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• 药学专栏 •

年龄相关性黄斑变性与氧化应激基因关联性研究进展

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文章亮点

1. 关键发现

• 活性氧簇 (reactive oxygen species, ROS) 表达失衡、补体系统过度激活、脂质代谢紊乱以及氧化应激相关基因的多态性会加大年龄相关性黄斑变性 (age-related macular degeneration, AMD) 的发病风险。

2. 已知与发现

• AMD 发病风险与部分氧化应激相关基因多态性呈相关性；基因治疗法克服传统治疗弊端，或将成为未来治疗重要方向。

3. 意义与改变

• 阐述氧化应激相关基因的异常表达与 AMD 产生的关联性，增加基因治疗的可行性，为 AMD 的防治提供新的思路。

[摘　要]　年龄相关性黄斑变性 (age-related macular degeneration, AMD) 是一种与氧化应激及多基因调控异常密切相关的视网膜黄斑区域进行性退化性疾病。由于黄斑区缺乏血管，因此对氧气的高度依赖使其特别容易受到氧化应激的影响。氧化应激反应影响视网膜色素上皮细胞 (retinal pigment epithelium, RPE) 功能，导致 RPE 细胞代谢异常、RPE 细胞凋亡与损伤；影响脉络膜血管功能，表现为新生血管异常和血管内皮细胞功能障碍；过度激活补体系统，使炎症细胞浸润与炎症因子释放引发炎症；这三者构成了 AMD 的发病机制之一。文章列举了抗氧化酶基因家族 (超氧化物歧化酶、过氧化氢酶、谷胱甘肽过氧化物酶)、炎症相关基因 (补体系统相关基因和细胞因子相关基因) 和其他相关基因 (血管内皮生长因子、血红素加氧酶-1、载脂蛋白 E、铁死亡相关基因、年龄相关性黄斑病变易感因子 2 基因) 的异常表达与 AMD 产生的关联性，并阐述了基因编辑技术纠正氧化应激相关基因缺陷和基于氧化应激基因靶点的药物治疗手段，以期为 AMD 的防治提供思路。

[关键词]　年龄相关性黄斑变性；氧化应激；基因；发病机制

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Research advances in the association between age-related macular degeneration and oxidative stress-related genes

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Abstract Age-related macular degeneration (AMD) is a retinal degenerative disease closely associated with oxidative stress and dysregulation of polygenic mechanisms. Due to the absence of blood vessels in the macular region, its high dependence on oxygen renders it particularly susceptible to oxidative stress. Oxidative stress impairs the function of retinal pigment epithelium (RPE) cells, leading to metabolic dysregulation, apoptosis, and cellular damage. It also disrupts choroidal vascular function, characterized by abnormal neovascularization and endothelial dysfunction. Moreover, excessive activation of the complement system promotes inflammatory cell infiltration and the release of pro-inflammatory cytokines. Collectively, these processes constitute one of the key pathogenic mechanisms underlying AMD. This paper highlights the pathogenic associations between AMD progression and dysregulated expression in antioxidant enzyme genes (e.g., superoxide dismutase, catalase, glutathione peroxidase), inflammation-related genes (e.g., complement and cytokine-related genes), and other relevant genes (e.g., vascular endothelial growth factor, heme oxygenase-1, apolipoprotein E, ferroptosis-related genes, age-related maculopathy susceptibility 2 gene). Potential therapeutic strategies, including gene editing to correct oxidative stress-related genetic defects and pharmacological interventions targeting oxidative stress-associated genes, are also elaborated, aiming to provide new insights into AMD prevention and treatment.

