Review Article

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The Association of Oxidative Stress and Reactive Oxygen Species Modulator 1 (ROMO1) with Infertility: A Mini Review

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Infertility is one of the disorders that worries many couples around the world, although novel and molecular methods can be used to cure this disease in different stages. One of the factors that causes infertility in men and women is the increased oxidative stress within the cells, which can lead to damage in zygote formation. ROMO1 is one of the most important proteins in the production of reactive oxygen species. This protein can enhance oxidative stress in the cells and body through cellular pathways, such as TNF-α and NF-κB routes, which will eventually lead to many diseases, especially infertility. We engage several international databases by using keywords; ROMO1, Infertility, and Reactive Oxygen Species, and gained a great quantity of information about ROMO1, Infertility, and Oxidative Stress. Although not proven, it is hypothesized that ROMO1 might elevate oxidative stress by activating NF-κB pathway in the cells, furthermore, TNF-α can arouse ROMO1 that can end up with apoptosis and cell death, which consequently can have a lot of disturbing effects on the body, especially the reproductive system. To sum up, revealing the exact cellular and molecular mechanisms of ROMO1-dependent TNF-α and NF-κB pathways in the pathogenesis of infertility might find interesting therapeutic and management strategies for this disorder.

Key Words: *Reactive Oxygen Species modulator 1; Infertility; Reactive Oxygen Species*

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INTRODUCTION

Infertility is the inability to conceive after one year of unprotected and normal sexual intercourse.[1] There is no denying that biological systems rely on maintenance of equilibrium.[2] In the female and male reproductive system, oxidative stress equilibrium is pivotal to fertility. Reactive oxygen species (ROS) have functional contributions at well-suited amounts, but can be destructive if they get out of control.[2] It is important to understand the exact pathways of oxidative stress, and their relationship with infertility.

Moderate amounts of ROS have crucial tasks in the reproductive system, such as oocyte maturation, folliculogenesis, embryogenesis, fetoplacental development, spermatogenesis, corpus luteum, and uterine function.[3] However, many studies have stated that the imbalance between antioxidants and oxidants have pathogenic effects on female and male reproductive system, which eventually end up causing reproductive system maladies, like infertility.[3,4]

There is no doubt that oxidative stress is associated with an inequality between ROS, like $O2^{-}$ or H2O2 and antioxidants, which are discarded using some pathways.[5] It is accepted that ROS is produced by different routes, like the electron transfer chain in the mitochondria, and also, some of oxidant molecules are formed by cellular aerobic pathways.[5] In addition, external agents, for stance chemicals and radiations contribute to produce ROS.[6] Subsequently, the accumulation of oxidant molecules, such as ROS leads

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to the cell and organ damage. However, when these oxidants are at equilibrium amounts within the cells, they have beneficial impacts on the body.[7] To illustrate, ROS and RNS are constructed by the host defense immune system cells, specifically phagocytes and neutrophils, and are engaged to remove many microorganisms.[7,8] Moreover, free radicals can be made by non-phagocytic NADPH oxidase isoforms; which in turn, can play a critical regulatory role in signaling pathways in different cell types, such as fibroblasts, cardiac myocytes, thyroid tissue, vascular smooth muscle cells, and endothelial cells.[7,9]

Reactive oxygen species modulator 1 (ROMO1) is a determining protein that found in the mitochondria inner membrane. ROMO1 motivates the production of ROS in the mitochondria, especially in the cells that have a high metabolism, such as sperm cells.[6] In 2006, Lee et al.[10] conducted research on ROMO1 in cancerous tissues and proved that this mitochondrial protein could cause drug and chemotherapy resistance.[11] On the other hand, it has been shown that ROMO1 can interact with various cellular and molecular pathways within the cell and be involved in the overproduction of ROS.[6]

For this reason, in the following sections of this review article, the role of ROMO1 in the production of ROS, and its association with oxidative stress and pathogenesis of infertility will be discussed.

In this overview, we use various international databases, such as Web of sciences, Scopus, Pubmed, and Google scholar. By using keywords 'Reactive Oxygen Species Modulator 1' OR 'ROMO1' AND 'Infertility' AND 'Reactive Oxygen Species' OR 'ROS' OR 'Oxidative Stress'. The consequential information about ROMO1, and also its related signaling pathways to oxidative stress and infertility was collected.

