DOI: 10.11844/cjcb.2026.06.0018
中国细胞生物学学报 Chinese Journal of Cell Biology 2026, 48(6): 1714–1724 CSTR: 32200.14.cjcb.2026.06.0018

氧化还原稳态与精原干细胞衰老: 抗氧化干预的分子网络与靶向策略

仇星云[1,2] 樊怡[3] 刘棒[1] 周戴[1]*

([1]湖南师范大学附属长沙市妇幼保健院, 区域遗传性出生缺陷防控研究湖南省重点实验室, 长沙 410000;
[2]宁夏医科大学第三临床医学院, 宁夏 750004; [3]湖南师范大学医学部, 长沙 410000)

摘要 男性生殖衰老是影响生育能力与生殖健康的重要问题, 日益受到学界关注。其中, 精原干细胞(spermatogonial stem cells, SSCs)功能的年龄相关性减退, 是男性生殖衰退的重要细胞学基础。现有研究提示, 活性氧(ROS)的异常积累不仅直接损伤SSCs, 还会波及支持其功能的睾丸微环境, 进而打破SSCs自我更新与分化之间的稳态。该文尝试围绕氧化还原稳态这一视角, 梳理近年来ROS在SSCs衰老过程中的病理作用, 并总结内源性与外源性抗氧化干预的相关机制, 重点归纳了抗氧化剂如何通过Nrf2/Keap1、SIRT1/FOXO及PI3K/Akt/mTOR等信号通路的互作网络, 调节细胞凋亡与线粒体自噬的平衡。此外, 鉴于ROS兼具生理信号分子的双重属性, 该文客观讨论了抗氧化干预中潜在的“还原应激”风险, 探讨了干预策略从“单纯清除”向“稳态重建”转变的思路。最后, 结合血睾屏障(blood-testis barrier, BTB)对药物递送的限制, 该文简要展望了纳米靶向策略在应对临床转化挑战中的应用潜力, 以期为男性生殖衰老的基础研究与个体化临床干预提供一份初步的理论参考。

关键词 精原干细胞; 衰老; 氧化还原稳态; 抗氧化干预

Redox Homeostasis and Spermatogonial Stem Cell Aging: Molecular Networks and Targeted Strategies of Antioxidant Interventions

QIU Xingyun[1,2], FAN Yi[3], LIU Bang[1], ZHOU Dai[1]*

([1]*Hunan Provincial Key Laboratory of Regional Hereditary Birth Defect Prevention and Control, Changsha Hospital for Maternal & Child Health Care Affiliated to Hunan Normal University, Changsha 410000, China*; [2]*the Third Clinical Medical College of Ningxia Medical University, Ningxia 750004, China*; [3]*School of Medicine, Hunan Normal University, Changsha 410000, China*)

Abstract Male reproductive aging is a critical issue affecting fertility and reproductive health, which has increasingly attracted the attention of the academic community. The age-related decline in the function of SSCs (spermatogonial stem cells) is the fundamental basis of this reproductive decline. Current studies suggest that the abnormal accumulation of ROS (reactive oxygen species) not only directly damages SSCs but also impairs the testicular microenvironment that supports their function, thereby disrupting the homeostasis between SSC self-renewal and differentiation. Focusing on the perspective of redox homeostasis, this review systematically outlines the pathological roles of ROS in the aging process of SSCs and summarizes the underlying mechanisms of endogenous

收稿日期: 2026-03-20 接受日期: 2026-04-27
国家自然科学基金(批准号: 82201771) 、湖南省自然科学基金(批准号: 2024JJ6083)和宁夏医科大学本科生创新创业计划(批准号: NYCXCYX047)资助的课题
*通信作者。Tel: 14789751785, E-mail: zhoudai@hunnu.edu.cn
Received: March 20, 2026 Accepted: April 27, 2026
This work was supported by the National Natural Science Foundation of China (Grant No.82201771), the Natural Science Foundation of Hunan Province (Grant No.2024JJ6083), and the Ningxia Medical University Undergraduate Innovation and Entrepreneurship Program Funding (Grant No.NYCXCYX047)
*Corresponding author. Tel: +86-14789751785, E-mail: zhoudai@hunnu.edu.cn

and exogenous antioxidant interventions. Particular emphasis is placed on how antioxidants regulate the balance between cellular apoptosis and mitophagy through the crosstalk of signaling networks, including the Nrf2/Keap1, SIRT1/FOXO, and PI3K/Akt/mTOR pathways. Furthermore, given the dual properties of ROS as physiological signaling molecules, this article objectively discusses the potential risk of “reductive stress” in antioxidant therapies and explores the paradigm shift in intervention strategies from “simple scavenging” to “homeostasis reconstruction.” Finally, considering the physical restrictions imposed by the blood-testis barrier on drug delivery, the application potential of nano-targeted strategies in overcoming clinical translation challenges is briefly prospected. This review aims to provide a theoretical reference for basic research and individualized clinical interventions in male reproductive aging.

Keywords spermatogonial stem cells; aging; redox homeostasis; antioxidant intervention

在男性生殖系统中, 精原干细胞(spermatogonial stem cells, SSCs)作为精子发生的基础与源泉, 通过精密的自我更新与分化过程, 维持着干细胞池的稳定与终身生育能力。然而, 随着年龄的增长, 男性通常会面临生殖衰老, 其核心表现为SSCs数量的逐渐减少以及其自我更新与分化潜能的显著减弱[1]。值得注意的是, 这一衰退过程往往并非是孤立发生, 而是与支持其功能的睾丸微环境(niche)的持续恶化密切相关的。SSCs内部功能的衰退与其外部微环境的退化相互交织, 共同构成了男性生育力下降的重要病理基础。

近年来的研究广泛提示, 氧化应激在上述生殖系统的衰老进程中扮演了核心角色。基于“氧化自由基衰老学说”, 活性氧(reactive oxygen species, ROS)在细胞内具有生理与病理双重属性。在正常的生理状态下, 适度水平的ROS可作为重要的“第二信使”参与信号转导, 调控干细胞的增殖、存活与分化等基础活动[2]。然而, 当ROS的积累超出细胞内抗氧化系统的清除能力时, 便会打破既有的氧化还原稳态, 造成DNA损伤、蛋白质不可逆氧化以及脂质过氧化[3]。这种病理性的氧化损伤不仅会诱发细胞周期阻滞、凋亡或衰老, 更被普遍认为是驱动SSCs功能衰退、破坏其干性稳态的关键机制。

因此, 探究ROS如何参与调控SSCs的命运, 并尝试通过抗氧化干预来重建其氧化还原稳态, 具有一定的科学探索意义与潜在的临床转化价值。本综述尝试梳理ROS在SSCs及其微环境衰老过程中的病理作用网络, 并归纳内源性及外源性抗氧化剂通过调控关键信号通路以延缓SSCs衰老的相关机制。同时, 结合当前研究面临的靶向递送与“双刃剑”效应等挑战, 本文也初步探讨了抗氧化疗法在防治衰老相关男性不育症中的应对策略, 以期为该领域的基础研究与临床干预提供一份客观的理论参考。

1 ROS扰乱SSCs稳态的病理机制

SSC的命运决定高度依赖于其细胞内的氧化还原状态与外部微环境的精密协调。当这一稳态被打破时, 由ROS介导的多维度损伤便成为推动其衰老的关键因素。

1.1 ROS的产生及其生理与病理作用

在SSCs中, ROS的产生主要源于线粒体氧化磷酸化过程中的电子“泄露”以及质膜上NADPH氧化酶(NADPH oxidase, NOX)的催化作用[4]。如前所述, 处于生理水平的ROS可作为细胞内的“第二信使”, 它们通过可逆性地氧化修饰MAPK、PTEN等关键信号蛋白的半胱氨酸残基, 适度参与调控SSCs的自我更新与存活等基础生命活动[5-7]。