Keywords age-related macular degeneration; oxidative stress; gene; pathogenesis

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年龄相关性黄斑变性 (age-related macular degeneration, AMD) 是一种进行性退化性疾病[1]，影响视网膜黄斑区域。干性 AMD 又称非新生血管性 (非渗出性)AMD，以黄斑区地图样萎缩为特点[2-3]。湿性 AMD 又称新生血管性 (渗出性) AMD(neovascular age-related macular degeneration, nAMD)，以脉络膜新生血管 (choroidal neovascularization, CNV) 异常生长为特征。AMD 发病率随年龄增长而上升，发病机制复杂，影响因素包括年龄、性别、缺氧、感染、脂质和脂蛋白沉积等，严重影响老年人的视力及生活质量。

由于黄斑区缺乏血管，因此对氧气的高度依赖使其特别容易受到氧化应激的影响[4-5]。氧化应激是指活性氧簇 (reactive oxygen species, ROS) 的产生与清除处于失衡状态，过量 ROS 在细胞内蓄积会造成氧化损伤[6]。视网膜色素上皮 (retinal pigment epithelium, RPE) 细胞的主要作用为维持视网膜功能稳态，对氧化应激易感[7]。长期氧

化应激导致 RPE 功能损伤和凋亡，脉络膜血管内皮屏障被破坏[8]，激活补体系统并上调白细胞介素-1β(inteleukin-1β, IL-1β)、IL-6 和肿瘤坏死因子-α(tumor necrosis factor-α, TNF-α) 等炎症因子表达[9-10]，引发炎症级联反应，血管生成因子释放增加，最终造成黄斑区脉络膜异常血管新生。探究氧化应激相关基因与 AMD 的关联性有助于理解疾病发生、发展的分子机制。

1 氧化应激基因在 AMD 发病机制中的作用

1.1 对 RPE 细胞的影响

1.1.1 RPE 细胞代谢异常

RPE 细胞是维持视网膜功能稳态的关键细胞[11]。正常情况下，眼部光感受器不断更新外节盘膜，RPE 细胞通过特定的受体和信号通路识别并吞噬脱落的外节盘膜，随后溶酶体等细胞器对其进行降解和代谢[12-13]。

ROS 过量生成不但引发 RPE 细胞上的吞噬受体氧化损伤，吞噬效率降低[14]，而且细胞溶酶体膜完整性被破坏还会引发酶外漏，外节盘膜的降解受阻[15]，同时干扰关键代谢酶和转运蛋白功能[16]，最终未被降解的物质形成脂褐素逐渐堆积[17]。脂褐素在光照中形成更多 ROS，加剧细胞的氧化应激[18]，持续的氧化应激最终导致 RPE 细胞凋亡[19]。

1.1.2 RPE 细胞凋亡与损伤

ROS 在细胞内大量积累导致 DNA 损伤[20]，p53 信号通路被激活后上调促凋亡蛋白 (Bax) 同时下调抗凋亡蛋白 B 淋巴细胞瘤-2 基因 (Bcl-2)，Bax/Bcl-2 比值升高，线粒体膜通透性增加，细胞色素 C 释放到细胞质中，激活半胱天冬酶 (Caspase) 级联反应，导致 RPE 细胞凋亡[21]。

氧化应激基因多态性干扰磷脂酰肌醇 3-激酶 (phosphatidylinositol 3-kinase, PI3K)/蛋白激酶 B (protein kinase B, PKB/AKT) 信号通路[22]。PI3K 基因多态性降低 PI3K 活性，PTEN 基因多态性增强磷酸酶活性，当 AKT 磷酸化水平降低时，糖原合成酶激酶-3β(glycogen synthase kinase-3beta, GSK-3β) 活性增强，促进细胞凋亡[23]。此外，氧化应激基因的多态性还会破坏 RPE 细胞内质网稳态[24]。这一系列的氧化损伤致使 RPE 细胞大量凋亡，削减的 RPE 细胞无法正常维持视网膜功能稳态，提示 RPE 细胞的活性恢复也成为治疗手段之一。

1.2 对脉络膜血管的影响

AMD 中氧化应激基因的应激状态可通过多种机制对血管内皮细胞造成损伤，进而影响视网膜血供[8,25]。

1.2.1 新生血管形成异常

核因子红系 2 型相关因子 2(nuclear factor erythroid 2-related factor 2, Nrf2) 的表达随年龄增长而下降，激活 Nrf2 对修复视网膜有积极作用[26-27]。吴国熙等[28]发现，瑞香素通过激活 Nrf2-Keap1/ARE 级联通路，缓解小鼠视网膜变性以及视网膜色素上皮细胞衰老。吴沛霖等[29]研究发现，表没食子儿茶素没食子酸酯 (epigallocatechin gallate, EGCG) 通过上调 Nrf2 表达，增强机体清除氧自由基的能力，保护视功能。