OXIDATIVE STRESS AND REPRODUCTIVE SYSTEM

Oxidative stress, because of its pivotal functions in the cells and signaling routes, can cause various diseases, especially reproductive system disorders, neoplasm, rheumatoid arthritis, osteoarthritis, retinal damage, atherosclerosis, and neurodegenerative diseases including Huntington's disease, Alzheimer's disease, and Parkinson's disease.[12-21] The reactive species within the cells can increase oxidative stress and these oxidant molecules might directly or indirectly cause crucial molecule damage, such as to DNA or some types of macromolecules, like imperative proteins. Ultimately, this damage to various parts of cells and tissues results in many disorders.[12,22-24]

Oxygen species and control of ROS and RNS by antioxidants contribute to the physiological processes of the reproductive system.[2] Physiological amounts of oxygen species play an important role, by some signal transduction routes, during uterine function, corpus luteum, folliculogenesis, testis function, spermatogenesis, oocyte maturation, fetoplacental development, embryogenesis, and embryonic implantation. Imbalances between the production of oxidants and antioxidants are responsible for the beginning and development of pathological processes that affect both female and male reproductive systems, especially infertility.[25-27]

One of the most consequential factors has been identified that affects fertility status is oxidative stress. Based on the previous research, scientists have proven that smoking causes oxidative stress, and this increased oxidative stress has a significant impact on decreased sperm count, enhanced axonemal damage, and increment sperm DNA fragmentation.[4] Several other studies have also shown the connection between oxidative stress and fertility complications. It has been proven that decreased antioxidant status enhances the risk of spontaneous abortion and infertility.[12,28] Furthermore, ROSs have been identified as a factor that can affect the development of premature rupture of the fetal membranes and initiating preeclampsia.[3]

ROMO1, OXIDATIVE STRESS AND INFERTILITY

ROMO1 is one of the most consequential proteins in the production of ROS. Structurally, this regulatory protein is related to several central proteins in the mitochondrial inner membrane, and also has two membrane domains (TMDs). One of these domains include an alpha helix, and the other is connected to the alpha helix by a base loop. Moreover, TMD2 has several polar amino acids, such as T59, S63, T69, K58, Q62, and T66.[6]

Much evidence has proven that ROMO1 is a ROS-producing protein in the cells.[29] It has also been involved in the proliferation and invasion of cancerous cells. Similarly, ROMO1-induced ROS leads to metastasis, proliferation, and growth of cancerous cells by different signaling pathways.[30] Subsequently, ROMO1-produced ROS launches cell proliferation through some agents, like transforming growth factor-β (TGF-β) and its downstream factors, which include Smad 2/3 protein, the extracellular-signal-regulated kinase (ERK) pathway, extra cellular matrix (ECM) and epithelial to mesenchymal transition (EMT) agents. As a result, ROMO1 surely affect various signaling routes in the cells.[30-34]

ROMO1 can affect the nuclear factor kappa-light-chain-enhancer of the activated B cells (NF-κB) pathway through two important directions. One of the pathways is to produce ROS via overexpression of ROMO1, and the other way is to increase the activity of κB kinase through controlling and degrading the κB kinase inhibitor by overactivation of ROMO1. Subsequently, the NF-κB translocates into the nucleus and triggers the expression of proinflammatory genes, like IL-6, Pro-IL1β, and NLR family pyrin domain containing 3 (NLRP3) and motivates inflammasome complex, which ultimately causes inflammation in the cells, and also actuates metastasis, proliferation, and invasion in cancerous cells.[31,35] Furthermore, the NF-κB induces the expression of factors involved in EMT signaling pathway such as, Zinc finger protein SNAIL1, 2, which will sub-

sequently activate the inflammasome complex, additionally leading to invasion, metastasis, and proliferation through degrading cell-cell connection and cell adhesion to various agents.[35,36] In a word, ROMO1 induces the NF-κB pathway via production of ROS and arousing of κB kinase, which finally enhances oxidative stress, inflammation, and cytokine storm in the cells, and eventually causes reproductive system damage (Fig. 1).