然而, 当ROS的产生速率超过细胞内抗氧化防御系统的清除阈值时, 便会诱发氧化应激。其对SSCs造成的病理损伤主要体现在三个维度: 首先是DNA损伤, 过量ROS不仅可直接攻击核酸碱基引发单/双链断裂, 还可能加速端粒缩短, 从而促发细胞周期的不可逆阻滞或凋亡[8]; 其次是蛋白质氧化, 关键结构蛋白或酶类的特定氨基酸残基遭到不可逆修饰, 导致其丧失原有活性或发生异常聚集[9]; 再次是脂质过氧化, ROS攻击细胞膜及线粒体膜上的多不饱和脂肪酸, 降低膜流动性[10]。值得注意的是, 近年研究提示这一脂质过氧化过程与铁死亡(ferroptosis)等新型程序性细胞死亡方式密切相关, 可特异性地削弱干细胞的干性储备与存活能力[11-12]。

1.2 线粒体多维功能障碍与自噬受损

线粒体在SSCs介导的生殖衰老网络中占据着核心地位。然而, 单纯依赖ROS的累积水平来评价

线粒体功能是较为单一且存在局限性的。事实上，细胞老化与氧化应激并非总是简单的直接线性相关。在SSCs复杂的驻留微环境中，线粒体实质上处于一种高度动态的复杂代谢模式之中。除了ROS的过量释放外，线粒体膜电位(ΔΨm)的去极化、基质内钙离子(Ca^{2+})稳态的失衡，以及电子传递链中各种氧化磷酸化(oxidative phosphorylation, OXPHOS)酶复合体活性的动态波动，均是独立且综合反映线粒体代谢灵活性与功能衰退的关键维度[13]。过量的ROS虽然会直接破坏线粒体DNA和呼吸链复合物，但其往往伴随着上述离子状态和膜电位的全面崩塌，进而导致能量代谢的不可逆受损。

在此过程中，线粒体自噬(mitophagy)途径的受损被认为是一个加速衰老的关键病理环节[14]。在正常生理状态下，受损的线粒体主要通过PINK1/Parkin等经典自噬通路被识别并降解。但在衰老的SSCs中，持续的氧化应激可能会干扰PINK1在线粒体外膜的稳定聚集，进而阻碍Parkin的有效招募，导致功能失调的线粒体无法被及时清除[15-16]。这些滞留的“垃圾”线粒体持续释放ROS及促凋亡因子，不仅加速了SSCs自身机能的崩溃，还可能通过旁分泌途径波及并恶化周边的睾丸微环境[17]。

1.3 睾丸微环境的氧化损伤与系统性衰退

SSCs的自我更新与分化并非孤立进行，而是高度依赖于睾丸微环境的精准调控的。现有文献提示，氧化应激对微环境的破坏，是间接推动SSCs衰老不可忽视的系统性因素[16]。

作为直接接触并滋养SSCs的“看护细胞”，支持细胞(Sertoli cells)对氧化损伤表现出较高的敏感性。ROS的过度积累会削弱支持细胞分泌胶质细胞源性神经营养因子(glial cell line-derived neurotrophic factor, GDNF)等关键维持因子的能力，并可能破坏血睾屏障(blood-testis barrier, BTB)的结构完整性，从而使得SSCs丧失维持干性所必需的物理依托与化学信号[18-19]。与此同时，位于间质区域的睾丸间质细胞(Leydig cells)在氧化应激下，其类固醇合成相关酶的表达与活性常受到抑制，导致局部睾酮水平明显下降[20]。睾酮的匮乏不仅直接影响精子发生，还会进一步削弱支持细胞的各项功能[21]。由此可见，微环境中支持细胞与间质细胞的退化，与SSCs的内部氧化损伤相互交织、彼此放大，共同编织了一个驱动男性生殖系统衰老的复杂病理网络(图1)。

2 抗氧化剂调控SSCs稳态的关键分子网络

SSCs的命运决定依赖于复杂的细胞内信号网络对氧化还原状态的精密感知与响应。现有研究提示，抗氧化剂的保护作用可能远不止于对自由基的简单清除，更关键的是通过调控核心信号通路，尝试在SSCs内部重建氧化还原稳态[22]。

2.1 Nrf2/Keap1/ARE信号防御轴

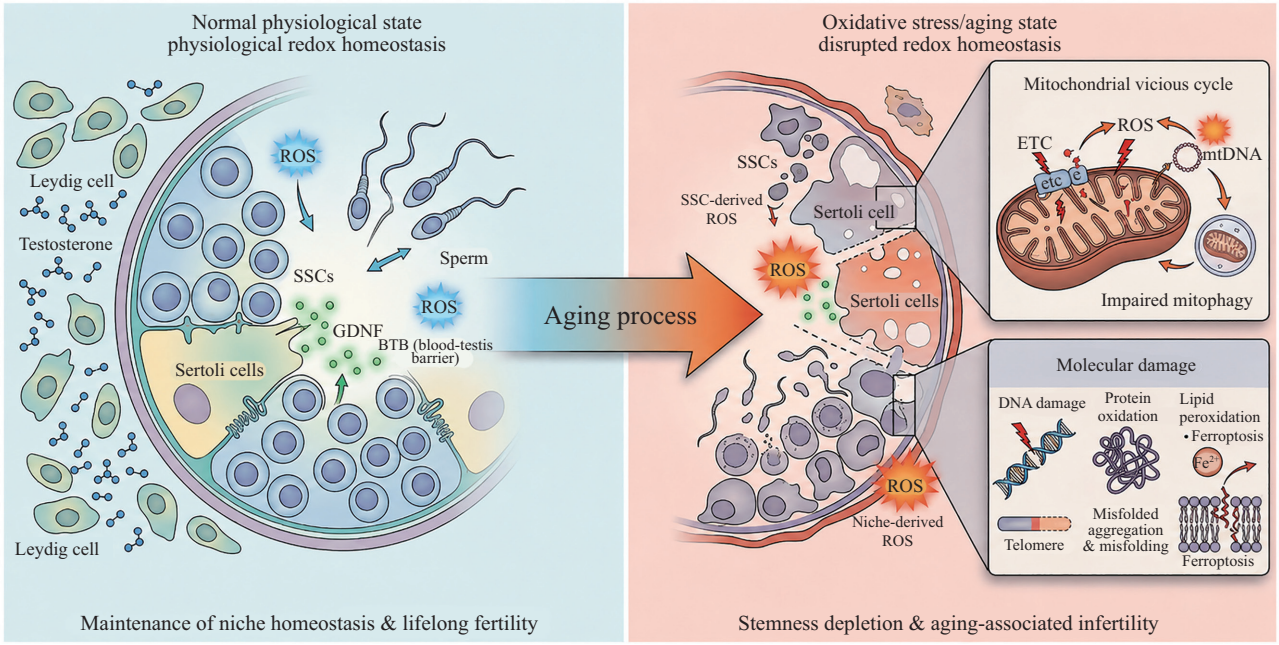
核因子E2相关因子2(nuclear factor erythroid 2-related factor 2, Nrf2)被广泛认为是细胞内源性抗氧化防御的主调节器。在基础稳态下，Nrf2在胞质中与其抑制蛋白Keap1结合，并通过泛素–蛋白酶体途径被持续降解。当遭遇氧化应激时，ROS对Keap1关键半胱氨酸残基的氧化修饰会导致该蛋白构象发生改变，促使Nrf2解离并稳定存在。随后，Nrf2转位进入细胞核，识别并结合抗氧化反应元件(antioxidant response element, ARE)，进而启动一系列下游保护性基因(如血红素加氧酶-1、超氧化物歧化酶等)的转录翻译[23]。在SSCs中，激活Nrf2信号通常能显著增强细胞的抗氧化能力[24]。目前观察到，包括白藜芦醇[25]、萝卜硫素[26]和姜黄素[27]在内的多种天然抗氧化剂，均有望通过促进Nrf2的核转位，并在一定程度上减轻氧化应激诱导的DNA损伤，从而协助维持SSCs的存活与自我更新潜能。

