·文献综述·

内质网应激在视网膜色素变性中的作用

欧 晨[1,2],谢 薇[2],彭清华[1,2]

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作者单位:[1](410007)中国湖南省长沙市,湖南中医药大学第一附属医院眼科;[2](410208)中国湖南省长沙市,湖南中医药大学中医学院

作者简介:欧晨,博士,主治医师,研究方向:眼底疾病。

通讯作者:彭清华,博士,教授,主任医师,研究方向:眼底病、青光眼、眼表疾病. pengqinghua@hnucm.edu.cn

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摘要

视网膜色素变性(RP)是以光感受器及色素上皮功能丧失为特征的退行性致盲疾病。内质网应激的激活是细胞的防御调节机制,旨在通过一系列分子信号通路进行自我调节以恢复内质网功能的稳定。视紫红质突变是 RP 的常见病因,内质网内视紫红质错误折叠和滞留,内质网应激诱发感光细胞和视网膜色素上皮细胞凋亡,均可导致 RP 的发生和发展。文章论述了内质网应激与其在 RP 发病机制中的作用,并对内质网应激抑制剂、中药和化学药物调控内质网应激在 RP 治疗中的作用进行总结,以期为内质网应激在 RP 的临床应用中提供理论依据,为 RP 的研究、预防和治疗提供新的思路。

关键词:内质网应激;视网膜色素变性;视网膜色素上皮细胞;感光细胞;视紫红质

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Role of endoplasmic reticulum stress in retinitis pigmentosa

Ou Chen[1,2], Xie Wei[2], Peng Qinghua[1,2]

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[1]Department of Ophthalmology, the First Hospital of Hunan University of Chinese Medicine, Changsha 410007, Hunan Province, China; [2]School of Traditional Chinese Medicine, Hunan University of Chinese Medicine, Changsha 410208, Hunan Province, China

Correspondence to: Peng Qinghua. Department of Ophthalmology, the First Hospital of Hunan University of Chinese Medicine, Changsha 410007, Hunan Province, China; School of Traditional Chinese Medicine, Hunan University of Chinese Medicine, Changsha 410208, Hunan Province, China. pengqinghua@hnucm.edu.cn

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Abstract

• Retinitis pigmentosa (RP) is a degenerative blinding disease characterized by the loss of the function of photoreceptor and retinal pigment epithelium. The activation of endoplasmic reticulum stress is a cellular defense regulatory mechanism, aimed at restoring the stability of endoplasmic reticulum function by self-regulation through a series of molecular signaling pathways. Rhodopsin mutation is a common cause of RP. Misfolding and retention of rhodopsin in endoplasmic reticulum and apoptosis of photoreceptor cells and retinal pigment epithelial cells induced by endoplasmic reticulum stress can lead to the occurrence and development of RP. This paper discusses endoplasmic reticulum stress and its role in the pathogenesis of RP and the role of endoplasmic reticulum stress inhibitors, traditional Chinese medicine and chemical drugs in regulating endoplasmic reticulum stress in RP treatment was summarized, in order to provide theoretical basis for endoplasmic reticulum stress in the clinical application of RP and provide new ideas for the research, prevention and treatment of RP.

• KEYWORDS: endoplasmic reticulum stress; retinitis pigmentosa; retinal pigment epithelium; photoreceptor cell; rhodopsin

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0 引言

视网膜色素变性(retinitis pigmentosa,RP)属于遗传眼病,是以光感受器细胞及色素上皮功能丧失为特征的退行性疾病,全球发病率为 1:4000[1]。RP 遗传方式主要为常染色体显性遗传、常染色体隐性遗传、X 染色体连锁遗传,其中约 20%为常染色体显性遗传[2]。RP 的一个常见病因是视紫红质的突变,特别是视紫红质 P23H 突变,会影响视紫红质的正常功能,进而引起视网膜变性[3]。临床上的常见表现有夜盲、进行性视野缩小、眼底骨细胞样色素沉着、视网膜血管变细、视盘蜡黄[4]。目前 RP 的治疗效果仍不能令人满意,探索其发病机制及治疗手段是急需解决的问题。内质网应激是一种保护性应激反应,当内质网腔内未折叠蛋白或错误折叠蛋白大量聚集时会激活促凋亡信号,造成病理性损伤[5]。大量研究证实内质网应激诱导的细胞凋亡与 RP 的发病机制密切相关[6-8]。正确的认