氧化应激使核因子 κB(nuclear factor kappa-B, NF-κB) 信号通路相关基因异常化。NF-κB 被激活后进入细胞核，促进血管内皮生长因子 (vascular endothelial growth factor, VEGF) 等血管生成因子基因的启动、转录和表达[30]。NF-κB 信号通路的激活还诱导 IL-6、TNF-α 等炎症因子表达并上调 VEGF 表达水平，使脉络膜新生血管形成异常。

1.2.2 血管内皮细胞功能障碍

一氧化氮 (nitric oxide, NO) 是公认的血管内皮素 (endothelin, ET) 松弛剂，改善脉络膜血流量[31]。大量的 ROS 会快速消耗 NO，生成过氧化亚硝酸盐，抑制一氧化氮合酶 (nitricoxidesynthase, NOS) 的活性，减少 NO 合成。此外如 MAPK 信号通路过度激活会间接抑制内皮型一氧化氮合酶 (endothelial nitric oxide synthase, eNOS)，炎症反应释放炎症因子也抑制 eNOS，使 NO 合成减少。Bhutto 等[32]发现，AMD 脉络膜中神经元型一氧化氮合酶 (neuronal nitric oxide synthase, nNOS) 和 eNOS 的降低与血管收缩和血流动力学改变有关[33]。当血浆中内皮素-1(endothelin-1, ET-1) 浓度升高和 NO 水平降低时，血管收缩剂和舒张剂失衡，导致血管内皮细胞功能发生障碍[34]。Alrashdi 等[35]研究发现血浆中内皮素-2(endothelin-2, ET-2) 通过与肾素-血管紧张素-醛固酮系统和 Nox1/4 相互作用，影响内皮素功能。当视网膜的血管舒缩

功能失调时，视网膜缺血、缺氧，最终影响视功能。

1.3　炎症反应介导机制

1.3.1　补体系统过度激活

氧化应激基因多态性会导致补体系统过度激活，引发炎症反应[36]。炎症因子分泌增加时，炎症细胞会产生大量 ROS 和活性氮 (reactive nitrogen species, RNS) 攻击细胞，而补体激活产物使血管内皮收缩，通透性增加，加重炎症和视网膜水肿[9, 37]。两者会加速 AMD 病情进展[38]。

1.3.2　炎症细胞浸润与炎症因子释放

氧化应激基因异常还会使线粒体功能障碍，产生 ROS 和释放线粒体 DNA(mitochondrial DNA, mtDNA)，诱导炎症因子产生[39]。Hu 等[40]发现，人参皂苷 Rg3 可抑制 ROS 介导的线粒体依赖性凋亡并减轻视网膜损伤[37, 40]。

研究发现铁死亡与 AMD 发病密切相关。AMD 患者视网膜内铁离子代谢紊乱导致铁过量堆积，经芬顿反应产生活性氧从而激发铁死亡[41]。Wei 等[42]发现铁死亡抑制剂通过减少谷胱甘肽 (glutathione, GSH) 的消耗来改善 AMD 症状。

2　氧化应激相关基因概述

2.1　抗氧化酶基因

2.1.1　超氧化物歧化酶基因

超氧化物歧化酶 (superoxide dismutase, SOD) 可以把有害的超氧自由基转化为过氧化氢 (H_2O_2)，通过过氧化氢酶 (catalase, CAT) 和过氧化物酶 (peroxidase, POD) 分解为完全无害的水。按所含金属辅基不同可分为 3 种[43]，见表 1。当 SOD 活性降低时，超氧阴离子自由基在视网膜色素上皮细胞和周围组织中积累，以致过氧化和炎症，从而引发 AMD[44]。

