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线粒体在年龄相关性黄斑变性中的作用和治疗新策略

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摘　要

年龄相关性黄斑变性(AMD)是全球老年人不可逆性视力丧失的主要原因，其发病机制复杂。近年来，越来越多的证据表明，视网膜色素上皮(RPE)细胞的线粒体功能障碍是AMD驱动的核心环节。在衰老和环境因素(如氧化应激)的共同作用下，RPE细胞中线粒体DNA损伤、活性氧(ROS)过量产生、线粒体动力学失衡以及线粒体自噬功能衰退相互交织，形成恶性循环。本综述系统阐述了线粒体在AMD病理进程中的关键作用，关注其作为氧化应激的主要来源、细胞凋亡的启动者以及细胞内稳态调控中心等多重角色，展望了以线粒体为靶点的AMD治疗新策略。

关键词

线粒体，年龄相关性黄斑变性，视网膜色素上皮

The Role of Mitochondria in Age-Related Macular Degeneration and New Therapeutic Strategies

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Abstract

Age-related macular degeneration (AMD) is the leading cause of irreversible vision loss among the elderly worldwide, and its pathogenesis is complex. In recent years, increasing evidence has shown that mitochondrial dysfunction in retinal pigment epithelial (RPE) cells is a central driver of AMD. Under the combined influence of aging and environmental factors such as oxidative stress, mitochondrial DNA damage, excessive production of reactive oxygen species (ROS), imbalance in mitochondrial dynamics, and decline in mitophagy in RPE cells intertwine to form a vicious cycle. This review systematically outlines the key role of mitochondria in the pathological progression of AMD, focusing on their multiple roles as major sources of oxidative stress, initiators of apoptosis, and regulators of cellular homeostasis, and explores novel AMD treatment strategies targeting mitochondria.

Keywords

Mitochondria, Age-Related Macular Degeneration, RPE

1. 引言

年龄相关性黄斑变性(AMD)是通过影响黄斑导致患者中心视力进行性下降的致盲性眼底疾病[1]。预计到 2040 年 AMD 患者人数将接近 2.88 亿，到 2050 年患病率将上升到 15% [2] [3]。早期 AMD 主要特征是视网膜色素上皮(RPE)出现色素变化和/或硬小的玻璃膜疣[4]；晚期 AMD 可表现为“干性”和“湿性”AMD 两种形式。干性 AMD (约占 85%~90%)目前无法治疗，地图样萎缩(GA)是干性 AMD 的晚期阶段，它的特点是 RPE、光感受器和脉络膜毛细血管的永久性丧失，最终导致视力严重下降。湿性 AMD (约占 10%~15%)的特点是血管内皮生长因子(VEGF)表达异常，脉络膜新生血管(CNV)形成，导致视网膜下出血、黄斑水肿和玻璃体内出血[5]。

年龄是 AMD 最主要的危险因素，而吸烟、高体重指数、高血压、高血脂和遗传也是重要的危险因素。AMD 是一种具有复杂病理变化的疾病，包括补体、脂质、血管生成、炎症和细胞外基质通路的失调，RPE 功能障碍在其病理生理学中起着关键作用[4]。光感受器和 RPE 之间代谢的相互作用至关重要，RPE 负责吸收过多的光以减少氧化应激、光感受器外部节段的周转、葡萄糖从脉络膜到光感受器的运输，以及 VEGF 的分泌[6]，而线粒体作为细胞内氧化应激的主要来源和调控中心，其结构完整性和功能稳定性直接影响 RPE 细胞的功能，因此，RPE 中的线粒体损伤是 AMD 变性的诱因。氧化应激和损伤是触发 RPE 变性的关键因素，这主要与线粒体中产生的过量活性氧(ROS)有关，而抗氧化机制可以防止 ROS 诱导的线粒体损伤和细胞死亡，从而增加 RPE 细胞的存活[7]。

鉴于线粒体功能障碍在 AMD 发病机制中的关键推动作用及其在疾病进展中的影响，且目前需要寻找更有效的干预靶点来减少 AMD 的发生及延缓其进展，我们进行了这篇综述，总结线粒体在 AMD 中的作用，讨论线粒体作为预防或治疗 AMD 的治疗靶点。

