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Review article

Role of nuclear factor erythroid 2-related factor 2 (Nrf2) in female and male fertility

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ABSTRACT

Oxidative stress refers to a condition where there is an imbalance between the production of reactive oxygen species and their removal by antioxidants. While the function of reactive oxygen species as specific second messengers under physiological conditions is necessary, their over-production can lead to numerous instances of cell and tissue damage. Nuclear factor erythroid 2-related factor 2 (Nrf2) is a master regulator of many cytoprotective genes that respond to redox stresses. Nrf2 is regularly degraded by kelch-like ECH-associated protein 1 through the ubiquitin-proteasome pathway. The kelch-like ECH-associated protein 1 and Nrf2 complex have attracted attention in both basic and clinical infertility research fields. Oxidative stress is implicated in the pathogenesis of female infertility, including primary ovarian insufficiency, polycystic ovarian syndrome, and endometriosis, as well as male infertility, namely varicocele, cryptorchidism, spermatic cord torsion, and orchitis. Most scientists believe that Nrf2 is a potential therapeutic method in female and male infertility disorders due to its antioxidant effect. Here, the potential roles of oxidative stress and Nrf2 in female and male infertility disorders are reviewed. Moreover, the key role of Nrf2 in the inhibition or induction of these diseases is discussed.

1. Introduction

This review article offers a comprehensive explanation of the mechanisms involved in the production of ROS and its associated processes. The discussion focuses on Nrf2 and its inhibitor, providing a detailed analysis. Moreover, we provide an overview of the physiological and inducible functions of Nrf2.Furthermore, it explores the involvement of Nrf2 in female fertility disorders such as polycystic ovary syndrome (PCOS), endometriosis, primary ovarian insufficiency (POI), and male fertility disorders like varicocele, cryptorchidism, spermatic cord torsion, and orchitis.

1.1. ROS production mechanism

Low concentration of reactive oxygen species (ROS) makes them a second messenger in triggering and regulating biological responses, while their high concentration is likely to have a toxic impact on molecules and cells, leading to oxidative stress (OS). Hence, the role of many of these molecules in health and disease is related to their production rates, steady-state concentrations, and the

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ability of the cellular antioxidant systems to modulate their activity. OS refers to an imbalance between ROS and antioxidant capacity [1]. A maximum of 1–2% of the oxygen consumed by the cell can be converted into oxygen radicals, which finally are converted into ROSs, such as oxygen radicals, like superoxide (O_2^-), and non-radicals, like hydrogen peroxide (H_2O_2). In an in vivo, the main source of ROS production is aerobic respiration, which occurs in the mitochondrial organelle. These ROSs are mainly produced by complexes (CO) I and III, which are regulated by several factors, including oxygen levels, substrate availability, and mitochondrial morphology [2–4]. The most important source of ROS production in mitochondria is CO I, which mainly produces O_2^- in the electron transport chain (ETC). Two different mechanisms occur to produce O_2^- in CO I. The first occurs when a Flavin Mononucleotide (FMN) center receives electrons from nicotinamide adenine dinucleotide hydrogen (NADH), and as a result, the FMN center acts as an entry point to the electron transport chain. Under the conditions when the rate of electron transferring through the ETC is slow, the content of the FMN center can decrease, then it reacts with oxygen, and thereby catalyzing the O_2^- production. This condition occurs when the NADH/NAD ratio is high. The second mechanism occurs when the rate of electron transferring from the ETC is high. In this situation, the Q enzyme (Q) located downstream of CO I decreases. Here, there is a high proton motive force, which can push the electrons in the reverse direction, i.e. the electrons are transferred from the coenzyme Q to the FMN Center CO I. This reverse electron transfer (RET) leads to the production of O_2^- [1,5,6]. As mentioned, CO III is another source of ROS production in mitochondria. Although the ROS production rate is significantly lower in the CO III than in the CO I, the CO III catalyzes a Q cycles where electrons are accepted from ubiquinone to be used to reduce cytochrome C (Cyto C) for subsequent transferring to the CO IV. During this process, ubiquinone binds to the Q0 site of the CO III and is subjected to one-electron oxidation, leading to the production of an unstable semiquinone radical. In most cases, semiquinone is quickly oxidized and its reaction with oxygen leads to the production of O_2^- [4,7] (Fig. 1). Another main source of ROS production is NADPH-Oxidases (NOXs), NOXs are mainly multi-protein enzyme COs that catalyze the transfer of electrons to molecular oxygen, and as a result, these ROS include mainly O_2^- and H_2O_2 [8,9]. The putative mechanism that can be stated for all pro-NOXs is that NOXs are considered an electron transport chain that transfers electrons from NADPH to FAD-Cofactor in flavoprotein or dehydrogenase and from FAD to heme moiety, and reduced heme moiety binds with oxygen leading to the production of Ferrous/Oxy, which is broken into ferric-heme and O_2^-. Evidence shows that all NOX isoforms first produce O_2^- and then special types of NOXs, such as NOX_4, convert O_2^- into H_2O_2 [10,11].

