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高度近视并发白内障相关机制研究进展

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摘　要

高度近视早期容易并发核性白内障并且病情发展较快，引起视力不同程度的下降，影响日常工作和生活，但是此病具体发生机制目前尚不清楚，因此本文在氧化应激损伤；蛋白组学；基因组学；内质网应激；房水中细胞因子、补体因子和蛋白浓度改变；房水和玻璃体中炎性细胞因子表达这几个方面进行阐述，对于了解其发生发展有重要意义。

关键词

高度近视并发白内障，发病机制

Research Progress on the Related Mechanism of High Myopia with Cataract

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Abstract

High myopia is easy to be complicated by nuclear cataract in the early stage and the disease develops rapidly, causing different degrees of vision decline in patients, affecting daily work and life. Therefore, this review focuses on oxidative stress injury; proteomics; genomics; endoplasmic reticulum stress; changes in the concentrations of cytokines, complement factors and proteins in the aqueous humor; and the expression of inflammatory cytokines in aqueous humor and vitreous, which are of great significance for understanding its occurrence and development.

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Keywords

High Myopia with Cataract, Pathogenesis

1. 引言

高度近视是指眼球屈光度大于−6.0D 或者眼轴长度大于 26 mm，是一种几乎对整个眼球的前节到后节都有影响的疾病[1]，是全球范围内导致失明的主要原因。亚洲人群中高度近视的患病率(6.8%~21.6%)，远高于其他人群(2.0%~2.3%) [2]。研究发现高度近视患者容易并发晶体疾病，导致晶体透明性下降[3]。高度近视患者比正常人更容易快速进展为核性白内障[4]，随着高度近视发病率的增加，高度近视白内障(HMC)的发病率也随之增加[5]。因此了解 HMC 可能的眼部特征和发病机制尤为重要。

2. HMC 眼部特征

HMC 患者通常视力较差，一方面由于晶体透明性下降引起，由于其早期易并发核性白内障，且病情进展快，对视力影响较大[4]；另一方面主要是由于高度近视容易引起眼底并发症造成的视力损害，如合并黄斑裂孔、黄斑劈裂、黄斑部出血、脉络膜新生血管、漆裂纹破裂、脉络膜视网膜萎缩、后巩膜葡萄肿和视网膜脱离等因素[6] [7] [8] [9]。

3. HMC 潜在发病机制研究

3.1. 氧化应激损伤

晶体具有低氧、还原性谷胱甘肽(GSH)和抗坏血酸水平通常很高以及含有密集但是排列有序的长寿蛋白，这些使晶体保持一定的透明性，而晶体蛋白的氧化损伤是白内障形成的重要机制[10]。研究发现[11]，白内障患者晶体中 GSH 和超氧化物歧化酶水平较低而氧化型谷胱甘肽(GSSG)水平较高，氧化作用在近视并发性白内障中更明显。白内障合并严重近视的患者晶体中丙二醛水平(MDA)升高，明显高于年龄相关性白内障中的水平，提示脂质过氧化可能参与 HMC 的发展[11] [12]，说明高度近视的眼睛抗氧化能力弱，容易受到氧化损伤[13]。

有学说认为，随着眼轴的增长，玻璃体腔被拉长，代谢物或者营养物质向晶体后方扩散减少，会导致局部抗氧化作用减弱，导致晶体代谢障碍，造成白内障发生[14]。有研究报道[15]，行高压氧治疗的患者，更容易发生核性白内障。完整的玻璃体，将晶体后表面与其他结构分割开，并给晶体提供一个低氧的环境[16]。另有研究发现，玻璃体切除术中以及术后较长时间，氧分压会增加，使晶体暴露在高氧环境中，可能导致核性白内障的发生[17] [18]。高度近视患者玻璃体液化发生率较高，使晶体长期暴露在高氧环境中，氧化应激会导致晶体上皮细胞受损，而晶体上皮细胞是晶体正常代谢的中心，进而导致晶体混浊，发生白内障[13] [19]。

高度近视患者血清中氨基丙二酸和棕榈油酸浓度升高，提示体内的氧化应激增加，既往研究证明氧化应激在近视进展中起作用，氧化损伤过程中自由基超氧化物的产生等会对晶状体等产生损害，进而发生白内障[19] [20]，这可能是 HMC 的发病机制之一。

