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文献综述 REVIEW

Nrf2–Keap1抗氧化系统与肝脏疾病

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Nrf2-Keap1 antioxidant system and hepatic diseases

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Abstract

NF-E2-related factor 2 (Nrf2) is an important transcription factor. When oxidative stress occurs, Nrf2 dissociates from Keap1 (Kelch-like ECH-associating protein 1), translocates to the nucleus, and regulates the expression of genes encoding phase II detoxifying enzymes and antioxidant proteins, thereby increasing the resistance to oxidative stress and electrophilic agents. Reactive oxygen species and oxidative stress play an important role in the development of hepatic diseases. In this article, we will summarize the relationship between the Nrf2-Keap1 system and hepatic diseases.

Key Words: NF-E2-related factor 2; Oxidative stress; Hepatic disease

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摘要

核转录相关因子(NF-E2-related factor 2, Nrf2)是重要的转录因子, 在氧化应激等情况下被激活与Kelch样ECH联合蛋白1(Kelch-like ECH-associated protein1, Keap1)解离进入胞质启动Ⅱ相解毒酶及抗氧化酶基因的表达, 增加细胞对氧化应激和亲电子化学物质的抗性. 活性氧族和氧化应激在肝脏疾病的发病中取着重要的作用. 本文对Nrf2-Keap1抗氧化系统与肝脏疾病的关系进行探讨.

关键词: Nrf2; 氧化应激; 肝脏疾病

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0 引言

Nrf2属于亮氨酸拉链家族的调节抗氧化应激反应的重要转录因子, Keap1是其特异性受体, 正常情况下Nrf2作用被Keap1抑制, 在氧化应激等情况下与Keap1解离被激活, 启动抗氧化反应元件(antioxidantresponseelement, ARE)调控的第Ⅱ相解毒酶及抗氧化酶基因表达, 增加细胞对氧化应激和亲电子化学物质的抗性[1-4]. Nrf2-Keap1抗氧化系统与疾病的关系是近几年的研究热点, 在预防癌症方面研究较多, 许多Nrf2诱导剂, 如莱菔硫烷(sulforaphane)、奥替普拉(oltipraz)、姜黄素(curcumin)等已经证明能预防癌症[5-8]. 除了癌症, 活性氧族(reactive oxygen species, ROS)及氧化应激与很多疾病都相关联. 因此, Nrf2-Keapl抗氧化系统在预防肺纤维化、糖尿病、神经系统疾病[9-11]等方面也有报道. Nrf2的研究对于理解抗毒防御途径如何调节、氧化应激如何促进疾病的发展打开了一个新的视野, 对于氧化应激介入疾病的预防和治疗可能是一个新的目标. 该文拟对Nrf2-Keap1抗氧化系统与肝脏疾病的关系作一简单概述.

1 Nrf2与Keap1的结构与功能

Nrf2被Kan在1996年克隆, 能与NF-E2珠蛋

■背景资料
氧化应激在肝脏疾病的发生发展中起着重要的作用, Nrf2-Keap1抗氧化系统与肝脏疾病的关系是近几年的研究热点.

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■研发前沿
Nrf2-Keap1抗氧化系统能增加肝脏抵抗氧化应激的能力, Nrf2可能是防治肝损伤和肝纤维化的一个新的靶标.

