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活性氧在眼科疾病的研究现状和进展

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摘　要

活性氧(reactive oxygen species, ROS)是在氧化磷酸化过程中产生的，在细胞及组织的增殖、分化及凋亡等方面发挥着重要作用。大量研究表明，ROS与视网膜母细胞瘤、葡萄膜黑色素瘤、年龄相关性黄斑变性、年龄相关性白内障、干眼症、翼状胬肉等眼部相关疾病的发生、发展密切相关。本文主要针对ROS的作用机制及在眼部相关疾病中的研究现况进行阐述，为进一步研究眼部相关疾病及治疗提供参考依据。

关键词

视网膜母细胞瘤，年龄相关性白内障，年龄相关性黄斑变性，活性氧，眼科疾病

Research Status and Progress of Reactive Oxygen Species in Ophthalmic Diseases

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Abstract

Reactive oxygen species (ROS) is produced in the process of oxidative phosphorylation, and plays

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an important role in proliferation, differentiation and apoptosis of cells and tissues. A large number of studies have shown that ROS is closely related to the occurrence and development of eye related diseases such as Retinoblastoma, Uveal Melanoma, Age-Related Macular Degeneration, Age-Related Cataract, Dry Eye and Pterygium. In this article, the mechanism of ROS and the research status of ROS in eye related diseases were expounded, so as to provide reference for further research on ophthalmic diseases and treatment.

Keywords

Retinoblastoma, Age-Related Cataract, Age-Related Macular Degeneration, Reactive Oxygen Species, Ophthalmic Disease

1. 引言

线粒体是协调细胞功能和新陈代谢的关键细胞器。线粒体与细胞通讯是通过活性氧(reactive oxygen species, ROS)信号传递[1]。ROS 主要来源于白细胞，特别是巨噬细胞和中性粒细胞。白细胞可表达还原型烟酰胺腺嘌呤二核苷酸磷酸(nicotinamide adeninedinucleotidephosphate, NAPDH)氧化酶。NADPH 氧化酶和线粒体是生物系统中 ROS 的两个主要来源[2]。Zou 等[3] [4]研究表明，ROS 在细胞及组织的增殖、分化及凋亡等方面发挥着重要作用。维持 ROS 有益的生物学功能和人类疾病之间的平衡，是未来眼部疾病研究的一个难题。本文主要针对 ROS 的研究现状进行综述，以期为 ROS 的研究提供参考依据。

2. ROS 概述

ROS 是在氧化磷酸化过程中产生的，在氧化磷酸化过程中，电子通过电子传输链(electron transport chain, ETC)传递，从而产生能够氧化和产生 ATP 的质子梯度。最终，氧被传输的电子直接还原，产生 ROS [5]。ROS 通过蛋白质修饰来微调众多信号通路，以适应营养和氧化环境的变化[6]。Saure 等[7]研究证实 ROS 参与了关键信号转导通路的调节，在生理条件下，适量的 ROS 是维持细胞生长和分化所必需的。ROS 含量的变化影响细胞的清除能力，组织中的 ROS 含量通常相对较低，然而，ROS 的持续增加会导致暂时的失衡，这会损伤氧化还原调节。线粒体产生 ROS 的速率在多种病理条件下增加，包括缺氧、衰老和线粒体呼吸的化学抑制[8] [9]。研究表明，ROS 的持续产生可能导致转导信号和基因表达的持续变化，从而导致氧化应激[10]。Saccà 等[11]研究表明氧化应激会造成脂质过氧化、脱氧核糖核酸损伤、蛋白质氧化等，从而改变或损害细胞的新陈代谢和活力，甚至导致细胞坏死或凋亡。Valko 等[12] [13] [14]研究证实 ROS 在神经退行性疾病和致盲疾病(如白内障、糖尿病性视网膜疾病、眼部恶性肿瘤)中起到一个特别重要的作用。随着研究的深入，ROS 影响的信号通路逐渐被证实，但由于 ROS 调控眼部疾病机制的复杂性，其作用及机制尚有待进一步探索及论证。

