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Commentary

New strategy against sperm oxidative damage: supplementing NaHS to enhance the activity of the H_2S antioxidant pathway mediated by E3 ubiquitin ligase ASB1

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Oxidative stress refers to a condition in which the antioxidant defense system of cells is overwhelmed, unable to eliminate the excessive production of reactive oxygen species (ROS). While ROS are essential for various cellular processes, they become disruptive at elevated concentrations [1]. This stress can lead to sperm dysfunction, which is a primary cause of male infertility due to its detrimental effects on both the structural and functional integrity of sperm. DNA damage, largely caused by oxidative stress, is a major contributor to sperm functional deficits [2, 3]. Sperm cells are particularly sensitive to oxidative stress because of their limited antioxidant defenses and rudimentary mechanisms for detecting and repairing DNA damage. Although substantial research has focused on the negative effects of oxidative stress during spermatogenesis, many aspects of potential intervention targets remain poorly understood.

Ubiquitination is a common form of post-translational modification of proteins [4]. While extensive research has highlighted the critical role of E3 ubiquitin ligases in spermatogenesis, their involvement in the oxidative stress response in sperm remains largely unexplored [5-7]. In a recent study [8], Lv et al. demonstrated that knockout (KO) of the E3 ubiquitin ligase ASB1 in mouse testes results in increased levels of ROS and DNA damage in sperm. This damage further impairs spermatid nuclear shaping and leads to oligospermia, asthenospermia, and teratospermia in *Asb1*-KO mice. Using this KO mouse model, the researchers elucidated the role of ASB1 in the male reproductive system and proposed a novel mechanism in which protein ubiquitination regulates oxidative stress during spermatogenesis.

Although hydrogen sulfide (H_2S) is commonly regarded as a hazardous gas with a distinct rotten egg odor, it also functions as an antioxidant by neutralizing reactive oxygen species (ROS) within cells, thereby protecting them from oxidative damage [9]. The sulfide-quinone oxidoreductase (SQOR) is crucial for maintaining H_2S homeostasis [10]. Through mass spectrometry analysis of ASB1-interacting proteins, Lv et al. demonstrated that ASB1 interacts with SQOR. Further investigation revealed that ASB1 facilitates the formation of K48-linked ubiquitin chains at the SQOR K207 and K344 sites, promoting its degradation via the ubiquitin-proteasome pathway. Additionally, supplementation with the H_2S donor NaHS significantly reversed the fertility defects observed in *Asb1*-KO mice.

The authors have, for the first time, demonstrated that the ubiquitin-mediated degradation of SQOR by ASB1 plays a critical role in mitigating

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oxidative stress damage in sperm. Additionally, they identified H_2S supplementation as an effective strategy to address spermatogenic disorders caused by oxidative stress. This study provides a new theoretical foundation for the clinical diagnosis and treatment of male infertility.

Disclosure of conflict of interest

None.

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