2. 线粒体与 AMD 病理生理学

2.1. 线粒体结构及特点

线粒体是一种双膜结构(外膜和内膜)的细胞器，它们划分不同的隔室(膜间腔和基质腔)。外膜含有多

种转运蛋白，对通过脂质双分子层的小分子(如氧、钙、糖)具有通透性。内膜富含心磷脂，内膜是电子传递和氧化磷酸化的部位[8]。心磷脂是一种带负电荷的脂质，可驱动带正电荷的分子通过外膜转运，是维持电子传递链(ETC)蛋白功能所必需的[9]。膜间腔是“离子驱动”的部位，氢离子被 ETC 复合体(I、III、IV)从基质中泵出而累积到这个隔室中。以上氢离子通过三磷酸腺苷合成酶回到基质中，产生三磷酸腺苷(ATP)。膜间腔也参与生成启动细胞凋亡的多种蛋白质，如凋亡诱导因子等。这些蛋白质从膜间腔释放到胞浆中，引发一系列事件，最终导致细胞凋亡和死亡[10]。

2.2. 衰老视网膜中的线粒体

线粒体功能障碍与正常衰老以及多种与年龄相关的疾病有关。细胞衰老在发育、组织再生和预防肿瘤增殖的机制中很重要，但衰老细胞的积累是衰老过程的一个驱动因素，它与多种年龄相关疾病的发病机制有关，包括 AMD [11]。许多研究报告了衰老过程中线粒体功能下降，包括氧化能力降低、OXPHOS 减少、ATP 产生减少[12]。在人类老化的视网膜中，RPE、神经节细胞、无长突细胞、水平细胞和视杆细胞都发现了细胞衰老变化：在玻璃膜疣周围可见明显的衰老 RPE 细胞的累积，而淀粉样蛋白(玻璃膜疣的一种成分)可诱导 RPE 衰老[13]。此外，N-视黄氨酸-N-视黄醇胺(A2E)是一种存在于脂褐素中的荧光团(在老化的 RPE 中积累)也可以通过破坏 DNA 和缩短端粒来诱导细胞衰老[14]。细胞衰老的另一个关键因素是衰老相关分泌表型(SASP)，其中衰老细胞释放生长因子、细胞因子、趋化因子、蛋白酶等，诱导炎症和 AMD 的发展[15]。

2.3. 线粒体功能障碍与 AMD

线粒体功能障碍指线粒体在结构与基因的完整性、动力学稳态及质量调控等层面的功能失衡，通过炎症通路过度激活、破坏代谢生态系统稳态、有害蛋白聚集引发毒性反应等机制推动疾病发展。

2.3.1. 炎症通路过度激活

炎症是机体对危害细胞的因素作出的快速反应，如受损的大分子、功能失调的线粒体以及长期的氧化应激[16]。线粒体损伤和 ROS 的产生通过激活 RPE 细胞中的 NOD 样受体热蛋白结构域相关蛋白 3 (NLRP3)信号通路而诱发炎症[17] [18]。由于衰老和 AMD 病理，自噬和抗氧化能力下降，导致受损线粒体的积累及其带来的有害影响，如 ROS 的产生和炎症小体的激活[19]。线粒体自噬是一种特殊形式的选择性自噬，为避免大量 ROS 产生以及进一步线粒体损伤和 ROS 释放的恶性循环，功能失调的线粒体必须通过线粒体自噬从细胞中清除[20]。线粒体裂变和自噬共同维持线粒体的功能，线粒体裂变增加会导致线粒体碎裂，而融合则会导致线粒体延长，线粒体中的任何过程发生异常都可能导致 RPE 变性[21]。具有自噬和线粒体功能障碍的退行性 RPE 细胞是组织中的危险物质，它们可以诱导周围巨噬细胞的炎症小体激活[22] [23]。