2.2 SIRT1与FOXO家族介导的表观遗传重塑

SIRT1是一种NAD^+依赖的组蛋白去乙酰化酶，在表观遗传层面调控细胞衰老与代谢的过程中发挥着关键作用[28]。在氧化应激的响应网络中，FOXO转录因子家族是SIRT1的重要下游靶标。研究表明，当SSCs面临轻度氧化应激时，被激活的SIRT1可对FOXO3a进行去乙酰化修饰，这种修饰特异性地改变了FOXO3a的转录活性谱：它倾向于促进抗氧化酶基因的表达，同时在一定程度上限制促凋亡基因的转录[29]。这一基于表观遗传修饰的“功能切换”机制，使得SSCs能够优先启动ROS清除程序而非凋亡程序。此外，研究表明SIRT1介导的去乙酰化修饰能够有效激活PGC-1α，进而通过促进线粒体生物合成以优化线粒体质量[30]。因此，靶向SIRT1/FOXO3a轴的干预策略(如使用白藜芦醇)[31]，有望成为延缓SSC氧化衰老的重要途径。

2.3 PI3K/Akt/mTOR通路介导的代谢与自噬平衡

PI3K/Akt/mTOR通路是偶联细胞代谢、生长与自噬的核心枢纽。在SSCs的氧化调控中，该通路的



左侧(正常生理状态): 在健康的生精上皮中, 生理水平的ROS作为第二信使参与精原干细胞(SSCs)的信号转导。此时, 支持细胞(Sertoli cells)与间质细胞(Leydig cells)功能完好, 血睾屏障(blood-testis barrier, BTB)结构完整, 共同维持SSCs自我更新与分化的平衡, 保障终身生育力。图中睾丸间质内的小分子颗粒代表睾酮以及微环境细胞分泌的各类旁分泌营养因子(如GDNF等)。右侧(氧化应激/衰老状态): 随年龄增长或病理刺激, 过量ROS累积打破氧化还原稳态。图中指示了病理性ROS的双重来源: 包括SSCs因线粒体功能障碍产生的内源性ROS(SSC-derived ROS), 以及退化的微环境释放的外源性ROS(niche-derived ROS)。一方面, ROS诱导内源性大分子损伤(包括DNA链断裂、蛋白质氧化聚集、脂质过氧化及铁死亡), 并引发线粒体电子传递链(ETC)受损与自噬障碍的恶性循环; 另一方面, 微环境细胞出现退行性改变, BTB结构受损, GDNF等营养因子及睾酮分泌水平随之下降。细胞内源损伤与微环境衰退相互作用, 最终造成SSCs耗竭, 引发生殖衰老。

Right panel (oxidative stress/aging state): with advancing age or pathological stimulation, the accumulation of excessive ROS disrupts redox homeostasis. The diagram illustrates the dual sources of pathological ROS: endogenous ROS generated by SSCs due to mitochondrial dysfunction (SSC-derived ROS), and exogenous ROS released from the degenerating microenvironment (niche-derived ROS). On one hand, ROS induces damage to endogenous macromolecules (including DNA strand breaks, protein oxidation and aggregation, lipid peroxidation, and ferroptosis), triggering a vicious cycle of mitochondrial ETC (electron transport chain) impairment and autophagy dysfunction. On the other hand, niche cells degenerate and the BTB is impaired, along with decreased secretion of testosterone and GDNF. Combined endogenous damage and microenvironmental decline result in SSC exhaustion and reproductive aging.

图1 活性氧(ROS)驱动精原干细胞稳态破坏与衰老的病理网络(根据参考文献[4-20]改编)

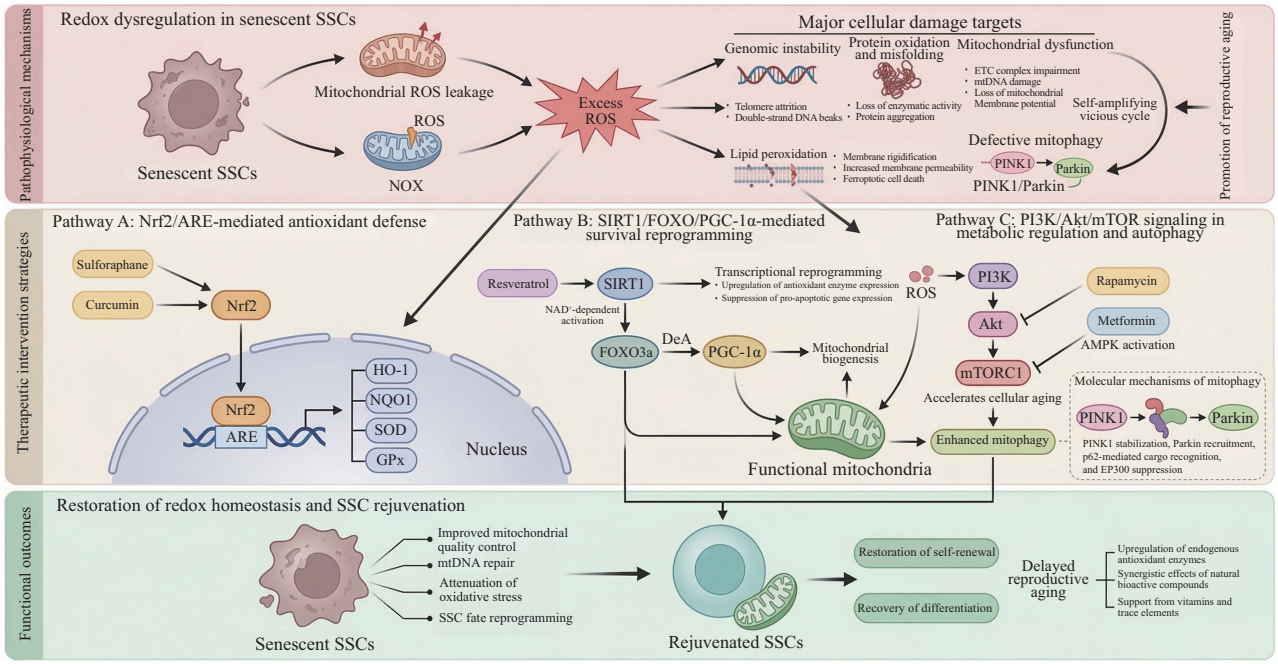
Fig.1 Pathological network of ROS-driven disruption of spermatogonial stem cell homeostasis and aging (adapted from references [4-20])

活性呈现出高度的复杂性: 适度激活是驱动细胞增殖所必需的, 但持续的过度活化则可能加速衰老进程[32]。具体而言, Akt的过度活化会导致mTORC1的持续活化, 这不仅可能抑制细胞自噬、阻碍受损线粒体的及时清除(进而引发ROS的二次累积), 还可能因蛋白质合成增加而加剧内质网的氧化负荷[33]。因此, 适度抑制mTOR通路被认为是延缓SSCs衰老的潜在策略之一。部分研究指出, 二甲双胍或雷帕霉素等干预手段可通过间接或直接下调mTORC1活性, 尝试恢复SSCs内的线粒体自噬通量, 从而减轻整体的氧化压力[32,34-36]。