识内质网应激与 RP 的关系,有助于 RP 的临床诊疗取得新进展。本文就内质网应激及其在 RP 发病机制中的作用、调控内质网应激在 RP 治疗中的潜力展开论述。

1 内质网应激

内质网是一种细胞内细胞器,由一层单位膜形成囊状、泡状和管状结构,并组合成一个连续的网膜系统,负责蛋白质合成、加工、运输和维持细胞内钙稳态[9]。多种因素如缺氧、营养缺乏、温度或 PH 变化、有毒物质污染、病毒或细菌感染、钙稳态失调等可能扰乱内质网的正常功能,引起内质网应激[10]。内质网应激的激活是细胞的防御调节机制,旨在通过一系列分子信号通路进行自我调节以恢复内质网功能的稳定。适度的内质网应激有助于机体抵御外来刺激、恢复细胞内稳态;而持续性的、强烈的内质网应激反而会导致内质网功能失代偿,启动相关细胞凋亡程序[11]。内质网应激信号主要由 3 类跨膜蛋白启动,即蛋白激酶样内质网激酶(protein kinase RNA-like ER kinase,PERK)、1 型内质网转膜蛋白激酶(inositol-requiring enzyme 1,IRE1)和活化转录因子 6(activating transcription factor 6,ATF6)[12]。正常生理状态下,3 类跨膜蛋白与内稳态感受器葡萄糖调节蛋白 78(glucose regulatory protein 78 kDa,GRP78 /BiP)处于结合状态,下游相关信号通路失活。内质网应激发生后,GRP78 /BiP 与跨膜蛋白 PERK、IRE1、ATF6 发生解离,同时与未折叠蛋白结合,导致下游相关信号通路激活[13]。

PERK 和 IRE1 都属于Ⅰ类跨膜蛋白。PERK 通过同源二聚化而磷酸化激活自身,随后在 Ser51 位点激活翻译起始因子 2 的 α 亚单位(eukaryotic translation initiation factor 2α,eIF2α)磷酸化,阻止新合成的蛋白进入处于应激状态的内质网中[14]。磷酸化的 eIF2α 选择性增强活化转录因子 4(activating transcription factor 4,ATF4)mRNA 的翻译,上调 C/EBP 同源蛋白(C/EBP-homologous protein,CHOP)的表达[15]。CHOP 通过调控线粒体途径和死亡受体途径两大经典方式激活 Caspase3 执行细胞凋亡。IRE1 有两种亚型,IRE1α 广泛分布于哺乳动物细胞中,IRE1β 仅在肠上皮细胞中表达。IRE1 一方面可激活凋亡信号调节激酶 1(apoptosis signal-regulating kinase 1,ASK1)/c-Jun 氨基末端激酶(c-Jun N-terminal kinase,JNK)信号通路,另一方面参与肿瘤坏死相关因子 2(TNF receptor-associated factor2,TRAF2)/ASK1 介导的募集,激活 p38MAPK 使其磷酸化,从而促进 CHOP 的表达[16]。IRE1 的另一个重要靶点是 mRNA 编码的 XBP1。IRE1 发生二聚体化和自身磷酸化,从而激活其对 XBP1 前体 mRNA 的核酸内切酶剪切活性,活化后的 XBP1mRNA 能够编码形成 XBP1 蛋白[17-18]。与前两类跨膜蛋白不同,ATF6 属于Ⅱ类跨膜蛋白,激活发生在高尔基体。ATF6 被高尔基体的 S1P、S2P 蛋白酶剪接为成分子量为 50kDa 的 PSOATF6,调控促凋亡蛋白 CHOP 使得含半胱氨酸的天冬氨酸蛋白水解酶(cysteinyl aspartate specific proteinase-12,caspase-12)发生活化,促进细胞凋亡的发生[19]。

2 内质网应激在 RP 发病机制中的作用

视紫红质突变是 RP 的常见病因,内质网内视紫红质错误折叠和滞留可导致 RP 的发生发展[20]。视网膜是高耗氧组织,RP 视网膜光感受器及色素上皮结构和功能的变化,可能导致视网膜对氧气的利用存在障碍[21-22]。此外 RP 患者视网膜血管变细,可能会影响视网膜的血液循环,减少视网膜的氧气供应,进一步加剧缺氧的情况[23]。而缺氧是引起内质网应激的关键因素,内质网应激可诱发感光细胞和视网膜色素上皮细胞凋亡,进而引起 RP,说明内质网应激可能在 RP 的发病机制中发挥着重要作用。