表 1　SOD1、SOD2、SOD3 基因结构与功能

Table 1　The structure and function of SOD1, SOD2, and SOD3 genes

类别	SOD1	SOD2	SOD3
基因位置	21 号染色体	6 号染色体	4 号染色体
编码蛋白	含铜(Cu)和锌(Zn)的二聚体蛋白	以锰(Mn)为辅助因子的蛋白	依赖 Cu 和 Zn 的分泌型蛋白
存在形式	二聚体	同源四聚体	同源四聚体
分布位置	细胞质、细胞核及内膜系统	线粒体	细胞外间隙
功能作用	清除细胞内局部超氧阴离子，维持细胞氧化还原稳态	清除线粒体呼吸链产生的超氧阴离子，维持线粒体功能和细胞能量代谢	清除细胞外超氧阴离子自由基，维持细胞外微环境稳态

2.1.2　过氧化氢酶基因

CAT 是维持细胞内氧化还原平衡的关键基因。氧化应激条件下，Nrf2 被激活，与 CAT 启动子区域的抗氧化反应元件 (antioxidant response element, ARE)，促进其转录，过氧化氢酶合成增加[45]。AMD 患者中，CAT 基因的突变或多态性会降低过氧化氢酶的活性。炎症因子等干扰 CAT 基因的转录，抑制 Nrf2 活性，降低 CAT 表达[46]。在转录后水平，微小RNA(microRNA,miRNA) 如miR-122-5p 可通过与 CAT mRNA 结合,进一步抑制过氧化氢酶的合成[47]。CAT 可在短时间内把 H_2O_2 分解为完全无害的水，保护细胞免受氧化损伤[48]。有研究者发现单核苷酸多态性 (single-nucleotide polymorphism, SNP) 降低 CAT 催化效率，未及时分解的过氧化氢转化为毒性更强的羟自由基 (·OH)，导致 RPE 细胞损伤。

2.1.3 谷胱甘肽过氧化物酶基因家族

谷胱甘肽过氧化物酶 (glutathione peroxidase, GPx) 基因家族广泛分布于胃肠道、细胞外液、内质网中，有效对抗机体氧化[49-50]。GPx 家族中以 GPx1 为代表，作为细胞内最丰富的异构体，清除 H_2O_2 以及脂质过氧化物，维持细胞氧化还原平衡[51]。GPx1 基因的 Pro198Leu(rs1050450)SNP 影响 GPx1 的酶活性[52-53]。Takata 等[54]提出，GPX1 基因变异 rs1987628 与 GPx1 酶活性呈负相关。由此可知，GPx1 基因 SNP 及 GPx 酶活性下降会加剧氧化应激损伤的累积，也是 AMD 的发病机制之一。

2.2 炎症相关基因

2.2.1 补体系统相关基因

补体因子 H(complement factor H, CFH) 通过抑制 C3 转化酶 (C3bBb) 形成和辅助因子 I 裂解 C3b，防止补体过度激活。基因的 Y402H 多态性降低其与 C3b 结合，C3b、炎症介质 C5a 和 ROS 集聚，损伤 RPE 细胞[9]。Kubicka-Trząska 等[55]发现 CFH 基因的 Y402H rs1061170 位点，CC 基因型和 C 等位基因与 AMD 发生相关，而 TT 基因型和 T 等位基因延缓 AMD。C2 是经典激活途径和凝集素激活途径的重要成分。Urban 等[56]发现 C2 基因的 R249C 和 S250C 突变体增强了补体依赖的细胞毒性。C2 基因多态性加速 C3 裂解、增强 C3bBb 稳定性，导致补体级联反应失控[57]，产生大量 C5a 等炎症介质和 ROS [9]。Lu 等[58]也提示 C3 的 rs1047286 多态性与 AMD 呈正相关。这些研究结果表明，补体相关基因的多态性在 AMD 的发病机制中起着关键作用，提示补体调控是靶向治疗 AMD 的重要方向，也为理解 AMD 的遗传易感性提供了分子依据。