1.2. *Nrf2 activation and infertility*

Basal concentration of these molecules needs to be regulated, a process where Nuclear factor-E2-related factor 2 (Nrf2) plays an essential role. Nrf2 is considered as one of the most important responses to redox stresses and helps in providing a homeostatic milieu for other basal mechanisms. Nrf2 is a transcriptional factor known as a master regulator of cellular responses versus oxidative and xenobiotic stresses. Recently, researchers have largely devoted their attention to this transcriptional factor and its own negative regulator Kelch-like ECH-associated protein 1 (KEAP 1), and widespread investigations are being done to determine the exact role of Nrf2 and its pathway [12]. The focus of study is on investigating whether Nrf2 can act as an infertility inhibitor, or whether Nrf2 should be purposed for anti-infertility therapeutic methods [13,14]. There are strong beliefs that increased Nrf2 activity should be considered in order to prevent not only infertility but also some other diseases induced by environmental stresses [15–17]. Nowadays, some new drugs, including curcumin, sulforaphane, bardoxolone methyl 13, and dimethyl fumarate, are used in the stage of clinical trials to demonstrate how they can activate Nrf2 and stop oxidative stress progression [18–24]. However, some studies have shown that spermatogenesis disruption and decreased sperm quality can be achieved by Nrf2 knockout; this knockout decreases Nrf2 activity and

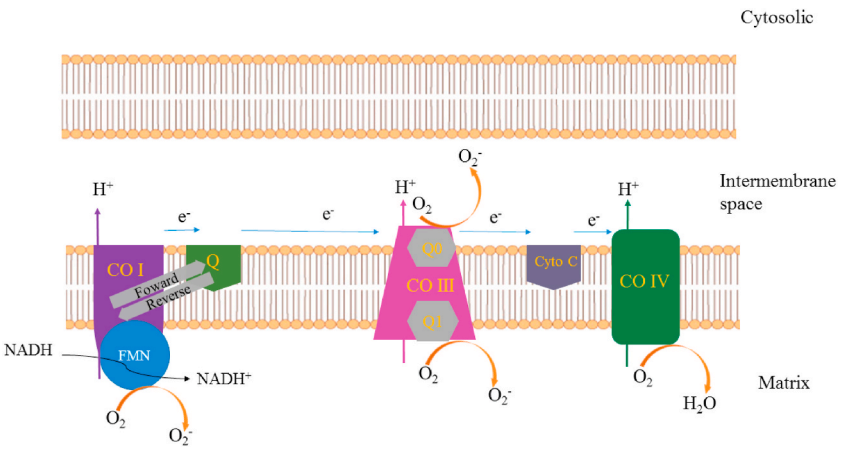

Fig. 1. Schematic portrayal of O2- production through ETC in the inner mitochondrial membrane. ROS production is carried out by CO I and III. CO I is composed by FMN which received electron from NADH and thereby catalyzed the O_2^- production. When the rate of electron transferring from the ETC is high, Q can push the electrons in the reverse direction and ROS production occurred. CO III reduced Cyto C through catalyzing the Q0 for subsequent transferring to the CO IV. The biquinone binds to the Q0 site which is subjected to one-electron oxidation, and can lead to the production of O_2^-.

is associated with lack of resistance versus environmental stresses and the inability to preserve fertility potential [14,25]. Clinical trial studies have shown that oligospermia patients have a low level of Nrf2 expression, indicating that the presence of Nrf2 is crucial for spermatogenesis and helps to maintain the sperm quality [13,14,25] The roles of Nrf2 and the quality of sperm and spermatogenesis have remained unresolved and are actively under discussion.