2.4 信号网络的互作(crosstalk)与细胞命运的抉择

值得强调的是, SSCs在氧化应激下的最终命运, 往往取决于细胞凋亡与自噬这两种对立统一程序的动态平衡。而上述信号通路在此过程中并非孤立运行, 而是构成了一个紧密交织的互作网络(crosstalk)。过量的ROS既可通过改变线粒体外膜通透性来启动Caspase依赖的凋亡级联反应, 也可作为自噬的诱导信号。

抗氧化剂的干预往往具有多靶向性: 它们不仅能通过提升整体还原能力(如*N*-乙酰半胱氨酸)来抑制凋亡信号的启动[37-39], 更能通过深度的信号串扰增强受损线粒体的选择性清除。例如, SIRT1的激活不仅能调节FOXO以抵抗凋亡, 还可能通过直接促进自噬相关蛋白的去乙酰化来增强自噬流[40]; 同时, Nrf2也能通过诱导p62的表达, 与自噬途径形成正反



针对衰老SSCs中由持续氧化应激和线粒体功能障碍引发的病理损伤, 抗氧化剂通过多靶点网络干预以重塑细胞稳态。通路A(抗氧化防御): 萝卜硫素等化合物促进Nrf2核转位并结合抗氧化反应元件(ARE), 上调HO-1、SOD等内源性防御酶表达, 增强自由基清除能力。通路B(存活切换): 白藜芦醇激活SIRT1, 通过去乙酰化修饰FOXO3a和PGC-1α, 抑制促凋亡信号并促进抗氧化转录与线粒体生物合成。通路C(代谢自噬调控): 雷帕霉素或二甲双胍(通过AMPK)适度抑制过度活化的PI3K/Akt/mTORC1通路, 恢复受损的线粒体自噬(如PINK1/Parkin途径), 及时清除功能障碍的线粒体。三大通路相互串扰(crosstalk), 协同消除内源性ROS, 修复mtDNA, 最终挽救SSCs命运, 恢复其自我更新与分化潜能。

In senescent SSCs, persistent oxidative stress and mitochondrial dysfunction induce pathological damage. Antioxidants reshape cellular homeostasis through multi-target network interventions. Pathway A, antioxidant defense: compounds such as sulforaphane promote Nrf2 nuclear translocation and binding to AREs (antioxidant response elements), thereby upregulating endogenous defense enzymes such as HO-1 and SOD and enhancing free radical scavenging capacity. Pathway B, survival switching: resveratrol activates SIRT1, which deacetylates FOXO3a and PGC-1α, suppresses pro-apoptotic signaling, and promotes antioxidant transcription and mitochondrial biogenesis. Pathway C, metabolic and autophagy regulation: rapamycin or metformin, via AMPK activation, moderately suppresses hyperactivated PI3K/Akt/mTORC1 signaling, restores impaired mitophagy such as the PINK1/Parkin pathway, and removes dysfunctional mitochondria. Crosstalk among these three pathways synergistically eliminates endogenous ROS, repairs mtDNA, rescues SSC fate, and restores self-renewal and differentiation potential.

图2 抗氧化剂通过关键信号通路网络重塑精原干细胞氧化还原稳态(根据参考文献[22-43]改编)

Fig.2 Antioxidants reshape redox homeostasis in spermatogonial stem cells through key signaling networks (adapted from references [22-43])

馈环路, 进一步放大细胞的抗氧化防御能力[41-42]。因此, 抗氧化策略的实质, 可能正是通过整合Nrf2介导的抗氧化防御、SIRT1主导的存活切换以及mTOR调控的代谢自噬, 最终在SSCs内部力求重塑氧化还原稳态, 恢复自我更新与分化的平衡[43](图2)。

3 抗氧化干预策略的分类及其在精原干细胞保护中的应用探讨

基于作用机制与物质来源的差异, 当前用于保护SSCs及其微环境的抗氧化策略大致可划分为内源性酶类、外源性天然化合物以及维生素与微量元素三大基础类别(表1)。在力求重塑细胞氧化还原稳态的过程中, 这三类物质往往展现出不同层面的机制互补性。

3.1 内源性酶类抗氧化系统: 稳态防御的基础屏障

细胞内在的酶类抗氧化系统是应对氧化应激的第一道防线, 主要包括SOD(superoxide dismutase)、CAT(catalase)和GPx(glutathione peroxidase)等。在SSCs中, 这一系统的基础活性水平在很大程度上决定了细胞面对外界刺激时的抗氧化储备[44]。

部分转基因动物模型研究提示, *SOD1*或*SOD2*的基因敲除通常会伴随睾丸组织氧化损伤加剧及生殖细胞凋亡数量增加; 相对地, 过表达这类抗氧化酶则可能在一定程度上减轻由辐射或化学毒物诱导的SSCs耗竭[45]。相对地, 过表达这类抗氧化酶则可能在一定程度上减轻由辐射或化学毒物诱导的SSCs

表1 代表性抗氧化策略在精原干细胞(SSCs)保护中的应用及其网络调控机制

Table 1 Representative antioxidant strategies for the protection of SSCs (spermatogonial stem cells) and their network regulatory mechanisms

抗氧化剂分类 Antioxidant class	代表性物质 Representative compounds	主要作用靶点/信号通路 Major targets/signaling pathways	在SSCs及微环境中的主要保护效应 Main protective effects in SSCs and their microenvironment	局限性与应用探索方向 Limitations and future directions
Endogenous enzymes	SOD (superoxide dismutase), CAT (catalase), GPx (glutathione peroxidase)	Basal antioxidant defense system (regulated by upstream Nrf2/Keap1 axis)	Establish the first-line antioxidant defense by scavenging superoxide anions and H_2O_2, thereby reducing testicular oxidative injury and germ cell apoptosis	Direct supplementation with purified enzymes is limited by poor stability and low transmembrane delivery efficiency; current strategies therefore favor the development of upstream targeted activators
Exogenous natural compounds	Resveratrol	SIRT1-FOXO3a axis; PGC-1α deacetylation	Protects SSCs against oxidative damage, improves epigenetic homeostasis, and optimizes spermatogenesis. Downstream transgenerational benefits may include enhanced serum antioxidant capacity, increased mitochondrial DNA copy number in offspring blastocysts, delayed telomere shortening, and potential blockade of paternal aging-associated transgenerational effects	Hydrophobic nature and low bioavailability limit its application; nanoparticle polymers such as PLGA and liposome-based delivery systems are commonly explored to improve delivery efficiency
	Melatonin	Broad-spectrum free radical scavenging; MT1/MT2 receptor-mediated signaling; Nrf2 pathway; SIRT1/MnSOD axis	Reduces lipid peroxidation products such as MDA, suppresses the Bax/Bcl-2/Caspase-3 apoptotic cascade, and markedly improves post-thaw viability of SSCs	Exhibits a dose-dependent "double-edged sword" effect; high concentrations may induce reductive stress. Future studies should explore targeted and controlled-release strategies, such as CD9-mediated delivery
	Astaxanthin	Regulation of the Bcl-2/Bax ratio	Shows superior efficacy to conventional vitamin E in improving post-thaw cell viability and total antioxidant capacity while reducing ROS accumulation	Strong lipophilicity limits broader application; it is mainly used for optimizing *in vitro* cryopreservation and culture systems
	Curcumin, quercetin	Nrf2/HO-1 pathway for curcumin; COX-2 inhibition and cAMP/PKA signaling for quercetin	Attenuates local inflammatory responses and oxidative damage, optimizes the local microenvironment, and supports testosterone synthesis	Both compounds have poor aqueous solubility and undergo extensive first-pass metabolism *in vivo*; carrier systems capable of crossing the BTB (blood-testis barrier) are urgently needed
Vitamins & trace elements	Vitamin E (α-tocopherol, e.g.), vitamin C	Interruption of lipid peroxidation chain reactions by vitamin E; electron donation and maintenance of the reduced state by vitamin C	Preserves SSC and mitochondrial membrane integrity, maintains a local reducing environment during *in vitro* culture, and supports vitamin E recycling	Their targets are relatively limited, making it difficult to achieve deep gene-level homeostatic remodeling; they are mainly used as basal supplements *in vitro* culture systems
	Se (selenium), Zn (zinc)	Essential cofactor for the GPx family for selenium; maintenance of SOD activity and stable protein conformation for zinc	Combined supplementation may reduce oxidative DNA lesions, such as 8-OHdG, suppress microenvironmental inflammation, and synergistically restore local testosterone levels	Serve primarily as basal metabolic support and should not be oversupplemented; metabolomics-guided individualized and combined supplementation strategies are needed