白基因启动子结合[12], 属于cnc(“cap ‘n’ collar”)亮氨酸拉链转录因子家族. 该家族有6个成员NF-F2、Nrf1、Nrf2、Nrf3、Bach1和Bach2. Nrf2几乎在所有的组织中表达, 对生长发育无影响, 但Nrf2敲除小鼠Ⅱ相酶和内源性的抗氧化剂的水平下降. 不同物种如人、大鼠和鸡的Nrf2基因区域含有6个功能区, 分别被命名为Nehl-6, Nehl区中有一个亮氨酸拉练结构bZIP[leucimezipper(bZIP)], bZIP与小Maf蛋白(smallMafproteins, 包括MafG、MafK、MafF)形成异二聚体, 识别ARE上DNA基序(GCTGAGTCA)并与之结合、启动目标基因转录[13]. Neh2的N末端区域包含7个与泛素结合的赖氨酸残基, 于是他对通过蛋白酶体介导的Nrf2的降解起负向调控作用[14]. Neh3的C-端对Nrf2的转录活性是必不可少的[15]. Nehl与Neh2之间有2个独立的激活区Neh4和Neh5. Neh4和Neh5与共激活因子CREB结合蛋白CBP[cyclicAMP-responseelememb; bindingprotein(CREB) bindingprotein]结合会促使CBP协同参与对Nrf2目标基因转录活性的激活[16]. Neh6尽管有大量的丝氨酸残基, 但其功能仍然不清楚.

Keap1有三个主要的区, N末端BTB区、一个连接片段(IVR)以及C末端DGR区. 连接片段富含半胱氨酸, 认为对Keapl的激活是必不可少的. C末端DGR区包含六个保守的Kelch重复序列, 与Nrf2的Neh2部位结合[17]. Keapl最初描述在胞质中锚定于肌动蛋白, 并和Nrf2结合, 在人类Keapl蛋白上的27个半胱氨酸残基组成一个分子开关, 当暴露于氧化应激或亲电试剂时而触发, 导致Nrf2与Keap1解离, 转移到细胞核, 与Maf蛋白形成异二聚体(heterodimer), 然后该异二聚体再与ARE结合, 调控Ⅱ相酶基因的转录活性, 包括Ⅰ型血红素氧化酶(heme oxygenase-1, HO-1)、醌氧化还原酶(NAD(P)H: quinone oxidoreductase 1, Nqo1)和谷胱甘肽-S-转移酶(glutathione-S-transferase, GST)、谷氨酸半胱氨酸连接酶(glutamate-cysteine ligase catalytic, GCLC and GCLM)、谷胱甘肽(glutathion, GSH)、环氧化物水解酶(epoxide hydrolase, EH)等, 这些酶能够保护机体免受活性物质(如ROS)及一些毒性物质(如致癌物、药物代谢活化产物等)的侵害[18-20].

2 Nrf2–Keap1抗氧化系统与肝脏疾病的关系

氧化应激与肝脏疾病的发生密切相关[21], 氧化应激主要通过启动膜脂质过氧化改变生物膜功能、与生物大分子共价结合及破坏酶的活性等在细胞因子(如TNF-α, NF-κB)的共同作用下引起不同程度的肝损伤, 所以抗氧化治疗对防治肝脏疾病取着重要的作用[22,23]. Nrf2-Keap1抗氧化系统涉及肝脏的各个领域, 如调节肝脏的代谢、解毒及促进肝细胞再生, 在肝损伤、脂肪肝、肝纤维化及肝癌等方面也具有保护作用.

在肝脏代谢方面, 运载体是肝脏对药物和环境化学毒物解毒的完整组件, Nrf2可调控运载体的表达, 肝脏的Nrf2-Keap1抗氧化系统通过Ⅱ相解毒酶和运载体调节代谢和转运过程来参与药物、胆固醇、糖的代谢及解毒. 如Nrf2缺失小鼠使扑热息痛的葡萄糖酸化降低, 导致*N*-乙酰-对-苯醌亚胺(NAPQ1)和肝毒性的增加, 激活的Nrf2通过Nqo1及经由运载体多药耐药相关蛋白3(Mrp3)增加对扑热息痛葡萄糖苷酸化代谢产物的排除来促进NAPQ1的解毒[24]. Nrf2缺失小鼠能抵制胆结石的形成, Nrf2在肝脏对胆固醇的摄取、代谢及排泄方面有一定的影响[25,26]. 在链唑霉素诱导的小鼠1型糖尿病中, Nrf2缺陷小鼠肝脏糖异生葡萄糖-6-磷酸酶和磷酸丙酮酸羧基激酶的mRNA增加并且糖酵解丙酮酸激酶的mRNA减少, 所以导致小鼠高血糖和尿排出量增加[27]. 楤木属根的乙醇抽提物对叔丁基-过氧化氢(t-BHP)所致的肝毒性的保护作用是经由Nrf2信号途径的抗氧化酶HO-1起作用[28].