In this review, we first briefly summarize the current knowledge of the activation, constituent subunits, and cellular mechanisms of Nrf2 and its inhibitors. We also display the activation of downstream genes. We conduct extensive research in order to determine the effect of Nrf2 on sperm, oocyte, and infertility and show the obvious role of this transcription factor on gamete cells.

1.3. Structural properties of Nrf2 and its inhibitor

Nrf2 is a master regulator of physiological and inducible genes expression and belongs to the cap'n'collar, basic region leucine zipper (bZIP). This factor is broken down into 7 conserved NRF2-ECH homology (Neh) domains, each of which has a different trait and function. The Neh1 belongs to the CNC-bZIP, allowing Nrf2 to shape heterodimer with the ZIP domain of small musculoaponeurotic fibrosarcoma (sMaf) proteins, which together bind to the regulatory region of DNA at a designated *cis*-acting antioxidant response element (ARE) with the 5′-GTGACNNNGC-3′sequence, called the CNC sMaf binding elements (CsMBEs) [26,27]. The Neh2 domain is centralized in the N-terminal area of Nrf2, which is crucial for degradation of Nrf2. ETGE and DLG are two important conserved degron motifs in the Neh2 domain that binds to kelch domain of Keap1 [28]. Some of these domains, including 3, 4, and 5, act as transcriptional activation domains through binding to transcription machinery components [29]. With two redox-independent degrons including DSGIS and DSAPGS, the Neh 6 is connected to E3 ubiquitin ligase, which mediates Nrf2 degradation in cells under oxidative stress [30]. Beta-Transduction repeat-containing protein (β-TrCP) is one of the F-box proteins that helps Nrf2 degradation. The DSGIS motif in Neh6 helps to recognize the Nrf2 via β-TrCP. The phosphorylation of two serine residues within the DSGIS is crucial for Nrf2 reorganization via β-TrCP [31]. The Nrf2 activity is suppressed by interaction of the Neh7 domain with the retinoic X receptor alpha (RXRa) [32]. Generally, the Nrf2 activity is regulated by Neh2, 6, and 7 domains. In basal condition, the Nrf2 is an inactive protein that is ceased by its inhibitor Keap1 through Neh2 domain. Keap1 has five main domains, each of which plays a crucial role in Nrf2 degradation. The Kelch domain and the C-terminal region with six repeated motifs bind to the Neh2 domain of Nrf2 [33]. The intervening region (IVR) plays a crucial role in redox homeostasis. This domain contains multiple cysteine residues which are oxidized under oxidative and xenobiotic stresses. Broad complex, tramtrack, and bric-a-brac domain (BTB) have many proteins that act as a substrate adaptor for the CUL3-RING E3 ligase complex [34]. The last region is the N-terminal region (NTR) (Fig. 2).

1.4. Physiologic and inducible activities of Nrf2

Keap1-Nrf2 complex has some other members, including culling 3 (cul3) and RING box 1 (Rbx1). Keap1 binds to cul3- Rbx1 in order to create ubiquitin E3 ligase complex, which directs Keap1-dependent degradation of Nrf2 by 26s proteasome [12,35–37]. Under unstressed conditions, Nrf2 is constantly and negatively polyubiquitinated by Keap1-cul3 ubiquitin E3 ligase and is degraded by the ubiquitin-proteasome pathway [12]. Other mechanisms may be involved in the activation of antioxidant phase 2 through Nrf2. There are 4 main known components in the detoxification of ROS, drugs, and toxins, which include Nrf2, Keap1, Maf, and electrophile