耗竭。然而, 考虑到直接补充外源性纯化酶存在生物稳定性较差与跨膜递送效率偏低等局限性, 目前学界更倾向于探讨如何通过激活上游信号通路(如Nrf2/Keap1轴)来内源性地上调这些酶的表达水平。

3.2 外源性天然化合物: 多靶点网络调控的探索潜力

近年来, 植物来源的外源性天然化合物因其潜在的多靶点调控特性及相对较低的毒性, 在SSCs保护研究领域受到较多关注。有别于单一的自由基清除, 该类天然产物可从多种信号通路层面实现调控作用。

以白藜芦醇为例, 作为一种非黄酮类多酚, 现有大量研究证实其能够靶向激活SIRT1信号通路。得益于优良的脂溶性, 白藜芦醇等天然抗氧化分子主要通过被动扩散(passive diffusion)的方式穿透细胞膜进入生精小管微环境[46]。在基础医学研究中, 这类小分子的跨屏障穿透与组织分布通常依赖于液相色谱–串联质谱联用(liquid chromatography-tandem mass spectrometry, LC-MS/MS)、放射性同位素示踪或偶联特异性荧光探针等药代动力学技术进行精确定量追踪[47]。在临床转化层面, 口服白藜芦醇等天然抗氧化营养补充剂, 已被探索用于特发性少弱精子症(oligo-astheno-teratozoospermia, OAT)的辅助干预[48]。现有研究证据提示, 该类补充剂适用于精索静脉曲张、环境毒物暴露、高龄诱发的轻中度氧化应激型男性不育, 可改善精液常规指标、下调精子DNA碎片率(DNA fragmentation index, DFI)[49]。动物实验结果显示: 老龄雄性小鼠补充白藜芦醇后, 小鼠子代囊胚中的线粒体DNA拷贝数得到显著回升、端粒长度得以有效延长, 这提示白藜芦醇可能有助于优化精子发生过程中的微环境氧化状态, 从而在一定程度上延缓父源衰老效应的跨代传递[8]。此外, 褪黑素作为一种兼具亲水与亲脂特性的分子, 不仅被认为能直接穿透细胞膜与线粒体膜清除自由基, 还可能通过激活Nrf2通路及结合局部广泛分布的MT1/MT2受体, 在多层次上尝试减轻SSCs、支持细胞及间质细胞的整体氧化负荷[50-52]。在体外研究中, 如SSCs的冻存复苏体系内, 添加褪黑素或虾青素(一种具有强抗氧化潜力的酮式类胡萝卜素)常被报道能帮助维持冻融后的细胞活力, 并通过调控Bcl-2/Bax值等方式抑制细胞凋亡[51,53]。同时, 槲皮素[54]等化合物也初步展现出基于各自特定靶点的抗氧化与抗炎协同潜力。

3.3 维生素与微量元素: 抗氧化网络的高效辅因子

在细胞的抗氧化网络中, 维生素与微量元素多作为必需的辅因子或结构保护剂, 保障整体防御系统的高效与稳定运转。例如, 脂溶性的维生素E(如α-生育酚)主要定位于细胞膜系统, 可通过中断脂质过氧化链式反应来保护膜结构的完整性[55]; 而水相中高效的电子供体维生素C, 则常在体外培养体系中与其他抗氧化剂联用, 协助维持局部的还原环境及维生素E的再生[56]。

在微量元素方面, 硒作为GPx家族活性中心的必需组成部分, 其缺乏易直接导致酶活性受抑, 使SSCs面临更高的氧化风险[57]。锌则在维持SOD活性及稳定蛋白质构象方面发挥基础辅助作用[58]。相关研究指出, 联合补充锌与硒等元素, 在尝试减轻环境毒物诱导的生精细胞DNA损伤[如降低8-羟基脱氧鸟苷(8-oxo-2'-deoxyguanosine, 8-OHdG)水平]及促进局部睾酮恢复方面, 表现出一定的协同干预价值[56]。

总体而言, 内源性酶类构筑了稳态的防御基石, 天然化合物尝试通过多靶点网络进行精细调控, 而维生素与微量元素则提供了不可或缺的代谢支撑。这提示在未来的干预研究中, 科学的联合应用策略可能比单一物质的补充更具前景。

4 面临的挑战与展望

尽管基于信号网络调控的抗氧化策略在延缓SSCs衰老方面展现出潜在的科学价值, 但该领域在迈向临床应用的过程中仍面临着一系列理论与技术层面的瓶颈。正视并尝试跨越这些鸿沟, 是未来研究的重要方向。

4.1 "双刃剑"效应与还原应激风险的界定

ROS在细胞内兼具生理与病理的双重属性, 这也构成了抗氧化干预的核心矛盾。过度或缺乏靶向性的强效清除, 不仅可能矫枉过正, 还可能诱发"还原应激"(reductive stress), 即细胞内还原当量(如NADH、GSH等)过度累积所导致的异常病理状态[59-60]。在SSCs中, 处于生理低水平的ROS被视为维持静息态与增殖平衡的必要信号分子。现有研究表明, 通过高剂量抗氧化干预彻底清除 ROS, 会引发多种不良后果: 不仅会抑制正常自我更新相关信号转导, 干扰自噬流的激活(低水平ROS是自噬的重要诱因), 还会阻碍内质网中蛋白质的正常氧化折叠等。因此, 学界逐渐认识到, 未来的干预策略或应从"全面清除"

的传统思路, 转向探索“氧化还原稳态的精细重塑”, 力求将ROS维持在合理的生理区间内。

4.2 突破BTB的靶向递送难题

SSCs定植于生精小管的基底区域。传统的观点往往强调BTB对药物分布的天然阻碍, 但实际上, 全身性给药的抗氧化剂若要靶向抵达SSCs微环境, 首先面临的是网状内皮系统(如肝脏中大量驻留的Kupffer细胞等巨噬细胞)对纳米颗粒的非特异性吞噬与大量清除。研究指出, 高达30%至99%的注射纳米颗粒最终会积聚并被滞留在肝脏中, 这极大地限制了其在靶组织的生物利用度[61-62]。在“逃逸”肝脏拦截后, 药物还需穿透复杂的睾丸微血管内皮屏障及管周肌样细胞层。这种多重组织学屏障导致多数游离还原性分子的靶向富集率极低。因此, 新兴的纳米靶向递送技术被认为是一种具备潜力的破局思路。

为克服上述多重生理屏障, 研究人员从多个维度对纳米递送系统的载体结构开展优化设计。首先, 在纳米颗粒表面引入细胞穿透肽(cell-penetrating peptides, CPPs)进行修饰。CPPs富含精氨酸、赖氨酸等带正电荷的氨基酸, 可通过静电相互作用结合带负电的细胞膜(如内皮屏障), 再经由直接穿透或胞吞作用(endocytosis), 依托非受体依赖途径实现高效跨膜递送[63]。其次, 针对肝脏等脏器易截留脂质纳米颗粒的问题, 现有研究普遍利用聚乙二醇化(PEGylation)修饰在载体表面构建水合空间位阻, 以此延长纳米载体在体内的血液循环半衰期[64]。在聚乙二醇化修饰的基础上, 通过偶联生殖微环境特异性的靶向肽或抗体, 能够引导纳米载体靶向富集至目标组织。考虑到血液微环境成分复杂, 研究人员多采用共价键将靶向肽稳固锚定在纳米颗粒表面的PEG链末端, 以避免靶向肽发生脱落、被提前降解。

