·文献综述·

小梁网细胞氧化应激在青光眼发病中的研究进展

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摘要
青光眼是一种常见的不可逆性致盲眼病,病理性眼压升高为主要临床特征。眼压的形成与房水循环密切相关,房水动力学异常,会引起病理性眼压升高。小梁网是房水外流通道的主要组成部分,对维持正常眼压起到非常关键的作用。氧化应激是导致青光眼眼压升高的直接危险因素,表现为氧化与抗氧化作用的失衡。小梁网细胞氧化应激可能导致细胞外基质的沉积与退行性变,使细胞发生自噬和衰老,造成小梁网细胞功能障碍,最终导致房水外流阻力增大,引起病理性眼压升高。本文将针对小梁网细胞氧化应激与青光眼关系的研究进展进行综述,以期为进一步的临床研究提供依据,为探讨青光眼的发病机制、预防及治疗青光眼提供参考。
关键词:青光眼;小梁网细胞;氧化应激;自噬;衰老;炎症
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Research progress of trabecular meshwork cell oxidative stress in the pathogenesis of glaucoma

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Abstract
• Glaucoma is a common irreversible blinding eye disease, pathological elevated intraocular pressure is the main clinical feature. The formation of intraocular pressure, related to aqueous circulation, will be pathologically elevated when the aqueous cycle is abnormal. Trabecular network, which plays a key role in maintaining normal intraocular pressure, is the main component of aqueous outflow channel. Imbalance of oxidative stress manifested as oxidation and antioxidant effects is a direct risk factor for elevated intraocular pressure in glaucoma. When it comes to the trabecular meshwork cells, a series of changes such as deposition and degeneration of extracellular matrix, autophagy and aging will eventually occur, and finally the dysfunction of trabecular meshwork cells and increased aqueous outflow resistance, causing intraocular pressure pathological elevated. In this paper, we reviewed the research progress on the relationship between oxidative stress in trabecular meshwork cells and the pathogenesis of glaucoma, in order to provide evidence for further research and reference for exploring the pathogenesis, prevention and treatment of glaucoma.
• KEYWORDS: glaucoma; trabecular meshwork cells; oxidative stress; autophagy; cell aging; inflammation

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0 引言

青光眼是一种常见的不可逆致盲性眼病,以病理性眼压升高为主要临床特征。眼压与房水循环密切相关,房水循环的流出通道主要包括小梁网(trabecular meshwork, TM)与Schlemm管,两者结构的病理性改变是引起眼压升高的主要原因,已有研究表明,50%~75%的房水流出阻力发生在邻管组织[1]。氧化应激(oxidative stress, OS)是细胞氧化与抗氧化作用的失衡,产生于细胞损伤等原因诱发的细胞防御机制启动、线粒体功能障碍、抗氧化系统受损,主要表现为产生过量的抗氧化成分活性氧(reactive oxide species, ROS),线粒体是ROS产生的主要场所[2-4]。适量的ROS可保护细胞免受OS损害,过量产生的ROS在细胞内积累导致了DNA、酶及结构蛋白和膜脂质等一系列细胞器的氧化损伤,影响细胞功能[5-7]。根据发生部位,OS常分为线粒体氧化应激与内质网应激,二者息息相关,内质网应激发生于线粒体氧化应激之后,可加剧线粒体氧化应激[8-10]。

青光眼患者的OS水平较高,提示青光眼的发病与OS有关[11-12]。已有研究表明,青光眼患者房水中丙二醛(monochrome display adapter, MDA)与谷胱甘肽(glutathione, GSH)等抗氧化成分水平显著降低而氧化酶

活性显著提高,这提示青光眼患者可能存在总抗氧化能力的降低[12-15]。此外,TM 组织作为眼压维持的关键,其筛状结构在房水引流、前房液体调节和维持眼压稳定方面起至关重要的作用,是前房组织中对 OS 最敏感的结构,OS 导致青光眼发病的原因或许与小梁网细胞(trabecular meshwork cells,TMC)病理性损伤密切相关[16]。OS 对 TMC 功能的影响体现在多个方面:TM 组织对房水的调节功能障碍、TM 细胞外基质发生变化、TMC 内发生自噬和衰老等,这一系列变化最终导致 IOP 升高。因此,研究 OS 导致的 TM 损伤及其与 TMC 病理变化之间的关系,有望成为青光眼新的治疗靶点及方向。

1 OS 与 TM 调节功能异常

TM 对房水的调节功能需要 TMC 的维持和调节,机体 OS 环境产生的代谢产物可以损伤 TMC 的结构功能,这导致 TM 组织不再有效地调节房水流出,最终导致病理性眼压升高[17]。