在体内和体外动物实验中发现, 氧化应激介导的胰岛素/胰岛素类生长因子抵抗是影响肝再生的机制, 使p38丝裂原-活化激酶、Akt激酶及下游目标酶在肝切除后受损, 导致肝细胞的死亡增加和增生延迟, Nrf2能调整胰岛素/胰岛素类生长因子的信号和修复组织, 在部分肝切除再生中取着重要的作用[29].

近来研究证明: 齐墩果酸可保护肝脏抵抗很多药物及毒物的攻击, 如对乙酰氨基酚、四氯化碳、镉、溴苯等, 其保肝的新的分子机制是能增加大鼠及小鼠肝脏Nrf2及下游Nqo1、Ho1及GCLM基因的表达[30,31]. Nrf2敲除小鼠对扑热息痛诱导的肝损伤、笨茋诱导的肿瘤和Fas-以及TNF-α介导的肝细胞凋亡很敏感, Nrf2敲除小鼠对化学毒物的高度敏感性是因为减少了解毒酶的表达[32]. 对姜黄素的研究中发现: 口服姜黄素不仅仅能保护二甲基亚硝胺(DMN)诱导的肝损伤, 而且使鼠肝的HO-1蛋白的表达和活性高度增加, HO-1的抑制剂锌-原卟啉Ⅸ能

废除姜黄素对DMN诱导肝损伤的保护作用. 姜黄素保肝作用在于能诱导Nrf2与ARE元件结合启动HO-1的表达[33]. Lamlé等[34]报道: Nrf2(-/-)小鼠对酒精的耐受性比野生型小鼠明显降低, 很快就发生了肝衰竭导致死亡. 辛伐他汀能增加大鼠肝脏及肝细胞Nrf2的DNA结合活性, 同时也增加两种Nrf2的下游基因HO-1和GPX2的mRNA的表达, 因此认为辛伐他汀通过诱导Nrf2/Keap1信号通路保护肝脏抵制氧化应激的损伤[35]. 白藜芦醇预处理能有效的保护暴露于氧化应激的原代肝细胞, 能增加过氧化氢酶(Cat)、超氧化物歧化酶(SOD)、谷胱甘肽过氧化物酶(GPx)、NADPH醌氧化还原酶(Nqo1)和谷胱甘肽S转移酶(GST)的活性, 白藜芦醇通过增加Nrf2的水平并且诱导其转入核内起着保护肝细胞的作用[36]. 乙醇诱导CYP2E1是乙醇引起氧化应激的重要途径, 在表达CYP2E1的HepG2细胞(E47细胞)中Nrf2被活化, 核内Nrf2水平、Nrf2抗反应元件结合活性、Nrf2调控基因(GCLC和HO-1)均增加, 并被CYP2E1的抑制剂和活性氧族的清除剂*N*-乙酰半胱氨酸阻断[37]. Nrf2在抵抗乙醇诱导的CYP2E1引起的氧化应激中起着重要的作用[38].

Nrf2的缺失明显加重了非酒精性脂肪肝的进程[39]. 在非酒精性脂肪肝后期中, Nrf2的激活和Nqo1活性的增加可能起着保护醌诱导的氧化还原损伤, GST活性的降低可能是中和了亲电子试剂[40].

近年来研究报道: Nrf2缺陷小鼠对CCl_4所致肝损伤的修复明显延迟, Nrf2敲除小鼠肝纤维化及炎症明显加重. 这是由于肝细胞目标基因Nrf2及其编码酶的减少, 对CCl_4和其代谢产物的解毒作用减弱所致. Nrf2可能是预防或减轻毒素诱导的肝损伤和肝纤维化的一个新奇的目标[41]. Aleksunes等[32]指出Nrf2可能在肝纤维化的预防上取到了重要的作用. 抗氧化剂tBHQ能促进细胞外基质中培养的静止肝星状细胞(hepatic stellate cell, HSC)的转化, 能诱导经由Nrf2的抗氧化反应元件(ARE)的表达[42]. 熊脱氧胆酸治疗原发性胆汁性肝硬化的一个机制是激活了肝脏Nrf的活化[43].

