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文献综述 REVIEW

NADPH氧化酶产生的活性氧簇对肝星状细胞内信号转导的调控

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Participation of reactive oxygen species generated by NADPH oxidase in regulating signal transduction in hepatic stellate cells

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Abstract
Reactive oxygen species (ROS) are established molecules that are injurious to such biomolecules as DNA and protein, and that can induce lipid peroxidation. However, it is now held that Nox/Duox family of NADPH oxidases generate ROS in a carefully regulated manner, which can act as second messengers influencing signal transduction in various cells including hepatic stellate cells (HSCs). This paper focused on mechanism of ROS generated by NOX/Duox regulating signal transduction, and then reviewed signal transduction of ROS-mediated liver profibrogenic factors, e.g., transforming growth factor-β (TGF-β), platelet-derived growth factor (PDGF), Angiotensin II (Ang II) and leptin, *et al* in HSCs.

Key Words: NADPH oxidase/Dual oxidase; Reactive oxygen species; Signal transduction; Hepatic stellate cells

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摘要
活性氧簇(ROS)长期被认为是一类损伤DNA、蛋白等生物分子, 引起脂质过氧化反应的细胞有害分子. 现在认为NADPH氧化酶(Nox)/Dual氧化酶(Duox)家族是以精确调节的方式产生ROS, 能作为第二信使影响包括肝星状细胞(HSCs)在内的各种细胞的信号转导. 本文讨论NOX/Duox产生的ROS调控信号转导的机制, 并对近年来关于ROS介导的促肝纤维化因子(如转化生长因子(TGF-β)、血小板衍生生长因子(PDGF)、血管紧张素Ⅱ(AngⅡ)和瘦素(leptin)等)在HSCs内信号转导的研究作一综述.

关键词: NADPH氧化酶/Dual氧化酶; 活性氧簇; 信号转导; 肝星状细胞

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0 引言
活性氧簇(reactive oxygen species, ROS)是一类氧衍生的分子, 包括超氧化物(superoxide, $O2^{-}$)、过氧化氢(hydrogen peroxide, H_2O_2)、羟自由基(hydroxyl radical)及各种脂质过氧化反应的产物, 线粒体偶联的酶, 细胞色素P450一氧化物酶(CYP 2E1)、NOX、黄嘌呤氧化酶(xanthine oxidase)及参与花生四烯酸代谢的酶都能产生ROS[1]. 由于ROS能与大多数细胞大分子发生反应, 使酶失活, 引起DNA损伤, 修饰翻译后的蛋白及脂质过氧化反应损伤细胞膜, 长期将ROS视为对细胞有害的分子[2-3]. 然而最近的研究发现, NOX/Duox家族产生的ROS参与介导细胞内许多信号通路, 参与调控细胞的生长, 细胞分裂,分化, 迁移, 凋亡及衰老等许多生理活动, 也与疾

■背景资料
肝星状细胞在肝纤维化的发病中扮演主要角色. 各种旁分泌、自分泌的促肝纤维化因子, 都要通过信号转导使肝星状细胞激活、转化、增殖、分泌细胞外基(ECM)及更多的促肝纤维化因子, 形成恶性循环, 导致肝纤维化、肝硬化. 近年来针对促肝纤维化因子在肝星状细胞内的信号转导有了更深入的研究, 阻断这些促肝纤维化因子在肝星状细胞内的信号转导有望减轻甚至逆转肝纤维化.

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■研发前沿
近年来, 在肝星状细胞信号转导的研究领域出现了新热点, NADPH氧化酶产生的活性氧簇作为细胞内信号转导的第二信史角色得到了国内外学者的重新认识和关注, 如抑制NADPH氧化酶表达或抑制NADPH氧化酶的活性, 减少活性氧簇产生可阻断TGF-β、PDGF及AngII等在肝星状细胞内的信号转导.

病的发生密切相关[4-5]. 下面我们就NOX产生的ROS调控细胞内信号转导的机制及其介导促肝纤维化因子在HSCs内信号转导的研究现状作一综述.