2.1 视紫红质 视紫红质是光感受器视杆细胞上最丰富的蛋白质,由视黄醛和视蛋白结合而成,每天在每个光感受器中可合成 10^7个。在 RP 患者中发现了近 200 种不同的视紫红质突变,这些突变许多会引起错误的变化,导致在内质网中错误折叠[24]。P23H 作为第一个被发现的视紫红质突变,是视紫红质基因第 1 外显子内的第 23 密码子有 C→A 的点突变,导致编码的脯氨酸转换成组氨酸[25]。Li 等[26]对 P23H 敲入小鼠进行 RNA 测序,发现了内质网应激相关的差异表达基因簇,提示内质网应激可能在 RP 进展中发挥重要作用。Chiang 等[27]通过检测 P23H 视紫红质敲入小鼠,发现在错误折叠视紫红质表达的光感受器中 IRE1 信号通路被明显激活,引起大量 P23H 视紫红质降解。而在感光细胞凋亡之前,视紫红质蛋白即发生丢失,揭示了内质网应激在光感受器中的早期病理生理作用是对错误折叠视紫红质蛋白的消除。Qiu 等[28]证实 P23H 小鼠视网膜感光细胞的退化是由于内质网应激诱导自噬激活导致了继发性蛋白酶体不足和细胞凋亡。而内质网应激相关通路蛋白的激活对于光感受器中错误表达视紫红质蛋白的清除是必需的,ATF6 的缺失最终会加速 P23H 小鼠的视网膜色素变性[29]。IRE1 的缺失会损害内质网的稳态,也会导致成人眼睛色素沉着的改变[30]。P23H 显性突变引起的退化还与细胞内钙离子的增加和钙蛋白酶的激活有关,钙离子的代谢失衡可引发内质网应激反应[31]。除了 P23H,视紫红质还有许多其他的基因突变与内质网应激相关。Yu 等[32]发现 R135W 视紫红质在内质网中积累,并诱导未折叠蛋白反应和细胞凋亡。此外,伴侣蛋白 HSP70 通过减轻内质网应激,阻止 R135W 视紫红质诱导的细胞凋亡。T17M 视紫红质能诱导细胞内质网应激,使内质网应激蛋白 BiP、GRP94、CHOP、eIF2α、ATF6 表达上调。化学分子伴侣苯基丁酸能缓解 T17M 诱导的内质网应激,视紫红质 T17M 突变增加细胞对内质网应激诱导剂衣霉素的敏感性[33-34]。

2.2 视网膜色素上皮细胞 视网膜色素上皮细胞是位于光感受器和 Bruch 膜-脉络膜复合体之间富含色素的单层上皮细胞,其主要作用是可通过自噬及溶酶体相关途径逐步降解被吞噬的膜盘,同时分泌多种免疫抑制因子和生长因子,发挥血-视网膜屏障作用,以保持细胞内环境稳定[35]。若视网膜色素上皮细胞功能异常,其处理代谢产物的能力下降,大量有害物质堆积,造成视功能障碍。衣霉素是诱导内质网应激的常用化合物,可引起细胞内质网中未折叠蛋白的积累并诱导内质网应激,导致 DNA 合成受阻和 G1 期细胞周期停滞。衣霉素处理人视网膜色素上皮细胞(ARPE-19 细胞)后 GRP78、caspase-3、caspase-12 表达水平显著升高[36]。全反式视黄酸可诱导 ARPE-19细胞产生内质网应激反应,其对 BiP、PERK、ATF6、ATF4、EIF2α、XBP1、CHOP 的表达均产生影响[37-38]。Earle's 平衡盐溶液通过饥饿诱导 ARPE-19 细胞的内质网应激,上调钙稳态相关蛋白 calpain-1 和 calpain-2[6]。内质网应激还参与氧化低密度脂蛋白诱导的 ARPE-19 细胞凋亡,调控内质网应激能抑制其细胞的凋亡[39]。ARPE-19 细胞在低氧条件下培养,内质网应激

