综述

NADPH氧化酶介导的氧化应激在细胞骨架相关调控活动中的作用

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摘要 细胞骨架是细胞赖以生存的内在支撑结构, 主要包括微管、中间丝状体及微丝。细胞骨架上游Rho GTP酶的活化、细胞骨架重塑过程和细胞骨架参与的相关细胞功能活动(如迁移和黏附等)均与胞内氧化应激压力有关。 NADPH氧化酶(NADPH oxidase, NOX)介导的氧化应激已成为细胞骨架相关活动的重要影响因素之一。因此, 认识NOX介导的氧化应激对了解细胞骨架调控相关活动至关重要, 为今后深入研究细胞骨架相关疾病奠定理论基础。

关键词 NOX; 氧化应激; 细胞骨架

NOX-Mediated Oxidation in the Regulation of Cytoskeleton-Related Activities

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Abstract Cytoskeleton is the internal support structure for cells to survive, mainly including microtubules, intermediate filaments and microfilaments. Studies have confirmed that the activation of cytoskeleton upstream Rho GTPase, cytoskeleton self-remodeling and cytoskeletal related cell functions such as migration, adhesion and other cell physiological activities are related to intracellular oxidative stress. In recent years, NOX-induced oxidative stress has become one of the important factors affecting cytoskeleton-related activities. This makes it essential for us to understand NOX-induced oxidative stress and cytoskeletal regulation and lay a solid foundation for the study of related diseases.

Keywords NOX; oxidative stress; cytoskeleton

NADPH氧化酶(NADPH oxidase, NOX)活化产生的活性氧类(reactive oxygen species, ROS)是影响细胞内氧化应激的重要因素之一。研究认为, NOX家族包括NOX1~5、DUOX(dual oxidase)1/2及其活化后产生的产物[包括超氧根离子O_2^-及过氧化氢(H_2O_2)等]会向胞外释放, 通过单纯扩散(如H_2O_2)及封闭的囊泡(如O_2^-)进入细胞内[1]。已有研究表明, NOX活化产生的ROS可以通过旁分泌、自分泌, 甚至是内分泌的方式, 调节细胞内信号通路[1]。尽管它们的活动与多种疾病状态有关, 但现在人们普遍认为, 在生理条件下, ROS是正常细胞功能所必需的。事实上, NOX产生的ROS参与宿主防御[2]、心肌修复[3]和细胞分化[4], 同时也是细胞骨架及其支持的细胞功能(如迁移和黏附)的重要调节因素之一[5]。研

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究证实, NOX介导的ROS参与了细胞骨架重塑相关蛋白质的信号转导, 也可能直接参与修饰细胞骨架构成或细胞骨架相关的蛋白质合成[6]。近年研究进一步证实, NOX介导的胞内氧化应激压力在诸多细胞骨架相关疾病(如器官纤维化进展及肿瘤迁移)的发生发展中起着重要的调节作用[7]。因此, 深刻认识NOX介导的氧化应激对认识细胞骨架相关调控活动至关重要。

1 细胞骨架相关结构

细胞骨架是维持细胞形态、内在排布及正常生理功能的重要细丝网络。目前研究发现, 细胞骨架分为三种, 即微管(外径约为25 nm)、中间丝状体(外径约为10 nm)以及肌动蛋白微丝(外径约为8 nm)[7]。细胞骨架的运动能让细胞实现多种重要功能, 如迁移、黏附、播散及增殖。除此之外, 细胞骨架还能协助蛋白质、囊泡及细胞器在胞内的转移或运动[7]。胞内存在的驱动蛋白(kinesins)、动力蛋白(dyneins)及肌球蛋白(myosins)等细胞骨架相关蛋白质能通过分解ATP使细胞骨架发生运动[8]。