1 NOX的结构、功能及其产生的ROS介导细胞内信号转导的机制

NOX是由6个亚基构成的多蛋白复合体, 最初在吞噬细胞发现他的表达. 吞噬细胞型NOX的结构和功能已研究清楚, 他的催化亚基gp91^{Phox}(又称为NOX2)和调节亚基p22^{Phox}在细胞膜上形成异二聚体(又称为黄素细胞色素b 558), 其他亚基通常位于细胞质, 包括p47^{Phox}, p40^{Phox}, p67^{Phox}和小G蛋白Rac(small GTPase Rac), 吞噬细胞型NOX激活的经典机制是各种刺激诱导p47^{Phox}, p67^{Phox}, p40^{Phox}和Rac激活, 然后这4种细胞质内的蛋白向细胞膜易位, 与其他两个亚基p22^{Phox}和NOX2相互作用, 结果将NADPH的两个电子连续传递给氧分子而产生超氧化物[6-7]. 非吞噬细胞型NOX在结构与功能上都与吞噬细胞型NOX相似, 只是不同类型的细胞NOX的亚基构成不同. 目前发现了6种gp91^{Phox}(NOX2)的同源蛋白(NOX1, NOX3, NOX4, NOX5, DUOX1和DUOX2), p47^{Phox}和p67^{Phox}也发现了他们的同系物, 分别是NOXO1(NOX organizer 1)和NOXA1(NOX activated 1)[8-9]. Rac蛋白的亚基有Rac1, Rac1b, Rac2和Rac3, Rac2只参与吞噬细胞型NOX的激活, Rac1则参与所有非吞噬细胞型NOX的激活[10].

NOX/Duox产生的ROS是受精确调节的, 他在信号转导、天然免疫和激素合成等许多生物学功能中发挥了关键作用[8,11]. 现已证明, ROS和活性氮(reactive nitrogen species, RNS)一样是细胞内信号转导的第二信使[12]. NOX产生的ROS介导了细胞内许多信号通路, 如丝裂原活化蛋白激酶(MAPKs)通路[13-14]、Janus激酶-信号传导子及转录激活子(JAK-STAT)通路[15]、核因子-κB(NF-κB)通路[16]等, 参与调控细胞的生长,细胞分裂, 分化, 迁移, 凋亡及衰老等许多生理活动, 也与疾病的发生密切相关[4,5,11].

蛋白酪氨酸激酶(protein tyrosine kinase, PTK)和蛋白酪氨酸磷酸酶(protein tyrosine phosphatase, PTP)分别使蛋白磷酸化和去磷酸化来调控细胞内信号传导通路, ROS一方面刺激酪氨酸及丝氨酸/苏氨酸磷酸化而激活PTK, 另一方面选择性地氧化修饰PTP活性中心的半胱氨酸残基(cysteine residue), 使PTP失活, 促进信号级联放大[17]. 半胱氨酸还以硫醇盐(thiolate)的形式存在于硫还氧蛋白(Trx), 蛋白激酶C(PKC), Rac蛋白、胱门蛋白酶(caspases)、激活蛋白-1(AP-1)和NF-κB上, 他们都可被ROS氧化修饰, 谷氧还蛋白可通过巯基-二硫键交换将他还原成硫醇盐, 从而恢复PTP的活性[12]. ROS还有调节离子通道的作用, 他能抑制慢钾通道(IKv)减少K^+电流[18], 激活Ca^{2+}通道触发Ca^{2+}的信号传导, 降低三磷酸肌醇(IP3)的阈值促进细胞内贮存的Ca^{2+}释放, 影响Ca^{2+}依赖的信号转导[19]. ROS还可能通过模似配体-受体相互作用直接激活生长因子受体[20].