指标和细胞内 Ca^{2+}表达水平升高[40-41]。Song 等[42]则证实了无论抑制氧化应激还是内质网应激都对光损伤造成的 ARPE-19 细胞损伤具有保护作用,提示光诱导的氧化应激可能引发 ARPE-19 细胞内质网应激的后续激活。N-亚视黄基-N-视黄基乙醇胺联合蓝光损伤视网膜色素上皮细胞,CHOP 和 Caspase-12 蛋白表达明显升高[43]。2 000 lx左右的光照可诱导 ARPE-19 细胞的内质网应激反应,导致细胞凋亡及炎症反应,而内质网应激抑制剂可降低细胞的凋亡率[44]。内质网对细胞毒性损伤非常敏感,毒性物质如银纳米颗粒可激活内质网应激反应,通过 IRE1/ASK1/JNK/Mcl-1 途径造成视网膜色素上皮细胞凋亡[45]。同样,镉的过度积累导致细胞活力丧失,内质网应激被激活,其标志物 BiP 显著上调[46]。

2.3 感光细胞 感光细胞位于视网膜的外核层,人的视网膜感光细胞由视杆细胞和视锥细胞组成。视杆细胞是感受弱光刺激的细胞,对光线的强弱反应非常敏感,视锥细胞则主要集中在后极部黄斑区,对强光和颜色具有高度的分辨能力[47]。光损伤条件下小鼠视网膜感光细胞(661W 细胞)中 PERK、IRE1、eIF2α、ATF6、ATF4 和 CHOP 的水平显著升高,并于光照的第 3 d 达到高峰。内质网应激抑制剂处理细胞可显著降低凋亡率,抑制光损伤时内质网应激相关蛋白的表达[42]。蓝色发光二极管蓝光照射促进 BiP、GRP94、ATF4mRNA 的表达,泛素化蛋白水平升高。主要可能是蓝光使 s-视蛋白聚集导致内质网应激,ATF4 的激活尤其明显[48]。Wang 等[49]向玻璃体腔内注射衣霉素诱导感光细胞内质网应激,促进其凋亡,光感受器层中 TUNEL 阳性细胞大部分同时呈 CHOP 阳性。二甲胺四环素激活了内质网应激相关 PERK/eIF2α/CHOP 信号通路,引起感光细胞凋亡[50]。Fresia 等[51]在不同葡萄糖条件下培养 661W 感光细胞,并在 mRNA 和蛋白水平上分析内质网应激标记物,发现低血糖条件下 661W 细胞的细胞生长速度低于对照细胞,细胞周期的 G2/M 期更长,细胞线粒体膜电位降低,触发内质网应激反应,促进细胞凋亡[52]。

目前已报道的内质网应激与视紫红质、视网膜色素上皮细胞和感光细胞的研究大都与细胞凋亡有关,涉及的主要分子包括 GRP78、BiP、PERK、ATF6、ATF4、EIF2α、XBP1、IRE1 和 CHOP。内质网应激抑制剂、中草药提取物、及一些化合物通过抑制内质网应激治疗 RP 已成为研究热点,内质网应激新靶点的不断确定,为 RP 治疗的有效药物的研发带来了希望。

3 调控内质网应激在 RP 治疗中的潜力

3.1 内质网应激抑制剂 4-苯基丁酸(4-phenylbutyricacid,4-PBA)是一种可以稳定蛋白质构象,提高内质网折叠能力,抑制内质网应激的小分子脂肪酸[53]。在疾病内质网应激的研究中,4-PBA 常作为阳性对照作用于内质网应激模型[54-55]。4-PBA 可抑制光诱导后视网膜的内质网应激,减少光感受器细胞凋亡,保护视觉功能,下调 BiP 和 CHOP 蛋白的表达[56]。牛磺熊去氧胆酸(tauroursodeoxycholic acid,TUDCA)由熊去氧胆酸的羧基与牛磺酸的氨基之间缩水而成的结合型胆汁酸,可显著降低凋亡分子如 Caspase-3 和 Caspase-12 的表达。其已被证明在体外和体内视网膜变性模型中具有保护作用,通过降低 CHOP 的表达来抑制细胞的内质网应激反应[7]。Salubrinal 是有效的选择性 eIF2α 磷酸化抑制剂,通过抑制 eIF2α 磷酸化阻断 PERK 通路的内质网应激途径,明显抑制 ARPE-19 和 661W 细胞诱导内质网应激的作用[37,46]。GSK2606414 是一种新型的、高度选择性的 PERK 抑制剂,已证实可以预防神经退行性病变。GSK2606414 处理后抑制了内质网应激下 ARPE-19 细胞 eIF2α 磷酸化,降低了 CHOP 和 VEGFmRNA 和蛋白的表达水平[57]。