2 NOX家族及细胞内氧化应激

NOX是一类细胞膜相关多亚基酶复合体, 主要包括NOX1~5及Duox1/2, 是胞内活性氧类(ROS)(主要包括O_2^-及H_2O_2等)的主要来源。NOX家族成员结构类似, 均包含一个6次跨膜结构域、胞质黄素腺嘌呤二核苷酸(cytosolic flavin adenine dinucleotide, FAD)及还原型烟酰胺腺嘌呤二核苷酸磷酸(nicotinamide adenine dinucleotide phosphate, NADPH)结合域。但不同的NOX复合体可能含有gp91^{phox}催化亚基以及p22^{phox}、p40^{phox}、p47^{phox}、p67^{phox}及Rac1等5种不同的调节亚基[9]。许多胞内外刺激物, 如AngII(angiotensin II)、PDGF(platelet-derived growth factor)及TGF-β(transforming growth factor-β), 会影响NOX的表达与活化产生ROS, 加重细胞内氧化应激。

研究发现, NOX的亚细胞定位与细胞骨架有关, 且不同类型的细胞及其胞内NOX的亚细胞分布也不尽相同, 比如p47^{phox}与膜突蛋白(moesin)、WASP家族Verprolin同源蛋白(WAVE)共定位于片状伪足。此外, 在不同亚型的血管平滑肌细胞中, NOX4集中分布于分化型细胞的应力纤维上, 但在增殖型细胞中集中分布于黏着斑(focal adhesion, FA)[10]。

3 NOX介导的氧化应激对细胞骨架相关蛋白质的调控作用

3.1 NOX介导的氧化应激与Rho GTP酶

Rho超家族中Rho GTP酶是一类与GTP相连的蛋白质, 其中研究最为广泛的包括RhoA(Ras homolog gene family, member A)、Rac1(Ras-related C3 botulinum toxin substrate 1)及Cdc42(cell division control protein 42 homolog)。Rho GTP酶在细胞生长、移动、极化及黏附中起着非常重要的作用[11]。研究表明, 嗜中性粒细胞会表达两种Rac亚型, 包括广泛存在于各种细胞中的Rac1及巨噬细胞特异型Rac2, 这两种Rac蛋白质可以向胞膜转移并与p67^{phox}及gp91^{phox}等亚基结合进而使嗜中性粒细胞活化[12]。

目前研究认为, Rho GTP酶不但可以作为NOX/ROS上游调控因子, 也可以作为NOX/ROS下游效应因子。研究发现, 在生长因子的刺激下NOX1可以与RacGEFβPIX(recombinant Rho guanine nucleotide exchange factor 7, ARHGEF7)结合使下游磷脂酰肌醇-3-激酶(phosphatidylinositol 3-kinase, PI3K)活化生成脂质产物, 刺激普列克底物蛋白底物同源(pleckstrinhomology, PH)结构域, 进而激活GEF(guanine nucleotide exchange factors)使Rac活化, 最终导致膜上NOX激活产生ROS[13]。此外, 当胞内NOX/ROS通路激活后, 胞内生成的NO_2(nitrogen dioxide)可以介导Cys16(cysteine 16)及Cys20之间形成二硫键抑制RhoA活性, 阻碍其与GEFVav2结合[14]。

RhoA作为骨架重构的重要Rho GTP酶家族成员, 其与NOX介导的氧化应激同样在诸多疾病病程中起着至关重要的作用。在一项肺动脉高压的研究中人们发现, 辛伐他汀能减少肺动脉高压模型大鼠肺内NOX2调节亚基p47^{phox}和p67^{phox}的表达, 减少胞内氧化应激压力, 进而抑制Rho激酶表达, 最终减轻肺动脉重构[15]。另一项关于血小板的研究也指出, 运用Rhosin抑制血小板中RhoA/ROCK(Rho associated coiledcoil forming protein kinase)/p47^{phox}信号通路产生的ROS可以减少RhoA/ROCK介导的MLC(myosin light chain)磷酸化, 从而抑制血小板活化[16]。同样, 在肾纤维化中, RhoA/ROCK作为Poldip2/NOX4上游可以调控ROS生成, 加重NRK-49F细胞内氧化应激, 促进肾纤维化的发生发展[17]。

3.2 NOX介导的氧化应激与微管蛋白

微管是由α-微管蛋白(α-tubulin)和β-微管蛋白(β-tubulin)组成的丝状结构。它们参与细胞分裂、细胞内结构的组织、细胞内运输、纤毛和鞭毛的活动。此外, γ-微管蛋白(γ-tubulin)作为第三种微管蛋白是一种专门定位于中心体的微管蛋白[18]。研究发现, 星形孢菌素(staurosporine)会刺激星形胶质细胞NOX1及NOX4产生ROS, 进而导致细胞骨架重塑, 使微管蛋白的表达量显著下降[19]。近期研究显示, 半胱氨酸氧化反应也参与到了微管蛋白的翻译后修饰过程之中[20]。