近年来, 已有研究成功构建了靶向生精小管微环境的纳米递送系统, 为该策略治疗生殖损伤提供了有力的辅助证据。例如, 利用纳米载体负载抗氧化剂(如白藜芦醇)不仅能显著提高药物的水溶性, 还能有效降低靶器官局部脂质与蛋白质氧化水平, 保护睾丸的生理结构与生精功能[65]。同时, 新兴的仿生纳米酶(如基于锰超氧化物歧化酶的纳米材料)已被证实能够有效穿透BTB, 在小鼠模型中实现睾丸内活性氧(ROS)的靶向清除, 并在化疗诱导的睾丸损伤中表现出显著的干细胞及体细胞保护作用[66]。

在靶向睾丸递送体系的探索中, 不同类型的纳米载体展现出各自的优劣势。脂质纳米颗粒具有较高的生物相容性, 适合封装疏水性天然抗氧化分子, 但对肝脏摄取的彻底规避仍具挑战性。聚合物纳米粒(如PLGA)能够提供更优异的物理稳定性和药物持续缓释性能, 适合需长期维持微环境氧化还原稳态的干预场景。此外, 细胞外囊泡[如外泌体(exosomes)]作为新兴的内源性纳米递送载体, 因其极低的免疫原性以及能够跨越BTB传递生物信息(如RNAs与蛋白质)的天然优势, 近年来在生殖医学与精子发生的调控研究中备受关注[67]。然而, 外泌体的提取纯化工艺复杂、批次异质性高, 仍限制了其大规模的工程化应用。尽管纳米靶向策略在动物实验中初步展示出优化抗氧化干预的效果, 但其在人体的长期安全性和靶向转化效率仍需更为严谨的临床前评估[68]。

4.3 证据转化的鸿沟与广泛病理场景的拓展探索

当前关于抗氧化剂保护SSCs的机制证据多源于经化学诱导或辐射构建的啮齿类动物模型。然而, 人类与小鼠在睾丸解剖结构、干细胞代谢动力学及物种寿命上存在显著差异。在小鼠模型中验证为安全有效的剂量, 直接外推至人体时可能面临生物利用度不足或因长期累积而产生毒性的风险。同时, 现有关于抗氧化剂干预的临床观察多以精液参数(如浓度、活力)为主要终点, 这反应的是已完成分化精子的状态, 学界尚缺乏直接证实抗氧化剂能有效延缓人类SSCs自身功能衰竭的坚实证据[16,69]。

面对衰老相关及特发性男性不育高度异质性的病因, 将靶向抗氧化策略的适应症仅仅局限于“自然衰老”是远远不够的。未来的基础研究与临床转化更应结合广泛的复杂病理状态进行探索。大量研究表明, 环境污染物(如内分泌干扰物邻苯二甲酸酯类、微塑料、重金属等)的长期暴露会诱发生精小管内微环境的严重氧化应激与脂质过氧化, 破坏相关氧化酶的活性平衡[70-71]。同时, 医源性损伤(如癌症化疗药物白消安、睾丸局部放疗)以及先天性或解剖性缺陷(如精索静脉曲张)均能引发睾丸微环境的剧烈代谢改变与不可逆退化[72-73]。在上述复杂的病理场景下, 采用纳米载体靶向递送还原型小分子化合物(如白藜芦醇、番茄红素或褪黑素), 不仅能单纯清除自由基, 更能有效干预线粒体离子的异常动态变化, 从而恢复SSCs的干性储备与自我更新能力[72]。因此,

未来的个体化干预策略需结合代谢组学等先进手段，深入描绘不同病理暴露下的线粒体动态代谢图谱，以期实现更加精准的靶向重塑与生殖健康管理。

5 结论

精原干细胞(SSCs)自我更新与分化稳态的维持，被普遍视为维系男性终身生育力的核心基础。现有证据提示，由过量ROS诱发介导的SSCs及其内部微环境功能障碍，是驱动男性生殖系统衰老的重要病理机制之一。持续的氧化应激不仅可直接引发细胞内大分子损伤，更可通过诱发线粒体功能衰退与支持细胞等微环境功能的恶化，形成一个不断自我放大的病理循环，最终可能导致SSCs的耗竭与生精能力的不可逆下降。

本文尝试梳理了抗氧化干预在延缓SSCs衰老方面的分子网络与靶向策略。综合当前研究提示，抗氧化剂的生殖保护效应往往并非局限于单一的自由基清除，而是深度依赖于Nrf2/Keap1/ARE防御轴、SIRT1/FOXO表观遗传切换以及PI3K/Akt/mTOR代谢调控等关键信号通路的串扰与互作。这些通路相互交织，协同调节受损线粒体自噬与细胞凋亡之间的动态平衡，共同决定了SSCs在氧化压力下的最终命运。在具体的干预应用层面，内源性抗氧化酶类、具有多靶点潜力的天然化合物，以及作为辅因子的维生素与微量元素，共同构筑了相互补充的稳态防御网络。

然而，将抗氧化策略有效应用于男性生殖健康与衰老管理仍面临客观的转化挑战。ROS兼具生理信号分子的“双刃剑”特性，提示未来的干预思路或许应从传统的“绝对清除”向“氧化还原稳态精细重塑”作审慎转变；同时，BTB对药物分布的天然阻碍，也亟待纳米靶向递送等新兴技术的实质性突破。综上所述，基于信号网络调控的抗氧化干预在理论上展现出了一定的生殖保护潜力，但从基础实验走向临床应用仍有较长距离。未来，仍呼唤学界通过开发更具人类生理相关性的动物模型与高质量的临床循证研究，进一步解析氧化还原动态网络，验证纳米靶向递送的长期安全性与有效性，以期为衰老相关的男性生育力下降提供更为科学、精准与个体化的应对参考。

作者贡献

仇星云：负责文章的总体构思、文献检索与筛选、数据/图表整合设计，以及论文初稿撰写。樊怡、刘棒：参与文献的补充查阅、资料信息的梳理归纳，以及论文部分章节的讨论与修改排版。周戴：负责综述主题的确定与框架设计、指导文章的撰写方向、对核心内容进行关键性的严格审阅与修改，并对最终稿件进行确认和定稿。

参考文献 (References)

[1] DIAO L, TUREK P J, JOHN C M, et al. Roles of spermatogonial stem cells in spermatogenesis andfertility restoration [J]. Front Endocrinol, 2022, 13: 895528.

[2] ZHANG Y X, DU Y Z, LE W D, et al. Redox control of the survival of healthy and diseased cells [J]. Antioxid Redox Signal, 2011, 15(11): 2867-908.

[3] CIRCU M L, AW T Y. Reactive oxygen species, cellular redox systems, and apoptosis [J]. Free Radic Biol Med, 2010, 48(6): 749-62.

[4] SINENKO S A, STARKOVA T Y, KUZMIN A A, et al. Physiological signaling functions of reactive oxygen species in stem cells: from flies to man [J]. Front Cell Dev Biol, 2021, 9: 714370.

[5] MURPHY M P. How mitochondria produce reactive oxygen species [J]. Biochem J, 2009, 417(1): 1-13.

[6] KRACUN D, LOPES L R, CIFUENTES-PAGANO E, et al. NADPH oxidases: redox regulation of cell homeostasis and disease [J]. Physiol Rev, 2025, 105(3): 1291-428.