3.2. 蛋白组学

晶状体蛋白(α-crystallin)是人类晶体中最丰富的结构蛋白，它包含两种亚型，分别为αA-晶体蛋白、αB-晶体蛋白[21]，αA-crystallin 不光是结构蛋白同时也是一种分子伴侣，防止晶体氧化损伤，在维持晶状体透明度方面起着关键作用，αA-晶体蛋白与晶体的纤维细胞质膜相联系会导致晶体混浊，引起白内障的发生[22]。在 HMC 患者晶体 αA-晶体蛋白 CRYAA 基因的启动子 CpG 岛被高度甲基化，因此 αA-晶体蛋白的表达下调，导致晶体透明性的改变[1] [13] [23]。

有研究发现高度近视患者房水中发现 87 种蛋白质表达下调，其中包括 6 种晶体蛋白(β-晶体蛋白 S、β-晶体蛋白 B2、γ-晶体蛋白 C、γ-晶体蛋白 D、β-晶体蛋白 B1 和 β-晶体蛋白 A3) [24]，它们对维持晶体的透明度以及参与白内障的形成起重要作用[25] [26]。因此，其表达下调，可能是 HMC 的发病机制之一。

3.3. 基因组学

HMC 相关的抗氧化应激因子还包括谷胱甘肽 S-转移酶 p1 (GSTP1)、核因子、红系样蛋白 2 (NRF2)、8-氧化鸟嘌呤 DNA 糖基化酶(OGG1)、硫氧还蛋白(TXN)、硫氧还蛋白还原酶 1 (TXNED1)和硫氧还蛋白还原酶 2 (TXNRD2)六种[13] [27] [28] [29] [30] [31]，GSTP1 和 TXNRD2 在 HMC 中的表达下调比在年龄相关性白内障(ARC)中明显，Zhu 等人[13]发现 HMC 人群的平均年龄低于 ARC，HMC 患者核颜色分级显著高于 ARC，说明 HMC 患者发生晶体混浊更早以及程度更严重，这可能与 GSTP1 启动子的高甲基化和 TXNRD2 甲基化参与了 HMC 的形成有关[31]。

既往研究证明 HMC 患者的晶状体上皮细胞凋亡与普通 ARC 患者的晶状体上皮细胞凋亡有很大不同[32]，Tian 等人研究发现高度近视晶体囊膜上基因数据中 KLF6 和 ATF4 两个基因差异表达，推测这两种基因可能在高度近视患者的晶体上皮细胞凋亡中起重要作用，并导致晶体中更多的蛋白损伤和降解，引起晶体透明性下降，最终造成白内障[33]。

LEPREL1 在眼睛发育中起重要作用，研究发现编码脯氨酰 3-羟化酶 2 (P3H2)的 LEPREL1 基因纯合子突变引起的高度近视容易较早并发白内障[34] [35]。P3H2 可以羟化胶原蛋白，这些胶原蛋白广泛表达于小鼠胚胎中含有胶原纤维的组织中，包括眼睛，脯氨酰羟化是 I、II、IV、V 等胶原蛋白的重要翻译后修饰，IV 型胶原存在于各种眼结构中，包括晶状体、虹膜、视网膜、视网膜色素上皮和小梁网，胶原蛋白修饰的破坏也是 HMC 的发病机制之一，但是具体机制还需进一步研究[35] [36] [37]。

3.4. 内质网应激

白内障是由内质网应激引起的晶体上皮细胞凋亡造成的[38]，在缺氧和氧化应激的状态下，由错误折叠的内质网蛋白积累引起的内质网应激称为未折叠蛋白反应(UPR) [39] [40]，大量未折叠蛋白可与免疫球蛋白结合蛋白(BIP)结合，从而激活 PERK/EIF2a/ATF4-ATF3-CHOP 和 ATF6 通路以及 IRE1/XBP1，诱导晶体上皮细胞凋亡[38] [41]，GRP78 也被称为 BIP，是主要的内质网伴侣蛋白，也是 UPR 的主要调节因子，研究发现 HMC 组 GRP78 水平明显上调[41]，说明内质网应激在 HMC 发生过程中起重要作用。