机体 OS 导致神经兴奋性相关物质的异常可影响 TM 的调节功能。已有研究发现,NO 通过收缩 TMC 来调节房水流出,其分泌异常可引发房水循环异常[5,11],OS 可影响 NO 与 TMC 的反应,导致 TM 功能障碍。在原发性开角型青光眼(primary open angle glaucoma,POAG)患者中,OS 增加的阴离子超氧化物等反应性基团与 NO 反应可直接损伤 TM 内皮细胞[10,18]。另外,De Souza 的一项研究显示,OS 时 TMC 中的 NO 内源性受体被氧化,导致 TM 调节功能障碍[7]。在前房中,OS 时机体释放大量的组胺,不仅增加了血管通透性使房水生成增加,也使房水流出减少[19]。而全身 OS 激活下丘脑-垂体-肾上腺轴,肾上腺应激时可分泌大量糖皮质激素,过量产生的糖皮质激素与 TM 上的相应受体反应,影响房水流出[20]。

2 OS 与 TM 细胞外基质退行性变

TMC 固有僵硬度增大是青光眼发病的主要原因之一,TMC 固有僵硬度增大是由 TM 细胞外基质(extracellular matrix,ECM)的异常积累及退行性变造成的[21-22]。ECM 是 TM 的重要组成部分,和 You 等[23]证明,OS 时 ECM 合成和水解失衡,使 ECM 异常积聚,房水流出阻力增大,最终导致青光眼发病。

ECM 组成部分的改变与线粒体氧化应激及内质网应激有关[24-25]。Shen 等[26]的研究发现,OS 上调与纤维化有关的 lncRNAs 表达,最终激活人 TMC 中的 ECM 基因,增加了 ECM 的产生。Rao 等与 Suri 等发现,与细胞纤维化有关的转化生长因子-β_2(transformed growth factor-β_2,TGF-β_2)不仅可加剧 TMC 氧化应激,还使 TM 中 ECM 重塑,而青光眼相关基因 LTBP2 可能参与了重塑的过程[27-29]。研究发现,ECM 中纤连蛋白沉积或在细胞内过表达纤连蛋白[24],可能与青光眼致病基因--Myocilin 基因突变有关,该基因突变使蛋白质异常折叠并积累在 TMC 内部,并诱发内质网(ER)应激,最终影响 TMC 的正常功能和/或存活,导致房水流出阻力增加,IOP 升高[30]。

3 OS 与 TMC 自噬

自噬(autophagy)是一种自降解过程,它依赖于溶酶体,使细胞内组分再循环、合成和降解,从而维持内环境的稳定。当细胞发生 OS 时,OS 的线粒体会进一步激活内质网应激,从而使细胞中 ROS 大量增加[14,22,31-33],这些过量产生的 ROS 导致了线粒体损伤,并发生自噬功能异常[34],细胞自噬功能异常则进一步导致了线粒体功能障碍、细胞功能障碍甚至死亡[35],最终诱发青光眼的发生。在大多数细胞中,自噬活动的异常与 P53 上调,线粒体转运和 E3 泛素连接酶的激活受抑制有关,导致受损的线粒体无法清除,最终导致细胞功能障碍[36]。此外,细胞发生过量自噬时,自噬相关 LC3 及 Beclin-1 和 Atg5 的蛋白水平大量上调,p62 的水平大量下降,促进了自噬细胞的死亡[34,37-38]。其中,LC3 与溶酶体相关膜蛋白阳性细胞器上的自噬受体相互作用,进一步导致 TMC 功能障碍[39]。此外,纤维骨架蛋白的变化可能参与了黏附、内吞和自噬的调节[31-32,40-42]。在 Nettesheim 等[43]的研究中表明在应激的 TMC 及其纤维化中自噬和 TGf-β 信号通路存在相互影响。自噬相关基因突变与 OS 诱发的青光眼发病有关。Rezaie 等[44]和 Formstone 等研究发现,细胞中 Optineurin(OPTN)基因的突变是自噬相关突变,可指导泛素化蛋白向自噬体的运输,影响受损线粒体的清除,使自噬过程异常,推测此基因突变可能是引发 POAG 的基因突变之一[45-48]。

4 OS 与 TMC 衰老

OS 作用下 TMC 衰老是重要的病理变化,可导致 TMC 损伤及青光眼发病。细胞衰老(cell ageing)与过度的 OS 关系密切,OS 可能导致 TMC 过早衰老:(1)衰老下调了核编码的氧化磷酸化基因表达,使线粒体功能障碍和 ROS 积累;(2)高水平的 ROS 导致线粒体 DNA 和蛋白质氧化,加剧细胞损伤,诱发细胞衰老[32]。在 TMC 中,增加的 OS 会激活衰老标记物,引起小梁内皮细胞功能障碍。