3.3 NOX及其介导的氧化应激与中间丝状体

中间丝状体(intermediate filament, IF)是另一种重要的细胞骨架蛋白, 编码基因超过70个。这些蛋白质通常形成10 nm长丝[7]。研究人员根据它们的结构和序列同源性将其分为5大类: I型~V型。II型IF包括酸性及中–碱性角蛋白(keratin)。III型IF由波形蛋白(vimentin)、结蛋白(desmin)、外周蛋白均聚物(peripherin)或胶质纤维酸性蛋白(glial fibrillary acidic protein, GFAP)组成。IV型IF包括神经系统内复杂的杂聚物, 如神经微丝蛋白NF-L(neurofilament light)、NF-M(neurofilament middle)和NF-H(neurofilament heavy)或均聚物α-internexin。V型IF包括核纤蛋白(lamin)A、C、B1/2等核内骨架蛋白[21]。研究表明, IF参与许多细胞生理活动, 包括运动、形变及细胞器的锚定和分布与胞内信号转导等[22]。

一项研究发现, 将由E6/7人类乳头状病毒(human papillomavirus, HPV)16型(GM16)诱导的永生牙龈黏膜角质形成祖细胞系*Nox1*基因过表达后会促进胞内ROS生成, 使细胞角蛋白8/18(cytokeratin 8/18, CK8/18)、波形蛋白等上皮间充质转化(epithelial-mesenchymal transition, EMT)标志物水平上升, 促进细胞管形成及细胞非锚定依赖生长[23]。研究人员在对高同型半胱氨酸血症(hyperhomocysteinemia, hHcys)模型小鼠运用重组鼠生长激素后会显著抑制小鼠体内NOX介导的胞内氧化应激途径依赖的过氧根离子的产生, 降低膜蛋白(podocin)及desmin的表达, 进而抑制hHcys导致的肾小球损伤及EMT过程[24]。另一项临床横断面研究显示, 适量摄入可可多元酚(cocoa polyphenols)会降低患者体内NOX2的表达, 减轻血清细胞CK18含量, 降低罹患非酒精性脂肪性肝炎(non-alcoholic steatohepatitis, NASH)风险[25]。另外, 神经微丝蛋白NF-L/M/H在脊髓、神经母细胞瘤、纹状突触体等处的氧化反应均与NOX依赖的H_2O_2生成有关[26]。

3.4 NOX及其介导的氧化应激与肌动蛋白

胞内肌动蛋白(actin)调节同样依靠胞内氧化应激。近年研究表明, 高浓度H_2O_2处理之后会显著促进β-actin的多聚作用[27]。质谱分析显示, α-actin C-端半胱氨酸(Cys376)或β-actin C-端半管氨酸(Cys374)能在G-actin及F-actin上被氧化[5]。另一项研究发现, β-actin的氧化发生在两个对氧化还原敏感的半胱氨酸残基Cys272及Cys374上, 而这一过程能被硫氧还蛋白(thioredoxin)及谷胱甘肽(glutathione)逆转[28]。进一步研究表明, Cys374被氧化后会导致抑制蛋白(profilin)亲和力下降, 减少actin的多聚作用, 最终导致F-actin不稳定并使ATP酶活性增加[29]。

细胞内ROS水平高低可对肌动蛋白运动和多聚作用产生不同影响。研究人员发现, 运用50 nmol/L H_2O_2处理兔腰肌纤维后肌动球蛋白(actomyosin)活性增强, 进而使actin-myosin介导的收缩运动减弱[30]; 相反的, 运用低剂量的(1~5 nmol/L)H_2O_2处理P388D1细胞后会增加应力纤维的形成[31]。另外, 胞内温和的氧化作用会促进actin-actin间二硫键形成, 加快肌动蛋白聚合作用。研究发现, 迁移中的内皮细胞用含黄素氧化酶DPI(diphenyleneiodonium)或过氧化物清除剂MnTMPyP处理后能抑制actin单体渗入倒刺末端(barbed end)[32]。此外, 提高嗜中性粒细胞中谷氧还蛋白1(glutaredoxin 1)含量(无其他外源性氧化剂)会增加actin的谷胱甘肽化, 并减少多聚作用[33]。由此可见, actin的氧化及多聚作用依赖NOX及其活化产生的ROS。