稳态信号传导(homeostatic signaling)要求ROS限制于细胞特定的空间内, 亚细胞定位NOX与PTP的功能发现, 这两个系统常共区域化(colocalization), ROS信号传导与Ca^{2+}瞬时增加过程也有区室化(compartmentalization)的现象[17]. 细胞内ROS的浓度也是受严格调控, 最近研究证明H_2O_2不能自由通过生物膜, 他受水通道蛋白(aquaporins)转运调节[21], 而$O2^-$则是通过氯通道-3(ClC-3)跨膜转运[22]. 各种生长因子, 细胞因子, 趋化因子及其他刺激可活化NOX产生大量的ROS[8]. 当内源性或外源性ROS增多时, ROS从原来限定的空间逃逸, 触发应激信号传导(stress signaling)[17], NOX持续产生过量的ROS可引起动脉粥样硬化、高血压、肺纤维化等各种慢性疾病[5].

2 NOX产生的ROS参与HSCs内的信号转导

HSCs表达非吞噬细胞型NOX, Bachmann *et al*[23]最早发现HSCs表达p22^{Phox}. 后来Bataller *et al*[24]发现在培养激活的HSCs及从肝纤维化患者新分离的HSCs内p47^{Phox}、gp91^{Phox}和NOX1的mRNA都有高表达, 但在静止的HSCs没有表达. Adachi *et al*[25]分别从mRNAs和蛋白水平检测到LI-90细胞(HSCs系)表达p22^{Phox}, gp91^{Phox}, p47^{Phox}和p67^{Phox}. Proell *et al*[26]研究发现在TGF-β刺激HSCs后24 h NOX4和p47^{Phox}的mRNA表达就已增加, 48 h NOX活性明显升高. Rac1被认为是NOX激活的关键亚基[27], NOX活化产生的ROS作为第二信使介导了各种促肝纤维化因子在细胞内信号转导.

2.1 ROS介导TGF-β在HSCs内的信号转导

TGF-β是关键的促肝纤维化因子, 他能激活HSCs转化为肌纤维母细胞(myofibroblast, MFB), 促进

细胞外基质(ECM)合成, 通过下调金属蛋白酶(MMPs)和上调金属蛋白酶组织抑制剂(TIMPs)的表达减少ECM降解[28]. 近年研究发现TGF-β能诱导各种细胞内的NOX激活, 产生的ROS介导了细胞内信号传导. 如TGF-β1诱导成心肌纤维细胞产生ROS介导Smad2/3的磷酸化[29], 诱导人肺动脉平滑肌细胞(HPASMC)产生ROS, 氧化修饰细胞外信号调节激酶1/2(ERK1/2), 使生长信号级联放大[30], 诱导人肺纤维细胞内H_2O_2增加, 进而引起Ca^{2+}内流, MAPK及AP-1激活[31]. Proell *et al*[26]研究发现在TGF-β促进HSCs转化为MFB的过程中依赖NOX的激活及ROS的产生. 可溶性的TGF-βⅡ型受体(TGF-βRⅡ)与TGF-β结合后, 能降低NOX的活性, 减少ROS产生,从而阻止HSCs的激活[32]. 抗氧化剂N-乙酰-l-半胱氨酸(NAC)能抑制TGF-β介导HSC内的Smad2、Smad3磷酸化和Smad7 mRNA的表达[33]. 维甲酸(retinoic acid)能阻断TGF-β诱导HSCs内ROS增加及钙内流, 抑制α-SMA表达, 减轻肝纤维化[34].