OS 相关蛋白酶及因子的变化与细胞衰老相互影响[36,49-50]。OS 下调了重组人氧化还原蛋白过氧化物酶 6(peroxiredoxin6,Prdx6)水平促使细胞衰老,而衰老的 TMC 中低表达的 Prdx6 进一步增强了 TMC 对氧化损伤的敏感性[51-52]。OS 的 TMC 可能伴有卷曲相关蛋白 1(secreted frizzled-related protein,SFRP1)的高表达,诱导了细胞的衰老和纤维化,而细胞衰老和诱发的 SFRP1 表达又可诱导邻近细胞进一步衰老和纤维化,增强和扩散衰老表型,并可能最终导致高眼压和青光眼发生[53]。一些 miRNA 异常表达可能导致青光眼房水流出途径的功能异常[54-56]。miR-183 在应激诱导的衰老人小梁网(HTM)细胞中表达上调,可能影响与 HTM 细胞中细胞周期和 DNA 修复相关的多个基因的表达,通过抑制细胞周期进程而加快细胞衰老[57]。

5 OS 与 TMC 炎症

之前的研究结果揭示了 OS 诱导的病理变化包括细胞死亡、细胞内 ROS 的产生、促炎因子的产生等,与青光眼的发生密切相关[58]。ROS 可通过细胞内信号级联激活促炎基因的表达[59],诱导 TMC 炎症,并最终导致青光眼的发生。

青光眼 TM 的炎症反应可能是由 OS 引发的。与正常 TMC 相比,在人青光眼 TMC 中,OS 保护性 Nrf2 信号通路下调[60],而氧化还原反应因子 NF-κB 和丝裂原活化蛋白激酶(MAPKs)被上调,导致炎症因子转录,这可能导致 TM 的收缩功能障碍[61]。此外研究证明,当原代培养的 TMC 暴露于慢性 OS 时,持续激活的 NF-κB 通路会产生炎症标志物,包括 IL-1α、IL-6、IL-8、ELAM-1[58,62],这些炎症应激标志物与青光眼发病相关[63]。

6 总结与展望

OS 是多种疾病的发病原因,OS 造成内皮细胞受损,

是导致心血管疾病发病的重要原因,亦可诱导肿瘤细胞凋亡,减少肿瘤细胞生长,而OS导致的TM损伤是青光眼发病的主要原因之一[64-68]。

目前对OS造成的一系列损伤主要通过抗氧化治疗为主,一般措施包括应用抗氧化剂,如补充大麻二酚等酚类物质[69-71],适量的运动,合适的饮食和制定个性化的生活方式等途径。可导致神经兴奋的物质在OS时分泌增多会造成TMC的损伤,这表明未来可能选择谷氨酸兴奋毒性抑制剂、一氧化氮合酶抑制剂、血流量增强剂、钙/钠通道阻滞剂、血管强张剂等对青光眼进行治疗[72-74]。已知自噬有助于维持细胞稳态,是参与生物体适应急性应激条件并修复应激诱导的损伤的重要机制,可保护细胞免受OS损伤[75-76]。未来治疗中,促进细胞自噬和预防及减慢衰老,是保护TMC免受OS损伤的重要方式[77-78]。近年来,一些通过促进自噬途径治疗和改善不同眼部病理过程的药物的疗效已得到证实。这些药物包括雷帕霉素(RAP)、AMPK激活剂、蛋白酶体抑制剂(MG-132)、氯喹和羟氯喹等,虽然这些药物或许可以有效地保护细胞,但这些药物因为作用机制及参与途径复杂,仍可能存在特异性低及产生不良反应[79]。此外,近年来发现,与OS密切相关的HIC-5基因,对于NADPH氧化酶表达和ROS生成至关重要,生成的ROS又可刺激HIC-5表达,这一过程在与癌症相关的成纤维细胞中与ECM沉积有关,并伴有自噬的激活[80-81],p16Ink4a在与年龄相关的细胞衰老中起重要作用[68],研究OS的TM衰老细胞中P16与HIC-5的相关作用,对减慢衰老进程,保护细胞功能有重要作用。另外,TMC来源于眼周间充质,由神经嵴细胞和颅旁轴中胚层的细胞组成,干细胞可修复损伤的TMC,清除房水中可阻塞房水流出的物质或碎屑,也可以保护细胞免受内质网应激损伤[29,82],在其他疾病中证明,干细胞移植可能会防止OS诱导的炎症反应和纤维化反应[83],并发性诱导多能干细胞衍生的TMC(iPSC-TM)移植入前房可以恢复房水流出,并恢复老年患者内源性TMC的增殖能力[84],这表明小梁网干细胞治疗可能是重塑TM的一种可行方法,预计可能成为青光眼的新型治疗手段。

综上所述,在OS所致的青光眼发病中,TMC结构功能损伤,造成TM组织对房水外流的调节功能受损、细胞ECM成分改变、细胞自噬激活、细胞衰老过程加剧及诱发细胞炎症。如何发现新的安全性更高的作用途径,如何有效及安全地应用现有研究发现的药物,如何发现新的治疗方式,抑制OS,保护TMC,以期延缓及/或减少青光眼的发生发展,仍有许多研究工作要做。

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