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活性氧在皮肤衰老中的作用

陈柳廷，刘晏伊*

重庆医科大学附属口腔医院，口腔疾病与生物医学重庆市重点实验室，重庆市高校市级口腔生物医学工程重点实验室，重庆

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摘　要

皮肤作为人体最大的器官，能够直观地反映机体整体的衰老水平。皮肤衰老可分为内源性衰老和外源性衰老，其细胞水平的主要表现是真皮层内成纤维细胞的老化，而其中ROS发挥着关键作用。ROS引起细胞老化的主要机制包括DNA损伤、线粒体氧化损伤、促炎细胞因子水平升高以及ECM的降解。在本综述中，将重点探讨皮肤衰老的特征、ROS的生成以及ROS导致皮肤老化的详细机制。

关键词

皮肤衰老，成纤维细胞，ROS

The Role of Reactive Oxygen Species in Skin Aging

Liuting Chen, Yanyi Liu*

Stomatological Hospital of Chongqing Medical University, Chongqing Key Laboratory for Oral Diseases and Biomedical Sciences, Chongqing Municipal Key Laboratory of Oral Biomedical Engineering of Higher Education, Chongqing

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Abstract

As the body's largest organ, the skin provides a visual reflection of the overall aging status of the organism. Skin aging can be categorized into intrinsic aging and extrinsic aging, with the primary cellular manifestation occurring in the aging of dermal fibroblasts. In this process, ROS play a crucial role. The major mechanisms through which ROS induces cellular aging include DNA damage,

*通讯作者。

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mitochondrial oxidative stress, elevated levels of pro-inflammatory cytokines, and degradation of the ECM. This review focuses on elucidating the characteristics of skin aging, the generation of ROS, and the detailed mechanisms by which ROS contributes to skin aging.

Keywords

Skin Aging, Fibroblasts, ROS

1. 引言

皮肤是覆盖在人体表面的器官，作为机体的首要防线，不仅能够抵御外界病原体入侵，还承担着排泄、调节体温和感知外部刺激的重要功能[1]。内源性老化，即程序性衰老，是生物体自然衰老的一部分[2]，主要由于机体内活性氧氧化累积所致。相对而言，外源性老化则是由外部因素如紫外线、吸烟、高温和空气污染等引起，其中以紫外线导致的皮肤老化最为普遍，即光老化[3] [4]。在结构上，皮肤由表皮、真皮和皮下组织组成。表皮主要包括角质细胞以及少量的黑色素细胞、麦克尔细胞和朗格汉斯细胞。真皮则主要由成纤维细胞及其产生的细胞外基质(Extracellular matrix, ECM)组成，而皮下层则由脂肪细胞构成。真皮层在皮肤结构和功能中发挥着关键作用，包括免疫、吞噬、血管、神经、汗腺和淋巴管等结构，为表皮提供营养并维持正常代谢。皮肤的衰老的特征包括真皮层中成纤维细胞的老化以及细胞外基质的降解[5] [6]，而活性氧(Reactive oxygen species, ROS)在这一过程中扮演着关键的调控角色。本文将着重探讨与衰老相关的皮肤变化以及 ROS 在皮肤衰老中的机制作用。

2. 皮肤衰老的特征

随着年龄的增长，人体的皮肤结构会发生一系列变化。这些变化包括角蛋白细胞的萎缩导致表皮层的变薄，进而引发经表皮水分流失的增加，加剧皮肤的干燥[7]。然而，皮肤老化的核心机制在于刺激因素激活了基质金属蛋白酶(Matrix metalloproteinase, MMPs)，导致真皮中支撑皮肤结构的胶原蛋白和弹性蛋白遭到过度降解[8] [9]，即细胞外基质的破坏。研究表明，随着年龄的增长，皮肤中的胶原蛋白总量减少，而胶原蛋白碎片随年龄增加，主要是由于老年皮肤中 MMPs 的上升表达。弹性蛋白是一种稳定的蛋白质，占真皮总蛋白的 2%，在人体早期发育中形成，一生中不再进行合成和补充[8]。MMPs 中的 MMP-1、-3 和-9 能够对弹性蛋白产生有针对性的影响，导致皮肤弹性减退，表现为皱纹和下垂，这是典型的衰老表征[10] [11] [12]。真皮层中成纤维细胞数量的减少[13] [14]，加上 ECM 降解黏附作用减弱导致成纤维细胞形态减小，会进一步使得皮肤变薄[15] [16]。在衰老过程中，皮肤汗液和皮脂分泌减少，脂肪组织变薄。一部分原因是由于真皮层中的成纤维细胞无法有效转化为脂肪细胞，导致脂肪细胞分泌的抗菌肽减少，进而削弱了皮肤的屏障功能，使其更容易受到外界感染的威胁[17] [18]。