In addition, one of the most consequential mediators and molecules in inflammation is Tumor necrosis factor-alpha (TNF-α). There are two important pathways in TNF-α signaling route, called complex I and II.[36] Complex 1 can arouse mitogen-activated protein kinase (MAPK) and NF-κB that finally ends up causing inflammation and oxidative stress. Another route results in apoptosis and cell death through the induction of complex II where in overproduction of ROS occurs. According to the research, ROMO1 can be a mediator between TNF-α and motivation of apoptosis pathway. There are crucial components in complex II, including Fas-associated death domain protein (FADD), TNF receptor-associated protein with death domain (TRADD), pro-caspase-8, TNF receptor-associated factor 2 (TRAF2), receptor interacting protein 1 (RIP1), which activate ROMO1 via binding to C-terminal of ROMO1. Then, ROMO1 through B-cell lymphoma-extra large (Bcl-XL), reduces the mitochondrial membrane potential, which leads to the overproduction of ROS. Afterwards, ROMO1-induced ROS results in the releasing of cytochrome C from the mitochondria which play a critical role in cell death and apoptosis by the provoking of kinases like c-Jun N-terminal kinase (JNK), apoptosis regulating kinase 1 (ASK1) and p38, which eventually results in cellular apoptosis and cell death. To sum up, TNF-α induces MAPK and NF-κB pathways by Complex 1, which will subsequently enhance oxidative stress and inflammation. On the other hand, the components of TNF-α complex II can produce ROMO1-induced ROS that finally end up causing cell death and apoptosis, therefor, TNF-α eventually causes reproductive system damage (Fig. 2).[36-40]

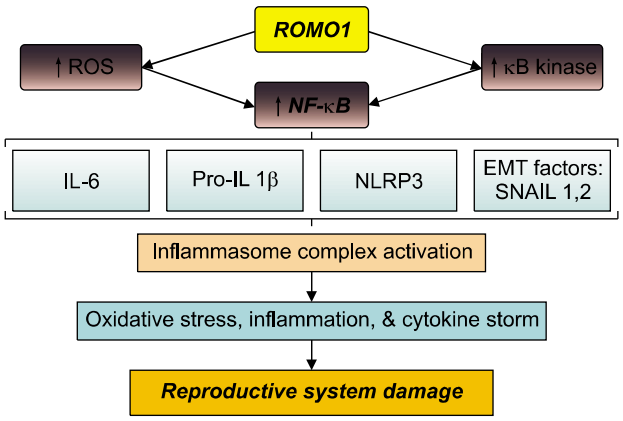

FIG. 1. This figure shows that ROMO1 can arouse the NF-κB pathway by overproduction of ROS and activating of κB kinase, which results in inflammasome complex activation and reproductive system damage.

Another point worth noting is that ROMO1 contributes to several cellular pathways, especially NF-κB and TNF-α routes.[37] As mentioned before, when ROMO1 activity increases, NF-κB can activate the expression of several proinflammatory genes that are associated with oxidative stress and inflammation in the cells.[36,37] Additionally, TNF-α overproduce of ROMO1-induced ROS and oxidative stress in the cells, in addition to mutations in the genomes,