Nrf2是肝癌的重要调节剂, Nrf2调整的抗氧化酶及解毒酶的基因多态性与肝癌的发生密切相关[44]. HBV的慢性感染和饮食中摄入黄曲霉素可增加肝细胞癌的发生率, 虽然乙型肝炎疫苗及减少食物储存过程中被黄曲霉素污染的措施已广泛采用, 然而完全排除黄曲霉素污染是不可能的. 所以用化学预防措施对黄曲霉素进行生理处理来降低肝细胞癌的发生率很关键. 在上海, 科学家正在研究饮用红茶以激活Nrf2的活性来预防黄曲霉素-B1诱导的肝癌. 对啮齿类动物及临床研究发现: Nrf2-Keap1-ARE信号诱导物能增加细胞保护酶的表达, 能有效地调节体内黄曲霉素的处理, 有效地降低肝细胞癌的发生; 齐墩果酸的同型物三萜系化合物1-咪唑是Ⅱ相酶诱导剂及有效的化学预防剂, 对黄曲霉素诱导的大鼠肝脏瘤前病变具有很好的抑制作用, 野生型及Nrf2敲除小鼠在用咪唑进行治疗后进行微阵列分析表明许多Ⅱ相酶和抗毒基因在Nrf2依赖模式被诱导, 认为咪唑在体内以Nrf2途径为目标具有较强的预防癌症的作用[45,46]. 3氚-1, 2-二硫杂环戊二烯-3-硫酮(D3T)和其同型物4-甲基-5-对二氮苯基-3氚-1, 2-二硫杂环戊二烯-3-硫酮(OLT)及5-叔丁基3氚-1, 2-二硫杂环戊二烯-3-硫酮(TBD)能通过Nrf2途径诱导解毒酶阻止或减轻早期肝癌[47]. 柑橘香豆素类通过诱导致癌剂解毒酶GST和/或Nqo1来发挥抗癌活性, Prince等[48]在对人肝癌HepG2细胞的实验中发现, 柑橘香豆素类诱导鼠肝GST和Nqo1的活性是经由Nrf2/ARE的机制. 对肝细胞癌两期模式F344大鼠的研究中表明: 抑制Nrf2可加重非诺贝特对肝脏的氧化应激, 导致非诺贝特诱导的肝细胞癌的恶化[49]. 用致癌物2-氨基-3-甲基[4,5-f]喹啉(IQ)治疗Nrf2缺陷小鼠和野生型小鼠52 wk, Nrf2缺陷小鼠肝癌的发生率远远高于野生型[50].

■相关报道

Liu等报道, 齐墩果酸可保护肝脏抵抗很多毒物的攻击, 如四氯化碳、镉、溴苯等, 其保肝的新的分子机制是能增加大鼠及小鼠肝脏Nrf2及下游Nqo1、Ho1及GCLM基因的表达.

3 结论

Nrf2可通过调节肝脏Ⅱ相酶基因的表达增加肝脏抵抗氧化应激的能力, Nrf2对于肝脏疾病的预防和治疗是一个重要的目标, 有望为肝脏疾病的防治提供新的思路.

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■创新盘点

Nrf2-Keap1抗氧化系统涉及肝脏的各个领域, 如调节肝脏的代谢、解毒及促进肝细胞再生, 在肝损伤、脂肪肝、肝纤维化及肝癌等方面也具有保护作用.

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■同行评价
本综述内容较新颖, 详细论述了Nrf2转录调控因子在氧化、肝损伤中的作用, 为肝脏疾病的治疗提供新思路.

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