4 NOX介导的氧化应激对细胞运动的影响

4.1 NOX介导的氧化应激在细胞迁移中的作用

细胞迁移是指细胞在某些刺激作用下产生的移动, 是正常细胞的基本功能之一。当环境中存在趋化因子时, 细胞会形成富含F-actin的板状伪足进行迁移运动。NOX在细胞迁移当中的作用同样至关重要。研究表明, NOX1可以调控弹弓蛋白1L(slingshot 1L, SSH1L)去磷酸化, 并能激活血管平滑肌细胞(vascular smooth muscle cell, VSMC)迁移所必需的丝切蛋白(cofilin)[34]。另外, 有研究发

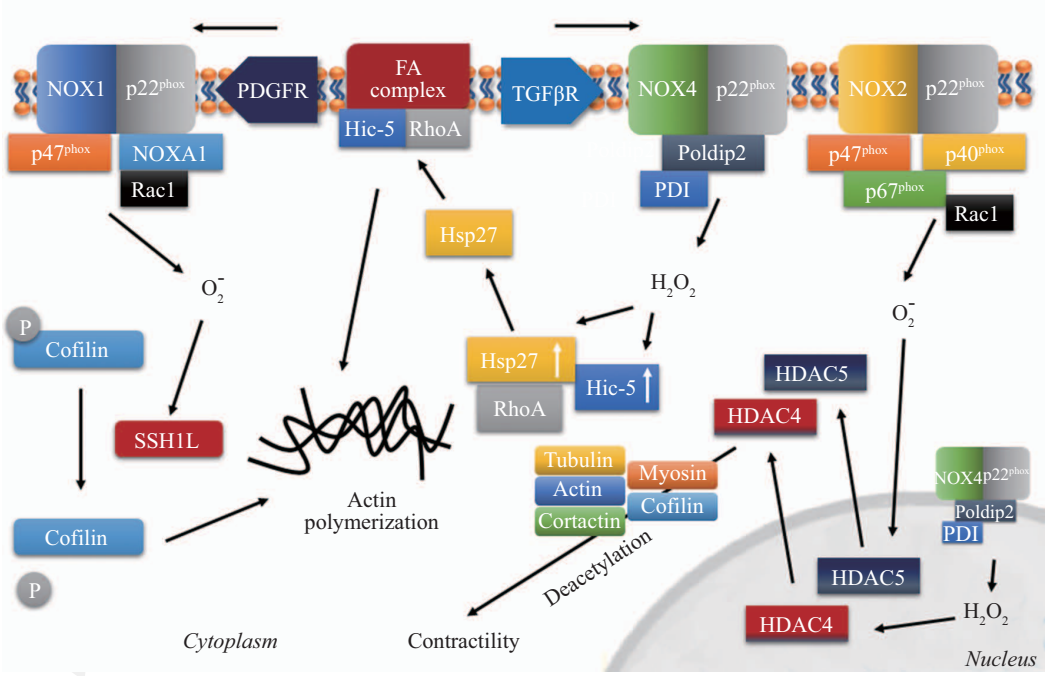
现, 敲除*Nox1*后会减少血管形成过程中内皮细胞(endothelial cell, EC)的迁移运动, 并抑制NF-κB调节因子PPARα介导的管状结构形成[34]。类似地, *Nox1*敲除的小鼠VSMC中PDGF(platelet derived growth factor)或bFGF(basic fibroblast growth factor)介导的胞内氧化应激活动减轻, 最终抑制细胞迁移运动, 而将小鼠体内*Nox1*基因过表达后会促进PDGF介导的VSMC迁移运动[35](图1)。