3.5. 房水中细胞因子、补体因子、蛋白浓度改变

高度近视眼随着眼轴增长会造成眼底营养代谢障碍，引起脉络膜视网膜萎缩进而会引起房水中转化生长因子-β-诱导因子(TGIF) [42]和色素上皮衍生因子(PEDF) [43]的表达发生改变，而 PEDF 在透明晶体的形态和功能中起重要作用，Segev 等人[44]发现色素上皮衍生因子表达的大幅下调可能导致白内障的形成。因此，色素上皮衍生因子浓度降低可能在 HMC 的形成中起重要作用。Shin 等人[45]发现高度近视患者房水中 VEGF 与 ARC 患者相比水平降低，以及 VEGF/PEDF 比率显着低于 ARC 组，VEGF 是由分化

的 RPE 细胞分泌，在高度近视患者中 RPE 出现退行性变，导致 VEGF 水平下降[46]，同时 Yuan 等人[47]的研究也发现高度近视患者房水中 VEGF 水平降低。PEDF 是一种内在的抗血管生成因子[48]，其和 VEGF 保持平衡，而研究发现在高度近视患者眼内 VEGF/PEDF 平衡被破坏[45]，这可能是 HMC 发展的一个机制。

近来有学者发现 HMC 患者房水中补体因子 H (CFH)的含量高于低度近视并发白内障和单纯白内障组患者房水中 CFH 含量[49]，既往研究发现 CFH 与 C3b 结合可以加速旁路途径 C3-转化酶(C3b-Bb)的衰退[50]，补体级联的激活产物有助于其他炎症介质的产生，因此可以促进炎症部位的组织损伤，这与 AMD 的发生有密切关系[51] [52]，同时研究发现 CFH 可在晶体中表达[53]，因此从分子学机制探讨 HMC 患者 CFH 含量的高低在疾病的发生发展中是否和 AMD 的发生过程类似，还需要大量实验进一步验证。

Wen 等人[54]对 HM 合并白内障患者使用 iTRAQ 房水蛋白质组学分析发现，与单纯白内障组相比，HMC 组中 PLG (纤溶酶原蛋白)的表达水平显着上调[55]，PLG 可被组织或尿激酶型纤溶酶原激活剂激活为活性纤溶酶，既往研究证实纤溶酶与炎症反应有关，通过 GO 富集分析房水中差异表达蛋白中的 PLG 可能是由于参与涉及补体系统的免疫过程引起的眼损伤[54]。因此，PLG 可能在 HMC 的发生中起重要作用，但是具体机制还需进一步探究。

3.6. 房水和玻璃体中炎性细胞因子表达

高度近视被认为是一种炎症相关性疾病[56]，有研究发现高度近视患者房水中有炎性细胞因子表达[47]。既往研究发现 HMC 与 ARC 患者房水中 IL-1ra 和 MCP-1 的表达有显著差异，与 ARC 患者相比，HMC 患者房水中 IL-1ra 的表达减少，MCP-1 的表达增加，进一步说明 HMC 患者前房存在炎症反应[57]。Zhang 等人[58]在对 HMC 和非近视性白内障患者房水的检测中，发现房水中 MMP-2 (基质金属蛋白酶)因子浓度明显升高。MMP-2 在高度近视眼轴形成过程中起重要作用，可能是通过 IGF-1/STAT3 通路介导的 MMP-2 在巩膜过表达加速近视眼眼轴的延长[59] [60]，同时 Zhang 等人进一步证明高度近视白内障患者房水中 Ang-1 升高，提示其与 HMC 可能有关[58]，但具体机制还需进一步探究。

研究发现高度近视患者房水中 TGF-β2 浓度升高，Zhang 等人[61]研究数据表明，HMC 患者的囊袋皱缩综合征患病率高于 ARC 患者，高度近视是 CCS 的一个危险因素并且发现 TGF-β2 在 CCS 形成中起发挥作用。Zhuang 等人[60]发现高度近视患者玻璃体内 MMP2 水平高于非高度近视者，其与转化生长因子-β2 水平呈显著正相关，表明玻璃体内 MMP2 水平升高可能与转化生长因子-β2 的调节有关，其可能促进 CCS 的发生。炎症因子在 CCS 的形成中起重要作用，提示我们 HMC 患者术后要常规使用抗炎眼药水，减少术后并发症的发生。

4. 总结和展望

本文对高度近视白内障患者的眼部特征以及从氧化应激、内质网应激以及房水中细胞因子以及炎性因子表达等方面对 HMC 可能的发病机制进行综述。由于高度近视白内障发展较快，对视力影响大，因此发现延缓疾病进展的问题丞待解决。随着这些机制的发现，可以为后期干预疾病的进展以及研究治疗疾病的药物提供可能。

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