3. ROS 与眼部相关疾病

3.1. ROS 与眼部恶性肿瘤

ROS 的增加是恶性细胞的属性之一，与“癌症”的形成有关。Zhang 等[15] [16] [17]研究表明，ROS

的增加通过不同的机制导致癌细胞的细胞毒性，细胞周期阻滞、凋亡和自噬。为了抵消 ROS 升高的潜在毒性反应，癌细胞存在促进氧化还原稳态的关键途径，例如 NADPH 和谷胱甘肽合成的磷酸戊糖途径[18] [19]。Tahmasebi 等[20]研究发现在癌症中 ROS 的产生导致基因组不稳定和 DNA 损伤，从而导致耐药性和复发率的增加。然而，Moloney 等[21] [22] [23]研究发现，如果 ROS 水平急剧增加到有毒的浓度，例如通过活性氧诱导剂，导致氧化应激增加，氧化应激会导致肿瘤细胞无法修复的损伤，适应能力不足，并最终导致肿瘤细胞凋亡。眼睛的原发性恶性肿瘤是一种相对罕见的疾病，葡萄膜黑色素瘤和儿童视网膜母细胞瘤加在一起，全世界每年大约有 15,000 例[24]。视网膜母细胞瘤(Retinoblastoma, Rb)是儿童最常见的原发性眼内恶性肿瘤，它是一种与体细胞突变或生殖系突变相关的恶性肿瘤[25]。葡萄膜黑色素瘤(Uveal Melanoma, UM)是成人最常见的原发性眼内恶性肿瘤。目前，这种恶性肿瘤最广泛使用的治疗是肿瘤切除、放射治疗和眼球剜除术等[26]。Vandhana 等[27]研究表明与非肿瘤性视网膜相比，氧化剂诱导的 RB 肿瘤细胞的 ROS 水平增加了 32~56 倍，因此 ROS 升高导致肿瘤侵袭性增加。然而，Tahmasebi 等[20] [28] [29]研究表明，持续增加 ROS 并随后激活半胱天冬酶(半胱天冬酶-3/7)可杀死 RB 细胞，促进 RB 细胞凋亡。Yan 等[30]研究发现用扁塑藤素(一种天然三萜类奎宁化合物)抑制 UM-1 (葡萄膜黑色素瘤)细胞的迁移和侵袭，导致 ROS 迅速升高，线粒体膜电位降低，诱导肿瘤细胞聚集在 G0/G1 期，最终导致细胞凋亡。由于肿瘤侵袭和转移是肿瘤治疗中最常见的问题，深入了解 ROS 介导肿瘤与肿瘤微环境相互作用的分子机制将有助于制定治疗策略，尽管这相当具有挑战性。

3.2. ROS 与年龄相关性眼病

ROS 在细胞正常代谢过程中不断产生，并在细胞信号传递中发挥重要作用。ROS 的正常水平由细胞抗氧化系统控制，包括抗氧化酶、小分子量抗氧化剂和 DNA 修复蛋白[31]。然而，在一些条件下超过细胞的抗氧化能力，导致氧化应激，这是年龄相关性眼病的发病原因之一[32]。在眼前段，氧化应激主要与年龄相关性白内障有关，而在眼后段，氧化应激主要与年龄相关性黄斑变性相关[33]。

3.2.1. ROS 与年龄相关性白内障

年龄相关性白内障(Age-Related Cataract)，是人类失明的主要原因之一，占所有失明原因的 47.8% [34]。年龄是白内障的最大风险因素，有时人们认为白内障只是这一衰老过程的放大，事实似乎并非如此。Babizhayev 等[32]研究发现年龄相关性白内障是由晶状体和晶状体纤维细胞中聚集的蛋白质沉积导致晶状体混浊、光散射和视力下降。上皮细胞线粒体的损伤可能会导致 ROS 的产生，而 ROS 的过量产生导致氧化应激会影响晶状体纤维细胞。Kruk 等[35] [36]研究发现 ROS 诱导的晶状体细胞损伤可能包括蛋白质氧化、DNA 损伤和脂质过氧化，这些都与白内障的发生有关。线粒体的保护和修复作用由还原剂、抗氧化剂和伴侣、抗氧化酶和特定的蛋白质修复系统介导。晶状体含有许多有效的抗氧化剂，包括谷胱甘肽及其相关酶，主要是谷胱甘肽还原酶和谷胱甘肽过氧化物酶[37]。Brennan 等研究[33]也发现谷胱甘肽是晶状体、角膜和视网膜抵抗 ROS 诱导损伤的主要保护剂。因此，选择性抑制 ROS 是年龄相关性白内障的一种潜在有效的治疗措施。

3.2.2. ROS 与年龄相关性黄斑变性

年龄相关性黄斑变性(Age-RelatedMacular Degeneration, AMD)是一种复杂的进行性眼病，是老年人失明和视力丧失的主要原因[38]。Kauppinen 等[39] [40]研究发现 AMD 是一种以视网膜沉积、脂褐素沉积、视网膜色素上皮(Retinal Pigment Epithelium, RPE)的氧化应激和死亡以及光感受器和脉络膜毛细血管的功能障碍，并且随着年龄增长会失明的疾病。Blasiak 等[41]研究发现过量的 ROS 会产生氧化应激，氧化应激在衰老中特别重要，因为它可能诱导早衰，也可能导致 DNA 损伤。He 等研究表明[42] AMD 中 ROS