NOX在细胞迁移中的作用可能并非单纯的激动剂。Meng等[36]率先发现了NOX1及NOX4介导的ROS在胰岛素样生长因子-1(insulin like growth factor-1, IGF-1)诱导的VSMC迁移中的作用。Haurani等[37]表明, NOX4过表达有效抑制了AngII诱导的成纤维细胞迁移运动。类似地, NOX抑制剂VAS2870也可以抑制由PDGF诱导的VSMC的迁移[38]。

4.2 NOX介导的氧化应激在细胞黏附中的作用

黏着斑(focal adhesion, FA)是一种包含整合蛋白(integrin)的大分子复合体。FA能将肌动蛋白细胞骨架与细胞外基质联系起来, 是介导该黏附作用的重要因素之一[39]。在细胞黏附的过程中, 位于细胞腹侧表面的FA会集合起来并调节相关信号蛋白的表达最终影响integrin活化。有效的细胞迁移伴随着细胞前端焦点复合体的形成。这种焦点复合体最终会转化为FA, 促进细胞黏附[40]。

NOX4及其产生的ROS在FA介导的细胞黏附中起到关键作用。研究发现, 将*Nox4*或其上游*Poldip2*基因沉默后会阻碍ROS生成, 进而抑制FA及应力纤维的形成; 而将*Poldip2*过表达之后会通过RhoA依赖途径刺激FA及应力纤维的形成, 并减少有PDGF诱导的细胞迁移[41]。研究人员在一项使用有丝分裂抑制剂诺可唑(nocodazole)刺激微管依赖的FA相关调控研究中发现, 将Poldip2过表达后会抑制FA降解[42]。此外, 过氧化氢诱导型克隆-5(hydrogen peroxide-inducible clone-5, *Hic-5*)最早发现是一种定位于FA上的H_2O_2及TGF-β诱导基因, 是桩蛋白(paxillin)蛋白家族成员之一。近期研究证实, 用TGF-β或Hic-5刺激VSMC同样会激活NOX4产生H_2O_2促进细胞黏附作用, 但具体机制仍有待阐明[6]。另外, FA通过微丝帽及actin多聚抑制蛋白热休克蛋白27(hot shock protein 27, HSP27)对NOX4的调控信



NOX1/2/4活化产生的ROS能直接影响不同细胞骨架信号转导通路。NOXA1: NADPH氧化酶活化子1; PDGFR: 血小板衍化生长因子受体; TGFβR: 转化生长因子β受体; PDI: 蛋白质二硫键异构酶; SSH1L: 弹弓式蛋白1L; HDAC: 去乙酰化酶。

Different cytoskeletal signaling pathways are directly influenced by NOX1/2/4-induced ROS. NOXA1: NADPH oxidase activator 1; PDGFR: platelet-derived growth factor receptor; TGFβR: transforming growth factor β receptor; PDI: protein disulfide isomerase; SSH1L: slingshot 1L; HDAC: histone deacetylase.

图1 NOX介导的氧化应激在细胞骨架调节活动中的作用

Fig.1 NOX-mediated oxidation stress in regulation of the cytoskeleton

号通路也对胞内氧化应激压力敏感[43](图1)。

5 结语

细胞骨架作为细胞内连接微观蛋白质分子与宏观细胞结构的重要桥梁, 在诸多疾病的发生发展中起着重要的作用。近年来, NOX在细胞骨架调控方面的作用逐渐成为人们研究的焦点。目前研究发现, 一些NOX抑制剂通过抑制细胞骨架相关的蛋白质对细胞的生理活动进行调控, 如NOX1抑制剂ML171会损伤大肠癌细胞功能伪足的形成[44]、NOX2及NOX4抑制剂VAS2870能减少F-actin在胞内的运动及神经突的过度生长[45]、$p67^{phox}$及Rac1抑制剂Nebivolol能抑制RhoA活性[46]、$p47^{phox}$磷酸化抑制剂Gliotoxin能调控人嗜中性粒细胞中actin细胞骨架重塑介导的吞噬活动[47]。这些抑制剂发挥的效应进一步证实了NOX产生的ROS会与其他相关信号分子相互作用导致细胞骨架重塑。尽管如此, 细胞骨架与相关疾病发生发展之间的关系仍未阐明。相信随着人们对细胞骨架研究的不断深入, 细胞骨架重塑将会成为未来相关疾病的诊断与治疗的新靶点。

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