3. ROS 的来源

ROS 包括超氧化物阴离子(O^{2-})和过氧化氢(H_2O_2)等，其主要产生于细胞内的线粒体呼吸链[19]。在能量代谢过程中，线粒体负责将糖类、脂肪和氨基酸氧化释放能量，生成 ATP 和水，而活性氧则被视为线粒体呼吸过程的副产品。在有氧呼吸中，大部分电子沿着呼吸链传递至末端与分子氧结合生成水，但

少量电子(2%~3%)可能会从呼吸链酶复合体 I 和III处泄漏，导致超氧化物的产生[20] [21]。电子流动速度越慢，超氧化物阴离子 O^{2-}产生越多。氧自由基的生成不仅发生在线粒体中，还可在过氧化物酶体和内质网中产生[22] [23]。紫外线中，UVB 主要作用于表皮细胞，而 UVA 具有更强的穿透力，能够达到真皮层，通过光敏反应引发超氧化物、羟基自由基和过氧化氢的产生[24]。外源性 ROS 的产生也可由抗癌的放射线介入治疗、化疗药物的毒性副作用、吸烟、饮酒等因素引发。

4. ROS 导致皮肤老化的机制

ROS 引起 DNA 损伤的类型包括碱基氧化修饰、单链断裂和双链断裂等，例如 DNA 氧化损伤中常用的生物标志物 8-羟基脱氧鸟苷酸(8-OHdG)的形成[25] [26] [27]。持续的核 DNA 损伤激活了 DNA 损伤反应(DDR)通路，进而激活了衰老效应器的信号通路，包括循环依赖性激酶 p53-p21，导致细胞周期不可逆转的停滞，最终诱发细胞衰老[28]。ROS 还可以作用于蛋白质和脂质，尤其是线粒体，导致氧化损伤和线粒体功能障碍[29] [30]，这进一步加剧了 ROS 的产生，形成了负反馈循环。有丝分裂激活蛋白激酶(MAPK)家族，包括细胞外信号调节激酶(ERK)、p38 和 c-Jun 末端激酶(JNK)，可以被 ROS 激活。ROS 通过激活 MAPK 信号通路，使其下游激活蛋白 1 (AP-1)表达增加，从而调控了基质金属蛋白酶(MMP-1、MMP-3、MMP-9 和 MMP-12)的表达[31] [32]。另一方面，ROS 激活的转录因子核因子-κB (NF-κB)也发挥关键作用。NF-κB 的激活促使炎症因子 IL1β、TNF-α、IL-6 的表达上调，进一步加剧了 MMPs 的产生并导致细胞外基质的降解[33] [34] [35]。除此之外，ROS 和 NF-κB 的上调还能激活 NLRP3 炎性小体，引发下游 caspase-1 的活化，切割非活性前体 IL-1β 和 IL-18，并刺激其分泌[36]。这一系列反应共同参与了皮肤老化的复杂机制。

5. 结语

活性氧在皮肤衰老中扮演着重要的角色，通过引发细胞衰老、影响胶原蛋白和弹性蛋白的合成与降解，以及诱导炎症反应等机制，促使皮肤老化的发生。对 ROS 在皮肤衰老中的深入了解不仅有助于我们更好地理解这一复杂过程，还为制定更有效的抗衰老策略提供了理论支持。

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