2.2 ROS介导PDGF在HSCs内的信号转导 PDGF是HSCs最有力的促有丝分裂剂, Sundaresan *et al*[35]很早就发现PDGF的信号转导依赖H_2O_2的产生. Catarzi *et al*[36]研究认为PDGF刺激NIH3T3细胞(鼠纤维细胞)引起磷脂酰肌醇(-3)激酶(PIP3)和蛋白激酶C(PKC)的激活与NOX活化产生的H_2O_2有关. 现已明确酪氨酸磷酸化和ROS是PDGF信号传导的两个轴, 控制着诸如成簇黏附激酶(FAK)、GTP酶活化蛋白(GAP)、含有SH2酪酸氨酸磷酸酶(SHP-2), 磷脂酰肌醇二磷酸(PIP2), 磷脂酶Cγ(PLCγ)、PI3K等许多下游信号通路的开放与关闭[37]. Adachi *et al*[25]研究表明, PDGF是通过诱导NOX活化产生ROS来激活HSCs及促他增殖的, PDGF-BB激活原代HSCs的NOX产生ROS, ROS刺激P38MAPK磷酸化, P38MAPK激活后诱导HSCs增殖, 使用NOX的抑制剂DPI(diphenylene iodonium)或加拿大麻素(apocynin)能抑制PDGF-BB诱导ROS产生及HSCs增殖. Adachi *et al*[38]发现高分子量脂联素(HMW Adiponectin)可通过激活腺苷单磷酸活化蛋白激酶(AMPK)来抑制PDGF诱导的HSCs增殖, 而AMPK抑制HSCs增殖的机制是通过抑制NOX产生ROS进而抑制AKT(又称为蛋白激酶B, PKB)信号通路, 使HSCs表达CDK抑制蛋白p27(kip1)和p21(cip1)增加. 值得注意的是, 抗氧化剂NAC虽然能阻断TGF-β信号通路[33], 但不能阻止HSCs的PDGFβ型受体及细胞内ERK、PKB/Akt磷酸化, 可能NAC介导细胞内的还原-氧化(cellular redox)不是特异作用于PDGF信号通路的[39].

2.3 ROS介导AngⅡ在HSCs内的信号转导 AngⅡ也是一个主要的促肝纤维化因子, 他诱导肝脏的炎症反应, 刺激HSCs激活、增殖、移行, 分泌促炎细胞因子及胶原[40-41]. Bataller *et al*[24]研究证实AngⅡ在肝内的致纤维化作用也是通过激活NADPH氧化酶产生ROS来实现的, AngⅡ与AT1受体结合后诱导$p47^{Phox}$磷酸化, NOX被激活并产生ROS, ROS通过氧化还原修饰使AKT和MAPKs磷酸化, 增强AP-1的DNA结合活性. NAC和DPI能减弱AngⅡ刺激HSCs引起的DNA合成、Ⅰ型胶原mRNA表达、细胞移行、TGF-β1和其他炎性细胞因子的分泌[24]. Li *et al*[42]研究发现, 表没食子儿茶素没食子酸脂(EGCG)能抑制AngⅡ诱导的NOX表达及ROS的产生, 阻断ROS依赖的p38和JNK信号通路从而抑制NF-κB的激活. AngⅡ依赖ROS激活的信号通路还有Src分子C端激酶(c-Src)、富脯氨酸的酪氨酸激酶2(proline-rich tyrosine kinase 2, Pyk2)、PI3-K等[43], 此外AngⅡ激活NOX产生的ROS还能抑制慢钾通道(IKv)减少K^+电流[18], 激活钙通道引起Ca^{2+}内流[44].

2.4 ROS介导leptin在HSCs内的信号转导 Leptin是近年来发现的促肝纤维化因子, 他能上调HSCs的TGF-βRⅡ表达[45], 并促进HSCs合成TGF-β[46]、金属蛋白酶组织抑制剂-1(TIMP-1)[47]、Ⅰ型胶原[45,48], 加重硫代乙酰胺(thioacetamide)诱导的鼠肝纤维化[46,49]. Saxena *et al*[50]研究发现Leptin依赖ERK和Akt磷酸化促进HSCs增殖并抑制他的凋亡. Cao *et al*[47]研究进一步发现Leptin是通过H_2O_2介导p38、ERK1/2信号通路及JAK/STAT通路激活, 从而促进HSCs合成TIMP-1的. 他也依赖H_2O_2激活ERK1/2、p38、JAK1和JAK2, 抑制基质金属蛋白酶-1(MMP-1)基因的表达[51], 促进Ⅰ型胶原的表达[52]. 单用二亚油酰磷脂酰胆碱(DLPC)或S-腺苷甲硫氨酸(SAMe)都能减少瘦素刺激的TIMP-1的mRNA和蛋白表达, 联合使用DLPC和SAMe能完全阻断ERK1/2、p38的磷酸化及TIMP-1的表达[53], DLPC和SAMe能阻止Leptin或甲萘醌(menadione)引起的H_2O_2产生, 恢复消耗的谷光苷肽(GSH), 阻断H_2O_2介导ERK1/2和p38的激活, 完全抑制Ⅰ型胶原的mRNA表达[54].