2.2.2 细胞因子相关基因

已有研究显示，AMD 与 TNF-α 和 IL-6 高表达有关[59]。TNF-α 高表达诱导 RPE 细胞产生 ROS，激活 NF-κB 信号通路，上调 iNOS，生成 NO[60]。NO 与超氧阴离子生成过氧化亚硝酸盐，加重氧化应激损伤[61]。此外，TNF-α 会释放 IL-1β 和 IL-8 等炎症因子。IL-6 通过激活 NF-κB 通路增强炎症反应而干扰 RPE 细胞正常代谢并促进其凋亡[62-63]。Droho 等[62]证实 IL-6 下降后 CNV 面积减少 42%，外源性 IL-6 直接促进 CNV 生成。其机制为 IL-6 激活 IL-6R$^+$巨噬细胞，诱导 STAT3 磷酸化及下游促血管生成因子 (如 VEGFA、TNF-α) 生成，氧化应激与炎症相互作用，最终导致视网膜组织慢性损伤。

2.3 其他

2.3.1 VEGF 基因

非病理状态下，VEGF 基因维持眼部血管生成和血管稳态[64-65]。氧化应激产生过量 ROS 时，MAPK 和 PKC 信号通路被激活，通过转录因子激活蛋白-1(activating protein-1, AP-1) 增强 VEGF 的转录。同时，激活缺氧诱导因子-1α(hypoxia-inducible factor-1alpha, HIF-1α)，VEGF 高表达，血管内皮细胞增殖。临床显示血管异常生成会导致血管通透性增加，形成湿性 AMD。子区域的 -2578C/A 多态性可增强 VEGF 的转录活性[66]，而 +405G/C 多态性则降低 VEGF 与受体的结合[67]。

2.3.2 HO-1 基因

血红素加氧酶-1 (heme oxygenase-1, HO-1) 可催化血红素分解为胆绿素、一氧化碳 (carbon monoxide, CO) 及亚铁离子 (Fe^{2+})[68]。胆绿素经胆绿素还原酶转化为胆红素后，能清除 ROS 和阻断脂质过氧化反应[69]；CO 抑制炎症因子的产生，增强免疫细胞功能[70-71]；而 Fe^{2+}与铁蛋白螯合可避免氧化损伤[72]。研究发现，短 (GT)n 重复序列基因型具有较高的 HO-1 转录活性，减缓 AMD 病情进展，而长 (GT)n 重复序列基因型则可能降低 HO-1 表达，视网膜细胞更易受到氧化应激和炎症损伤的影响[73]。

2.3.3 APOE 基因

APOE 基因是维护视网膜黄斑区脂质平衡的关键基因。APOE 功能异常时，甘油三酯等脂类物质在视网膜黄斑区正常代谢受阻，沉积后形成玻璃膜疣[74]，产生大量 ROS，并激活 NF-κB 信号通路，诱导炎症因子 TNF-α、IL-1β 及趋化因子 MCP-1 的产生[75-76]。APOE 基因的多态性在 112 和 158 密码子处，形成 ε2、ε3 和 ε4 三种等位基因[77-78]。APOE ε4 等位基因增加 AMD 的发病风险[79]，而 APOE ε2 对脂质代谢的调节相对有利[80]。

2.3.4 铁死亡相关基因

铁死亡相关基因的调控对于 AMD 的防治日益被重视[81]。GPX4 是抑制铁死亡的关键酶，清除脂质过氧化物保护细胞免受氧化损伤[82]。Nrf2

的活性降低会加剧 RPE 细胞的氧化应激和铁死亡。另一方面，酰基辅酶 A 合成酶长链家族成员 4 (Acyl-CoA synthetase long-chain family member 4, ACSL4) 和脂氧合酶 (LOX) 等基因通过促进多不饱和脂肪酸的氧化和脂质过氧化，正向调控铁死亡。通过基因调控抑制铁死亡相关通路 (如上调 GPX4 和 Nrf2，或下调 ACSL4 和 LOX)，也是 AMD 治疗的新途径。

2.3.5　ARMS 2 基因

年龄相关性黄斑病变易感性蛋白 2(age-related maculopathy susceptibility 2, ARMS2) 基因的多态性如 A695 因影响线粒体功能增加 AMD 风险[83-84]。Lu 等[85]发现抑制 HTRA 丝氨酸肽酶 1(htrA serine peptidase 1, HTRA1) 的蛋白水解活性，可保护血-视网膜屏障的蛋白水解不被破坏，所以抗 HTRA1 疗法有望成为抗 VEGF 治疗的补充。