的产生和积累的因素包括光、饮食、吸烟、光敏剂(即脂褐素)和心血管疾病等。Zheng 等[43]研究发现 ROS 的过量产生可能通过 p38 丝裂原活化蛋白激酶(p38 MAPK)诱导凋亡，此外还增加血管内皮生长因子的产生，导致视网膜血管内皮功能障碍和视网膜毛细血管细胞凋亡。Ruan 等[44]研究也发现 ROS 的过量产生使视网膜内皮功能障碍，损害了 NO 代谢的平衡，影响血管内皮细胞和平滑肌细胞对生理刺激的反应性。由此产生的内皮功能障碍的特征是内皮依赖性血管舒张减少以及促炎因子增多，导致视网膜毛细血管细胞凋亡，导致 AMD 的发生。大量研究表明降低细胞内 ROS 的含量可以延缓视网膜色素上皮的衰老，从而延缓 AMD 的进展[44] [45] [46]。因此，选择性清除 ROS 是 AMD 的一种有前途的治疗策略。

3.3. ROS 与眼表疾病

眼表疾病是常见的眼科疾病，它是角结膜正常结构和功能被损害的一类疾病。ROS 的外源性来源，如紫外光、可见光、电离辐射、化疗药物和环境毒素等，会导致眼组织的氧化损伤[10]。人眼经常暴露于这些损伤会使老化的眼睛面临相当大的风险。Uchino 等[47] [48]研究发现氧化损伤与多种眼表疾病相关，如干眼症、翼状胬肉等。干眼症(Dryeye)是一种泪液和眼表的多因素疾病，导致不适、视觉障碍和泪膜不稳定，并对眼表造成损害[49]。Wakamatsu 等[50]研究发现 ROS 过量产生导致腺泡萎缩、纤维化、细胞膜脂质过氧化、眼表－泪腺单位的炎症细胞浸润，导致干眼的形成。Zheng 等[51]研究表明 ROS 的持续上升会使 NLRP3 炎症小体以及 IL-1b 的分泌增加，而 NLRP3 炎症小体的表达增加会触发先天免疫反应，从而导致干眼、Behçet 病的进展。翼状胬肉(Pterygium)是一种纤维血管增生的结膜组织侵入角膜的慢性疾病。翼状胬肉的发病机制正在研究中，包括紫外线辐射、免疫炎症过程、病毒感染和遗传因素等[52]。Tsai 等[53]研究发现紫外线照射造成 ROS 增加，对眼表产生氧化损伤，产生 8-羟基脱氧鸟苷(8-OHdG)酶，并导致异常细胞生长和血管生成，从而导致翼状胬肉的发展。减少 ROS 的量来控制氧化应激是预防和治疗眼表疾病的潜在治疗策略。

4. ROS 与眼部其他疾病

糖尿病性视网膜病变(Diabetic retinopathy, DR)是一种以视网膜损伤和长期糖尿病背景下的视觉缺陷为特征的疾病。糖尿病诱导视网膜中 ROS 的过度产生[54]。Castilho 等[55]研究认为在细胞内，ROS 直接作用于蛋白质和脱氧核糖核酸，或间接作为第二信使调节导致糖尿病性视网膜病变发病的各种信号级联。Silva 等[56]研究也发现 ROS 过量产生促进微血管并发症、神经退行性变和病理性血管生成，这些都与糖尿病性视网膜病变的发生相关。因此减少 ROS 的形成在糖尿病性视网膜病变的治疗中尤为重要。Santana-Garrido 等[57]研究表明 ROS 的过量产生会导致脂质过度氧化，从而导致视网膜神经节细胞的功能障碍和凋亡，导致青光眼的形成。Iomdina 等[58]研究也发现 SkQ1，一种抗氧化剂，已被证明能逆转兔实验性青光眼的特征。高度近视的特点是随着眼轴长度的延长，眼后壁的拉伸引起各种特殊的并发症，这些并发症往往导致不可逆的视网膜感光器官损害和中心视力丧失[59]。Francisco 等[60]研究发现 ROS 过度产生会改变蛋白质、使有害的脂质过氧化和 DNA 裂解，从而导致光感受器和其他神经视网膜细胞的退化，从而导致近视的进展。因此对青光眼、高度近视患者及时抗氧化治疗能减轻 ROS 引起的病理损害。

5. 结论

活性氧的过量产生可导致多种病理过程，包括缺血状态下的细胞损伤、衰老和凋亡，导致氧化还原平衡受损，潜在地减少促生存信号并促进眼部疾病进展。抗氧化剂对部分眼科疾病具有预防和控制发展的效果，但其中有很多原理和机制仍不完善，因此，开发和实施针对活性氧提供保护的疗法对于预防和治疗眼部疾病将是重要的。

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