2.5 ROS还介导了其他促肝纤维化因子在HSCs内的信号转导 乙醛是酒精性肝病中的主要促

■创新盘点

本文就NADPH氧化酶/Dual氧化酶产生的活性氧簇调控信号转导的机制, 以及近年来关于活性氧簇介导的促肝纤维化因子在肝星状细胞内信号转导的研究作了较新且全面的阐述.

■应用要点
本文对防治肝纤维化有指导作用, 未来我们可以选择针对肝星状细胞的NOX表达或对NOX的活性有抑制作用的抗氧化剂, 来阻断促肝纤维化因子在肝星状细胞内的信号转导, 达到阻止静止的肝星状细胞激活、促进肝星状细胞凋亡, 减轻甚至逆转肝纤维化的作用.

肝纤维化因子之一[55]. Novitskiy *et al*[56]研究发现乙醛可引起小鼠HSCs内ROS产生增加, 雷洛昔芬(raloxifene)能抑制NOX产生$O2^{\cdot-}$, 减少乙醛引起H_2O_2和$O2^{\cdot-}$的产生. 乙醛诱导HSCs合成胶原也依赖H_2O_2介导PKCδ/ERK1/2及c-Abl信号通路的激活和过氧化物酶体增殖物激活受体γ(PPARγ)的磷酸化, 过氧化氢酶(catalase)能阻断乙醛诱导的PPARγ磷酸化, 抑制胶原产生[57]. Sugimoto *et al*[58]研究发现高糖溶液通过PKC依赖途径激活HSCs的NOX产生ROS, ROS介导MAPK磷酸化, 导致HSCs增殖并合成Ⅰ型胶原. Itagaki *et al*[59]发现雌二醇抗肝纤维化的作用是通过抑制NOX活性来减少ROS产生, 阻断MAPK信号通路及转录因子的激活, 从而抑制TGF-β1的表达和HSCs的激活, 孕酮则有相反的作用. 亮氨酸(leucine)也能诱导HSCs的NOX产生ROS, ROS介导了胰岛素受体/胰岛素样生长因子-Ⅰ受体(IR/IGF-IR)的激活和ERK, Akt及哺乳类动物雷帕霉素靶蛋白(mammaliantargeto-frapamycin, mTOR)的磷酸化, 最后导致HSCs合成Ⅰ型胶原增加, 这一作用可以被加拿大麻素和谷光苷肽阻断[60]. Kojima-Yuasa *et al*[61]研究发现锌缺乏的HSCs内谷光苷肽水平下降, 细胞产生H_2O_2增加, 导致HSCs激活. Zhan *et al*[62]研究显示凋亡小体使HSCs内的NOX活化进而激活HSCs促进肝纤维化. ROS还可能是其他各种促肝纤维化因子细胞内信号传导的共同第二信使, 如ROS介导了内皮素-1(ET-1)[63], 血管内皮细胞生长因子(VEGF)[64]等生长因子、细胞因子在其他细胞的信号转导.