研究表明，线粒体结构破坏的增加和线粒体 DNA 修复能力的降低与年龄呈正相关[24]，对 AMD 患者捐献的视网膜组织的研究发现，RPE 细胞中 mtDNA 突变(特别是 4977-bp 常见缺失)的数量显著高于年龄匹配的正常对照组[25]。当线粒体受损时，mtDNA 可被释放到细胞质中。胞质 mtDNA 作为损伤相关分子模式(DAMP)，被模式识别受体(如 cGAS-STING 通路)识别，从而启动炎症反应，促进干扰素和白细胞介素(如 IL-6)等促炎因子的表达，这种由 mtDNA 触发的慢性低度炎症环境，是玻璃膜疣形成的重要推动力，并直接参与脉络膜新生血管(CNV)的病理过程[26] [27]。

2.3.2. 有害蛋白聚集

线粒体功能障碍会直接影响到两个关键的蛋白质质量控制系统的运行：泛素－蛋白酶体系统(UPS)和自噬－溶酶体途径。UPS 负责降解短寿命和错误折叠的蛋白质[28]，而自噬负责清除受损的细胞器和蛋白质聚集体[29]。这两者的清除能力下降导致 SQSTM1/p62 等自噬受体蛋白堆积，后者通过激活炎症小体

(如 NLRP3)诱发视网膜慢性炎症[30] [31]。功能障碍的线粒体产生的过量的 ROS 会直接攻击蛋白质引起蛋白质侧链氧化、碳基化以及主链断裂，导致蛋白质结构破坏、功能丧失并易于形成不可溶的寡聚体或聚集体[32]，它们的积累干扰细胞器功能并可能直接引发毒性反应；受损的 RPE 细胞会分泌淀粉样蛋白(Aβ)等具有聚集倾向的蛋白质，进而成为玻璃膜疣的核心骨架[33]。综上所述，线粒体功能障碍破坏 RPE 细胞的蛋白质稳态，这导致有害蛋白质在细胞内(毒性聚集体)和细胞外(玻璃膜疣)异常聚集，并激活慢性炎症，共同推动了 AMD 的发生与发展。

2.3.3. “代谢生态系统”破坏

最近的研究主要集中在 RPE 和视网膜之间的代谢依赖关系，即“代谢生态系统”。视网膜光感受器利用葡萄糖通过糖酵解作用产生 ATP，而 RPE 主要依靠线粒体氧化磷酸化来产生满足其高代谢需求的能量[34]。然而，线粒体功能障碍迫使 RPE 依靠葡萄糖和糖酵解来供应其能量需求，打破了“代谢生态系统”，导致细胞饥饿和死亡，加速 AMD 的进展[35]。

钙离子稳态也在“代谢生态系统”中起重要作用：Ca^{2+}经 MCU 复合体进入线粒体基质可激活限速酶促进 ATP 合成，同时通过钠钙交换体(NCLX)介导外排避免钙超载[36] [37]；而长期氧化应激会削弱 MCU 的 Ca^{2+}摄取效率、下调 NCLX 表达，引发线粒体钙超载，进而导致线粒体通透性转换孔(mPTP)持续开放、线粒体肿胀破裂，并激活细胞色素 C 等凋亡因子诱发细胞凋亡[38] [39]。

3. 线粒体相关治疗

口服、滴眼液、玻璃体腔注射是目前 AMD 治疗中最常用的三种给药方式，其在靶向 RPE 线粒体治疗中的优劣差异显著，核心取决于药物跨 BRB (血视网膜屏障)效率、局部药物浓度及安全性，口服药物及滴眼液需跨越 BRB，富集于 RPE 细胞的效率较低，部分亲脂性药物滴眼液可通过角膜/结膜渗透至视网膜外层，这两种方式无创、患者依从性高，适用于早期 AMD 预防或中晚期联合玻璃体腔注射治疗[40]；玻璃体腔注射可结合缓释载体(如聚乳酸微球、明胶海绵)修饰线粒体靶向药物，药物可直接扩散至视网膜各层，是目前中晚期 AMD 线粒体靶向治疗的首选给药方式[41]。