3　基于氧化应激基因的 AMD 治疗策略

3.1　基因编辑

CAT、SOD 直接影响视网膜细胞对氧化损伤的抵御功能[86]。通过基因编辑技术 CRISPR-Cas9 系统精准修复突变位点可恢复其正常功能。运用 CRISPR/Cas9 消除 VEGF-A 基因[87-88]能有效减少 CNV 的生成。上调 HSP 基因的表达可有效缓解视网膜细胞的缺血、缺氧问题[89]，延缓 AMD 的发展进程。

3.2　药物研发新思路

3.2.1　*视网膜细胞靶向药物载体系统*

目前的基因载体包括病毒载体和非病毒载体[90]。Biswal 等[91]构建了一个携带 EPO 基因的 AAV 载体，导入 RPE 特异性缺失 SOD2 的小鼠的视网膜细胞内，延缓由氧化应激引起的 RPE 和视网膜退行性变；同样的，Ildefonso 等[92]在内毒素诱导的葡萄膜炎小鼠模型中，将注射 AAV-sGFP-TatM013 的眼与注射对照 AAV-GFP 的眼相比，玻璃体浸润细胞数量和 IL-1β 浓度显著降低。AAV 搭载基因一方面实现在 RPE 细胞中特异性表达，另一方面避免传统副作用。通过调控转铁蛋白受体、抗氧化防御系统 GPX4 可抑制铁死亡，保护 RPE 细胞免受氧化应激损伤[82, 93]。另一方面，通过优化脂质体、聚合物纳米递送系统提高靶向性也可以减少氧化损伤[94]。

3.2.2　*基于氧化应激基因靶点的药物设计*

抗氧化剂、补体抑制剂、VEGF 拮抗剂分别作用于氧化应激病理过程的不同阶段。蛋白 Deglycase(DJ-1) 是重要内源性抗氧化剂，Wu 等[95]采用 DJ-1saRNAs 修饰四面体框架核酸 (tetrahedral framework nucleic acid, TFNA) 合成新纳米复合物 (TFNAs-DJ-1saRNA)，能有效将 DJ-1saRNAs 转移至靶细胞，在保留线粒体结构和功能的同时抑制细胞凋亡。Avacincaptadpegol 眼内注射液 (商品名：Izervay) 是治疗 AMD 引发的地图样萎缩症 (geographic atrophy, GA) 的 C5 补体蛋白抑制剂。临床试验显示患者注射 Izervay 一年内 GA 增长速度下降 35%[96]。从补体系统的其他靶点来看，除了针对 C3、C5 的补体抑制剂，补体系统中的 D 因子、FB 等靶点也逐渐应用于眼科药物开发。Katschke 等[97]发现一种抗 D 因子 Fab 片段 (afd) 用于抑制晚期干性年龄相关性黄斑变性中的补体旁路途径。此外，一些传统中药提取物可上调 SOD 基因表达增强机体抗氧化能力。但目前相关研究多处于基础实验阶段，需要更多深入研究来验证其安全性和有效性。

4　结语

本研究深入探讨了 AMD 的氧化应激机制及其与多基因调控异常的关联性，并提出了基于氧化应激基因的治疗策略。氧化应激通过打破视网膜色素上皮细胞稳态和引起凋亡，促进炎症反应和新生血管化，推动 AMD 的病理进程。而抗氧化基因、补体基因等的基因多态性则直接或间接增加 AMD 的发病风险。除此之外，炎症因子的表达水平的异常升高也会扩大 CNV 面积。综上所述，氧化应激基因在 AMD 发生发展中的确切机制还需不断探索。

基因治疗克服了传统疗法需频繁注射并易引发眼内炎、高眼压等的弊端，尽管基因治疗优势突出且取得了一定的进展，但如何确保基因载体的安全性和长期有效性，以及如何实现更精准的基因调控等问题还有待解决。未来的研究需要进一步探索新型基因载体和优化基因治疗策略，以推动该领域从基础研究向临床应用转化，从而提高安全性和治疗效果。

声明

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