2.6 ROS介导NF-κB信号通路的激活 NF-κB可能不是介导HSCs激活和增殖的关键因子, 但他能使激活的HSCs/MFB持续活化或永生化[65]. 在HSCs激活过程中NF-κB的活性持续升高, 而IκB-α在细胞质与细胞核内持续减少[66]. HSCs内ROS的增加可能是NF-κB活性是持续升高的原因, 由于NF-κB存在半胱氨酸残基[12], ROS可通过氧化修饰直接激活NF-κB. 既往研究就证明各种抗氧化剂如维生素E, α-硫辛酸(a-lipoic acid), 丁羟甲苯(BHT)及NAC都能抑制NF-κB的激活[67]. 最近Li *et al*[68]的研究发现不对称二甲基精氨酸(asymmetric dimethylarginine, ADMA)诱导HSCs内ROS的产生后激活了NF-κB依赖的信号通路, 使TGF-β1表达增加, 导致HSCs激活, 抗氧化剂吡咯烷二硫代氨基甲酸盐(pyrrolidine dithiocarbamate)可以拮抗这一作用.

3 结论

既往我们对ROS在肝纤维化发病的认识局限在他损伤DNA、蛋白、与膜发生脂质过氧化反应, 而视之为损伤肝细胞的有害分子, 而上述的资料表明NOX产生的ROS作为共同的第二信使介导了许多促肝纤维化因子在HSCs内的信号转导, 这些信号通路与HSCs的活化、增殖及肝纤维化发病密切相关[69-70], 因此清除HSCs内过多的ROS, 能阻断这些促肝纤维化因子在HSCs内的信号转导, 达到阻止静止的HSCs激活、促进HSCs凋亡、减轻甚至逆转肝纤维化的作用. 但并非所有的抗氧化剂都能达到这一作用, 有报道抗氧化剂谷胱甘肽乙酯(GSH-EE)或水溶性生育酚(trolox)清除HSCs内ROS后, 反而阻止了内源性2-花生四稀酸甘油(2-AG)诱导的HSCs凋亡, 这可能与2-AG不是作用于NOX, 而是通过使线粒体产生大量的ROS有关[71]. 因此我们认为, 只有抑制HSCs的NOX表达或抑制NOX的活性来清除HSCs内过多的ROS, 才能阻断ROS介导的促肝纤维化因子在HSC内的信号转导,这将是治疗肝纤维化的一个新途径. 在这一领域中药有很大潜力,如上述绿茶中提取的EGCG[42]及丹参中提取的熊果酸(ursolic acid)[72]都能抑制NOX表达, 减少ROS的产生. 但NOX产生低水平的ROS介导稳态的信号传导, 完全抑制了NOX活性可能影响细胞正常的生长、分裂和分化, 这值得我们进一步研究.

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■名词解释

促肝纤维化因子: 本文提到的促肝纤维化因子指各种参与肝纤维化发病的生长因子(如转化生长因子-β),细胞因子(如瘦素), 激素(如孕酮)及其他介质(如乙醛)等.

■同行评价
本文选题较新, 对临床认识肝纤维化发生有一定的意义, 特别是对今后的抗肝纤维化提供了一定的理论基础.

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• 消息 •

世界华人消化杂志性质、刊登内容及目标

本刊讯 《世界华人消化杂志(国际标准刊号ISSN 1009-3079, 国内统一刊号CN 14-1260/R, Shijie Huaren Xiaohua Zazhi/*World Chinese Journal of Digestology*)》, 是一本由来自国内23个省、市、自治区、特别行政区的496位胃肠病学和肝病学专家支持的开放存取的同行评议性的旬刊杂志, 旨在推广国内各地的胃肠病学和肝病学领域临床实践和基础研究相结合的最具有临床意义的原创性及各类评论性的文章, 使其成为一种公众资源, 同时科学家、医生、患者和学生可以通过这样一个不受限制的平台来免费获取全文, 了解其领域的所有的关键的进展, 更重要的是这些进展会为本领域的医务工作者和研究者服务, 为他们的患者及基础研究提供进一步的帮助.

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《世界华人消化杂志》报道的内容包括食管、胃、肠、肝、胰肿瘤, 食管疾病、胃肠及十二指肠疾病、肝胆疾病、肝脏疾病、胰腺疾病、感染、内镜检查法、流行病学、遗传学、免疫学、微生物学, 以及胃肠道运动对神经的影响、传送、生长因素和受体、营养肥胖、成像及高科技技术.

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