3.1. 改善线粒体能量代谢

3.1.1. 补充线粒体代谢物前体

血烟酰胺腺嘌呤二核苷酸(NAD+)作为线粒体能量代谢的核心辅酶，随年龄而下降，补充烟酰胺单核苷酸(NMN)、烟酰胺核糖(NR)等 NAD+前体可通过提升 NAD+水平，激活 Sirtuins 去乙酰化酶家族，增强线粒体生物合成和功能，改善细胞能量状态[42]。

3.1.2. 调节线粒体呼吸链功能

吡咯喹啉醌(PQQ)等生物活性化合物已被证明可以通过激活过氧化物酶体增殖物激活受体 γ 共激活因子 1α (PGC-1α)信号通路来改善线粒体呼吸[43]，其改善 ATP 水平的效果优于 NMN 等前体物质[44]。

3.2. 增强线粒体抗氧化能力

3.2.1. 线粒体靶向递送抗氧化剂(MTA)

传统抗氧化剂(如维生素 C/E)因难以穿透线粒体双层膜而疗效受限，靶向修饰技术实现了抗氧化作用的精准定位[45]。三苯基膦(TPP+)是目前最成熟的线粒体靶向基团，其核心作用原理为：TPP+带有高度亲脂性的正电荷，细胞膜(−30 至−60 mV)与内线粒体膜(−150 至−180 mV)之间的电化学梯度，为亲脂阳离子积累到线粒体提供了极大动力，通过静电引力将连接的抗氧化剂分子主动富集到线粒体基质中，富集效率可达胞质的 100~1000 倍[46]。目前已开发的 MitoQ、MitoTEMPO 均以 TPP+为靶向基团，分别将辅

酶 Q10、超氧化物歧化酶(SOD)模拟物与 TPP+偶联，实现线粒体 ROS 的精准清除[47]。Visomitin 滴眼液是第一种也是迄今为止唯一一种基于 SkQ1 的药物(线粒体靶向抗氧化剂质体醌基癸基三苯基膦)，SkQ1 以癸基三苯基膦为靶向基团，兼具 TPP+的线粒体靶向性和更优的亲脂性，可通过角膜上皮渗透至视网膜外层，抑制 OXYS 大鼠 AMD 样病理的进展，其作用机制与抑制 P38 MAPK 和 ERK1/2 信号通路活性有关[48]，也有研究表明其通过降低 Aβ 水平和抑制视网膜中 mTOR 的活性来延缓衰老[49]。

麦角硫因(EGT)则通过 OCTN1 转运蛋白直接穿透线粒体膜，清除羟基自由基等活性物种，保护 mtDNA 完整性，被称为“线粒体特异性抗氧化剂”[50]。研究表明体外 RPE 细胞和体内小鼠视网膜组织中有效减轻 SI 诱导的严重氧化损伤和细胞死亡[51]，但未来需要对其分子机制、长期毒性和临床试验进行广泛的研究，有望成为治疗 AMD 的新型抗氧化剂。

3.2.2. 激活内源性抗氧化通路

Keap1-Nrf2-ARE 通路是调控细胞抗氧化稳态的核心枢纽。在正常情况下，Nrf2 与 Keap1 结合，转移到细胞核，与 ARE 结合并介导一系列抗氧化蛋白基因 [52]。多苯磺酸钙(CaD)、多酚、α-硫辛酸(ALA)、叶黄素/玉米黄质异构体(L/Zi)、香豆素和桧木醇均可通过激活 Nrf2 通路，提升 RPE 细胞的抗氧化能力[53]-[56]。此外，桧木醇抑制 DNA 片段化并减轻自噬功能障碍，从而有助于维持细胞稳态[57]。

3.3. 促进线粒体质量控制

3.3.1. 激活线粒体自噬

有研究利用 AMD 小鼠模型发现，尿石素 A 可能有助于防止与 AMD 相关的视觉功能丧失，它可以帮助细胞回收受损的溶酶体，而溶酶体负责帮助分解和回收其他细胞部分[58]。二甲双胍可以通过激活 AMPK 途径刺激自噬，从而保护 RPE 细胞免受 H_2O_2 诱导的氧化损伤，流行病学研究表明，服用二甲双胍的糖尿病患者患 AMD 的风险较低[59] [60]。