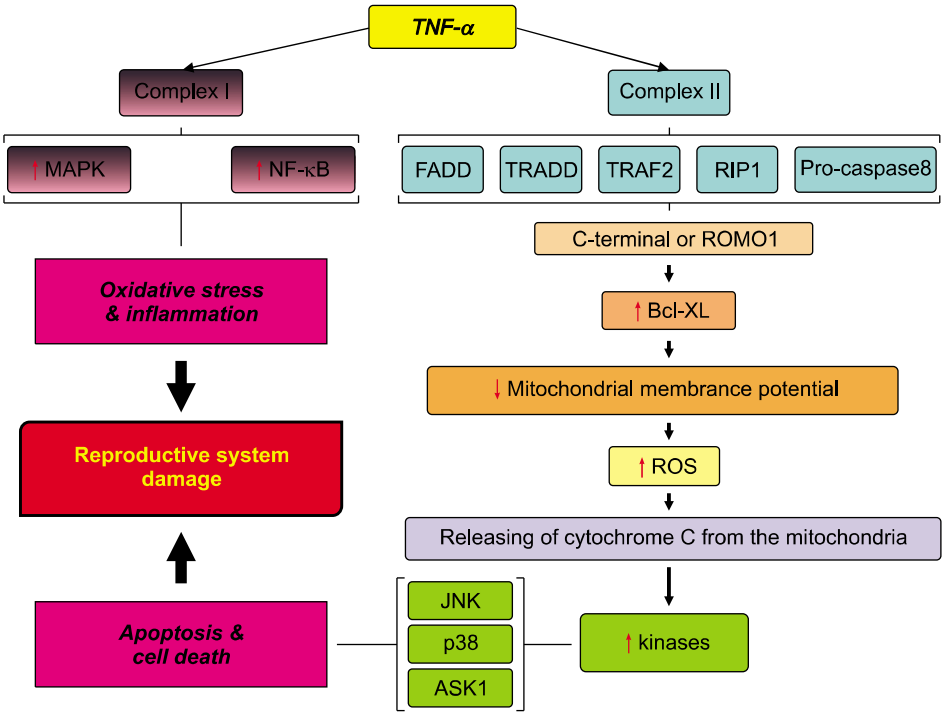

FIG. 2. This figure shows that TNF-α can activate the NF-κB and MAPK which enhances oxidative stress and inflammation via complex I, and also causes overactivation of ROMO1 by complex II, which finally ends up cell death, apoptosis, and reproductive system damage.

leads to cell and tissue damage, especially in male and female reproductive system.[36,38]

In 2019, Abdillah et al.[41] conducted a study on the protective effects of Iodixanol on sperm cryopreservation and showed that Iodixanol can reduce the expression of ROMO1 and pro-apoptotic genes, which in turn will improve protamine level and reduce reactive oxygen species of canine sperm. Similarly, in 2020, Qamar et al.[42] carried out research on the protective effects of kinetin supplementation on the post-thaw motility, viability, and structural integrity of dog sperm and proved that kinetin supplementation could decrease the expression of ROMO1 and pro-apoptotic genes, such as BCL2-associated X, BAX which would eventually reduce oxidative stress and improving the post-thaw quality of dog semen. Moreover, in 2021, Da Luz et al.[43] have done a study on altered transcriptome in cumulus cells of infertile women with advanced endometriosis with and without endometria and showed that ROMO1 expression in these patients had a significant increase, and also oxidative stress was elevated within the cells, and also proved that using antioxidant supplements can reduce the expression of ROMO1 and oxidative stress.

As mentioned before, this protein is found to be evaluated in many other diseases, such as neoplasm, and its association with various cellular pathways has been demonstrated. For example, in 2015, a study by Lee et al.[44] identified that ROMO1 is an upstream gene in the invasive and metastatic process of hepatocellular carcinoma (HCC). They showed that this protein activates the NF-κB pathway as a proinflammatory route, which induces oxidative stress-induced tumor cell invasion. Moreover, in 2019, Amini et al.[45] conducted a study on the tissue and serum of patients with gastric cancer and showed that the ROMO1 gene expression in cancer tissue had significantly increased, and also the oxidative stress parameters in the serum of these patients compared to the control group was greatly elevated.

In short, according to these studies, this consequential mitochondrial protein can produce ROS under normal cell conditions, and maintain oxidative stress at a basal and beneficial levels within the cells.[6] However, when the expression of ROMO1 increases, it can enhance oxidative stress, inflammation, and cell death through NF-κB and TNF-α pathways, and consequently cause cell and tissue damage, which will eventually lead to the onset and exacerbation of many diseases, especially infertility.

CONCLUSIONS

In conclusion, ROMO1 is one of the most pivotal proteins within the mitochondrial inner membrane, which is associated with several crucial proteins and signaling pathways, especially the TNF-α and NF-κB routes. These pathways play a central role in oxidative stress and inflammation. For this reason, it is hypothesized that ROMO1 might directly or indirectly induce oxidative stress by activating NF-κB pathway. On the other hand, TNF-α can motivate ROMO1 that result in apoptosis and cell death, which consequently can have a lot of disturbing effects. In a word, understanding the precise regulatory role of ROMO1, in the pathogenesis of infertility, will pave the way to the development of strategies for effective potential therapeutics for this disorder.

CONFLICT OF INTEREST STATEMENT

None declared.

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