHQ是一种Nrf2激活剂, 研究显示, 用香草乙酮和TBHQ的组合药物干预TBI模型小鼠, 可激活Nrf2相关通路, 减轻氧化

应激,从而保护小鼠的大脑灰质^[53]。还有研究显示,TBHQ预处理可有效减弱TBI后氧化应激,上调Nrf2蛋白水平,提示TBHQ可作为TBI患者的潜在神经保护剂^[54]。

综上,右美托咪定、氯胺酮、EDA、姜黄素、岩藻黄素和TBHQ可以通过激活Nrf2来减轻TBI后的神经炎症、氧化应激和神经元凋亡。但上述研究多为动物实验,其结果仍需大型多中心临床试验进一步评估。

4 小结

综上所述,Nrf2可能通过减轻氧化应激、促进线粒体生物合成、减轻内质网应激、诱导自噬及抑制铁死亡而对TBI发挥保护作用,因而靶向Nrf2能够有效治疗TBI,目前其靶向治疗药物主要有右美托咪定、氯胺酮、EDA、姜黄素、岩藻黄素、TBHQ。但由于TBI的病理生理机制十分复杂,目前仍存在许多亟待解决的问题,如TBI后Nrf2抑制铁死亡的机制目前仅有间接证据,故需要更多的临床研究进一步探索Nrf2对TBI的具体保护作用机制。

作者贡献:李小蝶进行文章的构思与设计、文章的可行性分析及文献资料收集、整理,撰写论文;李小蝶、吴红月、牟思瞳进行论文的修订;唐华民负责文章的质量控制及审校,对文章整体负责、监督管理。

本文无利益冲突。

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- (收稿日期: 2022-10-20; 修回日期: 2022-12-09)
(本文编辑: 崔丽红)

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- (收稿日期: 2022-10-20; 修回日期: 2023-02-06)
(本文编辑: 崔丽红)