[7] REN F, WANG K, ZHANG T, et al. New insights into redox regulation of stem cell self-renewal and differentiation [J]. Biochim Biophys Acta, 2015, 1850(8): 1518-26.

[8] TERAMOTO N, OKADA Y, ABURADA N, et al. Resveratrol intake by males increased the mitochondrial DNA copy number and telomere length of blastocysts derived from aged mice [J]. J Reprod Dev, 2024, 70(4): 247-53.

[9] DEMASI M, AUGUSTO O, BECHARA E J H, et al. Oxidative modification of proteins: from damage to catalysis, signaling, and beyond [J]. Antioxid Redox Signal, 2021, 35(12): 1016-80.

[10] SUN D Y, WANG L F, WU Y F, et al. Lipid metabolism in ferroptosis: mechanistic insights and therapeutic potential [J]. Front Immunol, 2025, 16: 1545339.

[11] YUAN W Z, SUN Z B, JI G G, et al. Emerging roles of ferroptosis in male reproductive diseases [J]. Cell Death Discov, 2023, 9(1): 358.

[12] YANG X, CHEN Y H, SONG W X, et al. Review of the role of ferroptosis in testicular function [J]. Nutrients, 2022, 14(24): 5268.

[13] COSTA J, BRAGA P C, REBELO I, et al. Mitochondria quality control and male fertility [J]. Biology, 2023, 12(6): 827.

[14] MOUSTAKLI E, GRIGORIADIS T, STAVROS S, et al. Artificial intelligence in assessing reproductive aging: role of mitochondria, oxidative stress, and telomere biology [J]. Diagnostics, 2025, 15(16): 2075.

[15] XU X Y, PANG Y, FAN X Q. Mitochondria in oxidative stress, inflammation and aging: from mechanisms to therapeutic advances [J]. Signal Transduct Target Ther, 2025, 10(1): 190.

[16] XIA K, LUO P, YU J J, et al. Single-cell RNA sequencing reveals

transcriptomic landscape and potential targets for human testicular ageing [J]. Hum Reprod, 2024, 39(10): 2189-209.

[17] ZHU W Z, YUAN Y J, LIAO G N, et al. Mesenchymal stem cells ameliorate hyperglycemia-induced endothelial injury through modulation of mitophagy [J]. Cell Death Dis, 2018, 9(8): 837.

[18] ZHANG D C, CHEN R, CAI Y H, et al. Hyperactive reactive oxygen species impair function of porcine Sertoli cells via suppression of surface protein ITGB1 and connexin-43 [J]. Zool Res, 2020, 41(2): 203-7.

[19] MAO B P, BU T, MRUK D, et al. Modulating the blood-testis barrier towards increasing drug delivery [J]. Trends Pharmacol Sci, 2020, 41(10): 690-700.

[20] LI J, GAO L, CHEN J, et al. Mitochondrial ROS-mediated ribosome stalling and GCN2 activation are partially involved in 1-nitropyrene-induced steroidogenic inhibition in testes [J]. Environ Int, 2022, 167: 107393.

[21] SAWAIED A, LEVY B E, ARAZI E, et al. Follicle-stimulating hormone and testosterone play a role in the regulation of Sertoli cell functions following germ cell depletion *in vitro* [J]. Int J Mol Sci, 2025, 26(6): 2702.

[22] SENOS DEMARCO R, JONES D L. Redox signaling as a modulator of germline stem cell behavior: implications for regenerative medicine [J]. Free Radic Biol Med, 2021, 166: 67-72.

[23] 李珊珊, 陈忠云, 李婧, 等. Keap1/Nrf2/ARE信号通路在中枢神经系统疾病中的研究进展[J]. 中国全科医学(LI S S, CHEN Z Y, LI J, et al. Research progress on the role of Keap1/Nrf2/ARE signaling pathway in central nervous system diseases [J]. Chinese General Practice), 2014, 17(30): 3641-4.

[24] SIGNORINI C, SASO L, GHAREGHOMI S, et al. Redox homeostasis and Nrf2-regulated mechanisms are relevant to male infertility [J]. Antioxidants, 2024, 13(2): 193.

[25] KUMAR A, RAMANARAYANAN S. Redox homeostasis and therapeutic modulation: the central role of oxidative stress and nuclear factor erythroid 2-related factor 2(Nrf2) activation in systemic diseases and reproductive dysfunction [J]. Can J Physiol Pharmacol, 2026, 104: 1-29.

[26] 王泽, 于涵, 焦磊, 等. 萝卜硫素通过增强抗氧化能力抑制髓核细胞铁死亡[J]. 解放军医学院学报(WANG Z, YU L, JIAO L, et al. Sulforaphane inhibits ferroptosis in nucleus pulposus cells by enhancing antioxidant capacity [J]. Academic Journal of Chinese PLA Medical School), 2025, 46(4): 354-61.

[27] HEMATI U, MOSHAJARI M, JALALI M F, et al. The effect of curcumin on NRF2/Keap1 signalling pathway in the epididymis of mouse experimental cryptorchidism [J]. Andrologia, 2022, 54(10): e14532.

[28] ABDULKHALIQ A A, ALASIRI G, KHAN J, et al. SIRT1 in aging and diseases [J]. J Cell Biochem, 2025, 126(10): e70069.

[29] HWANG J W, YAO H, CAITO S, et al. Redox regulation of SIRT1 in inflammation and cellular senescence [J]. Free Radic Biol Med, 2013, 61: 95-110.

[30] CHEN J Y, LIU B Y, YAO X L, et al. AMPK/SIRT1/PGC-1alpha signaling pathway: molecular mechanisms and targeted strategies from energy homeostasis regulation to disease therapy [J]. CNS Neurosci Ther, 2025, 31(11): e70657.

[31] WANG X B, ZHU L, HUANG J, et al. Resveratrol-induced augmentation of telomerase activity delays senescence of endothelial progenitor cells [J]. Chin Med J, 2011, 124(24): 4310-5.

[32] YANG L L, LIAO J Y, HUANG H Y, et al. Stage-specific regulation of undifferentiated spermatogonia by AKT1S1-mediated AKT-mTORC1 signaling during mouse spermatogenesis [J]. Dev Biol, 2024, 509: 11-27.

[33] HOBBS R M, LA H M, MAKELA J A, et al. Distinct germline progenitor subsets defined through Tsc2-mTORC1 signaling [J]. EMBO Rep, 2015, 16(4): 467-80.

[34] HATMAL M M, ABUYAMAN O, AL-HATAMLEH M A I, et al. Influence of OCT2 gene variants on metformin efficacy in type 2 diabetes: insights into pharmacogenomics and drug interactions [J]. J Transl Med, 2025, 23(1): 884.

[35] KOFMAN A E, MCGRAW M R, PAYNE C J. Rapamycin increases oxidative stress response gene expression in adult stem cells [J]. Aging, 2012, 4(4): 279-89.

[36] MENG J, CHEN Y H, WANG J Z, et al. EGCG protects vascular endothelial cells from oxidative stress-induced damage by targeting the autophagy-dependent PI3K-AKT-mTOR pathway [J]. Ann Transl Med, 2020, 8(5): 200.

[37] RICCI J E, GOTTLIEB R A, GREEN D R. Caspase-mediated loss of mitochondrial function and generation of reactive oxygen species during apoptosis [J]. J Cell Biol, 2003, 160(1): 65-75.

[38] LUCHETTI F, CARLONI S, NASONI M G, et al. Tunneling nanotubes and mesenchymal stem cells: new insights into the role of melatonin in neuronal recovery [J]. J Pineal Res, 2022, 73(1): e12800.