3.3.2. 改善线粒体代谢环境

褪黑激素可以通过靶向 MT2/SERCA2 轴抑制 SI (碘酸钠)引发的 ER 应激和细胞内钙过载，并恢复线粒体膜电位和抑制 NLRP3 炎症小体激活[61]。线粒体衍生肽如人道素(HN)能够抑制线粒体膜通透性转换孔(mPTP)的开放，从而抑制细胞凋亡[62]。

3.4. 基因治疗与干细胞治疗

3.4.1. 线粒体靶向基因治疗

基因治疗是一种通过修饰受体细胞或组织中有缺陷的 DNA 来达到预期治疗效果的方法，目前，AMD 的基因治疗主要集中在利用载体系统表达可阻断 VEGF 通路的抗血管生成蛋白[63]，靶向线粒体的基因治疗也引起了关注。视网膜下注射腺相关病毒(AAV)载体递送的 NADH-泛醌氧化还原酶(ophNdi1)在 NaIO3 诱导的干性 AMD 小鼠模型中被证明可以降低 ROS 水平、改善线粒体形态和线粒体功能[64]。将 mtDNA 编码基因(如 ND4)进行重新设计，为其添加核表达所需的信号肽和线粒体靶向序列，然后整合到 AAV 载体中。当该基因在细胞核中表达后，其产物可以被运输到线粒体并整合到线粒体复合物中，从而恢复其功能[65]，这种策略已在 Leber 遗传性视神经病变(LHON)的临床试验中取得成功，为治疗同样涉及线粒体复合物缺陷的 AMD 提供了概念验证。

3.4.2. 干细胞移植改善线粒体功能

移植健康的 RPE 细胞(来源于诱导多能干细胞 iPSC 或胚胎干细胞 ESC)替代萎缩的 RPE 层，是治疗地理样萎缩(GA)的可行策略。临床研究表明，iPSC-RPE 移植相对安全，局部类固醇控制的排斥反应极小，

尽管存在轻微免疫反应或视网膜前膜形成等轻微并发症，但移植物仍能保持稳定至少 1 年，移植后显示出视力稳定或适度改善[66]，但晚期 AMD 患者的 Bruch's 膜通常已经老化、增厚并伴有沉积物，这为移植的 RPE 细胞附着、存活和发挥功能提供了一个不良的“土壤”[67]，故尽管干细胞对 AMD 的视网膜再生有效，但它们的使用受到伦理和免疫学问题的限制，需要进一步的研究来完善细胞来源、分化方法和移植技术，以确保持久和安全的临床结果。

3.5. 中医药成分的线粒体保护作用

多种中药活性成分被证实具有多靶点线粒体保护效应。例如，姜黄素的化学结构使其能够直接中和 ROS；二是其通过激活 Nrf2 诱导抗氧化酶的表达[68]；白藜芦醇可以提升 SIRT3 活性，促进线粒体呼吸链复合体去乙酰化修饰，增强能量代谢效率[69]。这些成分通过多途径协同作用，展现了在 AMD 防治中的独特价值，但其具体靶点和临床疗效需进一步验证。

4. 总结与展望

线粒体作为一种重要的细胞器，通过多种机制参与调节正常视网膜活动和 AMD 的病理过程，目前，针对线粒体靶向的 AMD 干预策略虽已在机制研究层面展现出良好潜力，但相关研究大多仍停留在细胞与动物实验阶段，靶向线粒体的药物递送效率优化、治疗靶点的特异性验证以及临床转化研究的缺乏等问题，仍是制约该方向发展的关键瓶颈。未来，随着对线粒体调控网络与 AMD 病理机制关系研究的不断深入，结合新型靶向递送技术、基因编辑手段的创新应用，有望研发出更具特异性与安全性的线粒体靶向治疗药物。希望在不久的将来，这些研究成果能够顺利实现临床转化，为 AMD 患者提供全新的治疗方案，减轻 AMD 对全球人群视力健康的威胁。

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