3.2 中药 芍药苷来源于中药赤芍、白芍等芍药属植物的根,是一种蒎烷单萜苦味甙。研究表明,芍药苷具有清热、抗炎、解痉、保护神经、保护大脑、清除体内自由基、免疫调节等多种药理学作用[58]。Zhu 等[59]发现芍药苷可通过 GRP78/PERK/eIF2α/ATF4/CHOP 调节细胞的内质网应激,可以显著性的逆转全反式视黄酸对细胞的毒性作用。川芎嗪是从伞形科藁本属植物川芎中提取的生物碱,对神经功能损伤具有保护作用[60]。川芎嗪通过减轻内质网应激提高光感受器的功能,主要与 ATF4 介导的通路有关[52]。欧洲越橘属于杜鹃花科越桔亚科植物,富含花色苷类化合物,具有抗氧化、抗癌、改善视力疲劳、缓解视网膜病变等方面的效果[61]。越桔提取物可以减少光诱导的光感受器细胞凋亡和缩短视椎视杆细胞外节。视网膜电图结果显示其视功能提高,其机制主要通过抑制 s-视蛋白的聚集、ATF4 的激活以及内质网应激相关因子的表达[62-63]。葡萄籽提取物是从葡萄籽中提取分离得到的一类多酚类物质,广泛存在于植物性食物中,主要由原花青素、儿茶素、没食子酸、表儿茶素、表儿茶素没食子酸酯等多酚类物质组成。葡萄籽提取物是一种高效的抗氧化剂,可以通过多种分子机制表现出抗氧化应激、抗炎、抗凋亡等生理功能[64]。Chu 等[63]证实葡萄籽提取物影响 ARPE-19细胞内质网应激标志物的蛋白表达水平,补充其主要成分原花青素减少细胞凋亡,抑制 elF2 和 IRE1 的磷酸化,降低 CHOP 的表达[65]。我们团队多年来一直运用枸杞子丹参治疗 RP,疗效较为显著。研究发现枸杞子丹参通过减轻视网膜色素上皮细胞内质网应激反应,从而改善视功能[66]。

3.3 其他 叶黄素是存在于人眼视网膜黄斑区的主要色素,具有保护视力的作用,可用于延缓 RP 的发病进展[67]。Yu 等[68]使用叶黄素干预光感受器受损的小鼠模型,结果显示 ERG 波幅明显升高,TUNEL 阳性细胞数量明显减少,通过调控 GRP78、PERK、ATF4、ATF6 下调内质网应激反应。萝卜硫素是一种异硫氰酸盐,由硫代葡萄糖苷经植物体内黑芥子酶水解所得,具有很强的抗氧化和抗癌能力。萝卜硫素可减少光感受器凋亡,升高 ERG 中 a 波、b 波振幅,降低 GRP78/BiP 的表达,从而改善视功能[69]。Humanin 是三种线粒体衍生肽之一,参与细胞抗凋亡、抗氧化过程[70]。线粒体和内质网在解剖学上相互接近,分别是氧化应激和内质网应激的主要作用场所,Humanin 通过氧化应激和内质网应激相关途径保护视网膜色素上皮细胞[71]。

4 总结

近年来,内质网应激的研究在 RP 中取得了突破。内质网应激与视紫红质蛋白关系密切,多种诱发因素如光照、毒性物质、细菌病毒等均可导致视网膜色素上皮和感光细胞发生过度的内质网应激,通过 PERK、IRE1、eIF2α、ATF6、ATF4 及 CHOP 等信号通路促进细胞凋亡。内质网应激抑制剂 4-PBA、TUDCA、Salubrinal、GSK2606414 可显著抑制 RP 发病进展,中药相关芍药苷、川芎嗪、越桔提取

物、葡萄籽提取物、枸杞子和丹参等可通过抑制内质网应激发挥对 RP 的保护作用。内质网应激在 RP 的发展过程中发挥了重要作用,但其疾病发展机制与内质网应激之间的分子机制仍不清晰,治疗和预后不明确。研究其作用机制不仅有助于加强对 RP 疾病机理的了解,还能为新药的研发提供依据。随着人们对内质网应激与 RP 相关认识地加深,未来针对内质网应激靶向调控可能会成为 RP 的重要治疗手段之一。

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