[39] TANEL A, AVERILL-BATES D A. Inhibition of acrolein-induced apoptosis by the antioxidant N-acetylcysteine [J]. J Pharmacol Exp Ther, 2007, 321(1): 73-83.

[40] LEE I H. Mechanisms and disease implications of sirtuin-mediated autophagic regulation [J]. Exp Mol Med, 2019, 51(9): 1-11.

[41] DARVEKAR S R, ELVENES J, BRENNE H B, et al. SPBP is a sulforaphane induced transcriptional coactivator of NRF2 regulating expression of the autophagy receptor p62/SQSTM1 [J]. PLoS One, 2014, 9(1): e85262.

[42] PIETROCOLA F, LACHKAR S, ENOT D P, et al. Spermidine induces autophagy by inhibiting the acetyltransferase EP300 [J]. Cell Death Differ, 2015, 22(3): 509-16.

[43] YAN F, ZHAO Q, LI Y, et al. The role of oxidative stress in ovarian aging: a review [J]. J Ovarian Res, 2022, 15(1): 100.

[44] OBEME-NMOM J I, ABIOYE R O, REYES F S S, et al. Regulation of redox enzymes by nutraceuticals: a review of the roles of antioxidant polyphenols and peptides [J]. Food Funct, 2024, 15(22): 10956-80.

[45] ISHII T, MATSUKI S, IUCHI Y, et al. Accelerated impairment of spermatogenic cells in SOD1-knockout mice under heat stress [J]. Free Radic Res, 2005, 39(7): 697-705.

[46] GAMBINI J, INGLES M, OLASO G, et al. Properties of resveratrol: *in vitro* and *in vivo* studies about metabolism, bioavailability, and biological effects in animal models and humans [J]. Oxid Med Cell Longev, 2015, 2015: 837042.

[47] AZORIN-ORTUNO M, YANEZ-GASCON M J, PALLARES F J, et al. Pharmacokinetic study of trans-resveratrol in adult pigs [J]. J Agric Food Chem, 2010, 58(20): 11165-71.

[48] MONGIOI L M, PERELLI S, CONDORELLI R A, et al. The role of resveratrol in human male fertility [J]. Molecules, 2021, 26(9): 2495.

[49] SMITS R M, MACKENZIE-PROCTOR R, YAZDANI A, et al.

Antioxidants for male subfertility [J]. Cochrane Database Syst Rev, 2019, 3: Cd007411.

[50] CARLONI S, NASONI M G, PERRONE S, et al. Melatonin and mitochondrial function: insights into bioenergetics, dynamics, and gene regulation [J]. Biocell, 2026, 50(2): 1-22.

[51] HEIDARIZADI S, RASHIDI Z, JALILI C, et al. Melatonin protects mouse type A spermatogonial stem cells against oxidative stress via the mitochondrial thioredoxin system [J]. Cell J, 2023, 25(11): 741-52.

[52] FENG T Y, LI Q, REN F, et al. Melatonin protects goat spermatogonial stem cells against oxidative damage during cryopreservation by improving antioxidant capacity and inhibiting mitochondrial apoptosis pathway [J]. Oxid Med Cell Longev, 2020, 2020: 5954635.

[53] FATHI S, NAZARI H, ARABI M, et al. The antioxidant capacity and protective ability of astaxanthin in cryopreservation of mouse spermatogonial stem cells [J]. Cryobiology, 2025, 120: 105261.

[54] FAGHANI M, ALIJANI M, ESMAEILI-B A, et al. Quercetin ameliorates nicotine-induced spermatogenesis damage via modulation of sperm miR-151a-5p and testicular Cep72 gene expression [J]. Basic Clin Androl, 2025, 35(1): 40.

[55] MAGUIRE J J, WILSON D S, PACKER L. Mitochondrial electron transport-linked tocopheroxyl radical reduction [J]. J Biol Chem, 1989, 264(36): 21462-5.

[56] SAID L, BANNI M, KERKENI A, et al. Influence of combined treatment with zinc and selenium on cadmium induced testicular pathophysiology in rat [J]. Food Chem Toxicol, 2010, 48(10): 2759-65.

[57] GUERRIERO G, TROCCHIA S, ABDEL-GAWAD F K, et al. Roles of reactive oxygen species in the spermatogenesis regulation [J]. Front Endocrinol, 2014, 5: 56.

[58] SHARIF R, THOMAS P, ZALEWSKI P D, et al. The role of zinc in genomic stability [J]. Mutat Res, 2012, 733: 111-21.

[59] YANG R H, GUO Z H, LI B H. NADH reductive stress drives metabolic reprogramming [J]. Trends Cell Biol, 2026, 36(3): 177-89.

[60] MOUSTAKLI E, CHRISTOPOULOS P, POTIRIS A, et al. Reductive stress and the role of antioxidants in male infertility: a narrative review [J]. Arch Gynecol Obstet, 2025, 312(5): 1503-14.

[61] CHEN Y N, LI M Q, ZHANG H J, et al. Nanoparticle-based drug delivery systems: a promising approach for the treatment of liver fibrosis [J]. Int J Pharm X, 2025, doi: 10.1016/j.ijpx.2025.100411.

[62] HE Y X, WANG Y F, WANG L, et al. Understanding nanoparticle-liver interactions in nanomedicine [J]. Expert Opin Drug Deliv, 2024, 21(6): 829-43.

[63] HAO M L, ZHANG L, CHEN P. Membrane internalization mechanisms and design strategies of arginine-rich cell-penetrating peptides [J]. Int J Mol Sci, 2022, 23(16): 9038.

[64] GUIDOTTI G, BRAMBILLA L, ROSSI D. Cell-penetrating peptides: from basic research to clinics [J]. Trends Pharmacol Sci, 2017, 38(4): 406-24.

[65] ALFAWAZ M, ELMORSY E M, ALSHAMMARI A N, et al. Nanoparticle-based delivery of resveratrol suppresses Ehrlich ascites carcinoma and protects testicular function via antioxidant, anti-angiogenic, anti-inflammatory, and pro-apoptotic mechanisms [J]. Biomolecules, 2025, 15(11): 1605.

[66] AN C L, SUN J F, MA A, et al. Biomimetic nanotechnology overcoming the blood-testis barrier for testicular protection in chemotherapy [J]. Biomater Res, 2026, 30: 0314.

[67] CHEN C, ZHANG Z H, GU X, et al. Exosomes: new regulators of reproductive development [J]. Mater Today Bio, 2023, 19: 100608.

[68] LI C Y, LIU S P, DAI X F, et al. The emerging role of exosomes in the development of testicular [J]. Asian J Androl, 2023, 25(5): 547-55.

[69] FANG F, LI Z L, ZHAO Q, et al. Human induced pluripotent stem cells and male infertility: an overview of current progress and perspectives [J]. Hum Reprod, 2018, 33(2): 188-95.

[70] ZHAO Y, BAO R K, ZHU S Y, et al. Lycopene prevents DEHP-induced hepatic oxidative stress damage by crosstalk between AHR-Nrf2 pathway [J]. Environ Pollut, 2021, 285: 117080.

[71] DEHDARI E N, PARSA S, NOZARI F, et al. Protective effects of melatonin against the toxic effects of environmental pollutants and heavy metals on testicular tissue: a systematic review and meta-analysis of animal studies [J]. Front Endocrinol, 2023, 14: 1119553.

[72] ALLEN C M, LOPES F, MITCHELL R T, et al. Can antioxidants protect against chemotherapy in a rat spermatogonial stem cell line [J]? Reprod Fertil, 2021, 2(4): L7-L9.

[73] CUI Y H, REN L P, LI B, et al. Melatonin relieves busulfan-induced spermatogonial stem cell apoptosis of mouse testis by inhibiting endoplasmic reticulum stress [J]. Cell Physiol Biochem, 2017, 44(6): 2407-21.