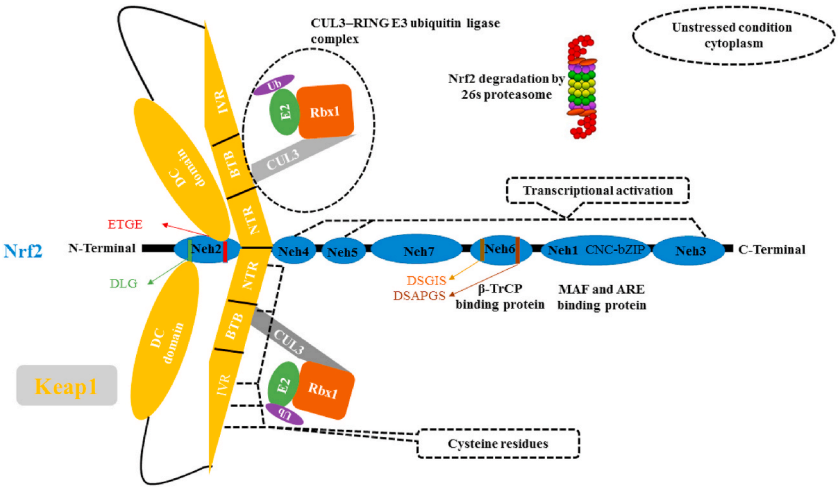

Fig. 2. Schematic portrayal of the Nrf2-Keap1 system with Cul3-RING E3 ubiquitin ligase complex. These complex are bounded together with specific regions of each other under unstressed conditions. All the Neh domains of Nrf2 are shown in their relative positions. Keap1is bounded through its DC domain to Neh 2 of Nrf2. Keap1 binds to CUL3-RING3 ubiquitin ligase complex, which directs Keap1-dependent degradation of Nrf2 by proteasome. NTR and IVR have numerous constituent cysteine residues, which act as a highly reactive sensor to oxidative. Nrf2 bind to MAF and ARE through its Neh1and induce some downstream antioxidant genes. More details are provided in the main text.

responsive element (EpRE) or antioxidant response element (ARE) [38,39].

Keap1 has numerous constituent cysteine residues that contain more than 20 thiol groups, which act as a highly reactive sensor to oxidative and electrophilic stresses for Nrf2. Under stress conditions, Keap1 cysteine residues are modified by ROS [38,40–42]. Keap1 modifications decrease the ubiquitination activity by disrupting the integrity of the Keap1-cul3-Rbx1 E3 ligase complex, thereby preventing the Nrf2 degradation. This conversion help to simplify accumulation of Nrf2. In fact, Keap1 acts as a sensor for xenobiotic, which help to transmission to the transcription activation [43] (Fig. 3).

1.5. Heterodimerization of Nrf2 and sMAf

Nrf2 has a contributory region, called CNC bZip domain, in the C-terminal for DNA binding and heterodimerization with sMaf. SMaf proteins are a kind of transcriptional factors that have a characteristic bZip domain for DNA binding and heterodimerization with CNC bZip domain of Nrf2 [44]. Finally, transcriptionally active heterodimers are formed by binding of Nrf2 to sMaf [27]. This heterodimer identifies the ARE as a *cis*-acting sequence in the promoters of a regulatory region genes, including phase II detoxification enzymes and antioxidant to induce their transcriptions, e.g., NAD(P)H:quinone oxidoreductase 1 (NQO1) and glutathione S-transferase (GST) [45]. More than 100 genes are regulated by the Nrf2-Keap1 in this regulation [46–52]. For instance, the reduction of ROS is achieved by direct regulation of the enzymatic formation by Nrf2. In addition, it is essential for cells to protect themselves from toxic molecules, and the Nrf2 pathway plays a crucial role here. Detoxification of toxic molecules, such as ROS and toxins, is carried out by the Nrf2 pathway through thioredoxin (Trx) and glutathione (GSH) systems [53]. Both of these systems are involved in the ROS balancing, and not only protect it from fertility but also support it [54–56] Nrf2 has another effect, called drug resistance. It is carried out by the induction of the multidrug resistance-associated proteins. Furthermore, Nrf2 can convert aspects of oxidative and xenobiotic stresses into adaptive cytoprotective responses [57].

2. Sources and methodology

In this research, we structured a narrative paper following the guidelines of preferred reporting items for systematic review and meta-analyses guideline (PRISMA). Google scholar, Scopus, PubMed and PubMed/Medline databases were searched, from beginning to 12 July 2023, for studies that comprised the following keywords in the abstract and title: Polycystic ovarian syndrome [MeSH Terms], OR Endometriosis [MeSH Terms], OR Primary ovarian insufficiency syndrome [MeSH Terms], OR Varicocele [MeSH Terms], OR Cryptorchidism [MeSH Terms], Spermatic cord torsion [MeSH Terms], OR orchitis torsion [MeSH Terms]. The bibliographies of the chosen articles were also reviewed to identify any further relevant articles.

3. Role of Nrf2 in female and male infertility disorders

Oxidative stress, a label that reports an imbalance between pro-oxidant molecules, such as ROS and RNS, and the body's scavenging activity can lead to multiple female and male reproductive disorders such as polycystic ovary syndrome (PCOS), endometriosis, primary ovarian insufficiency (POI), varicocele, cryptorchidism, spermatic cord torsion and orchitis [58]. Special cellular mechanisms

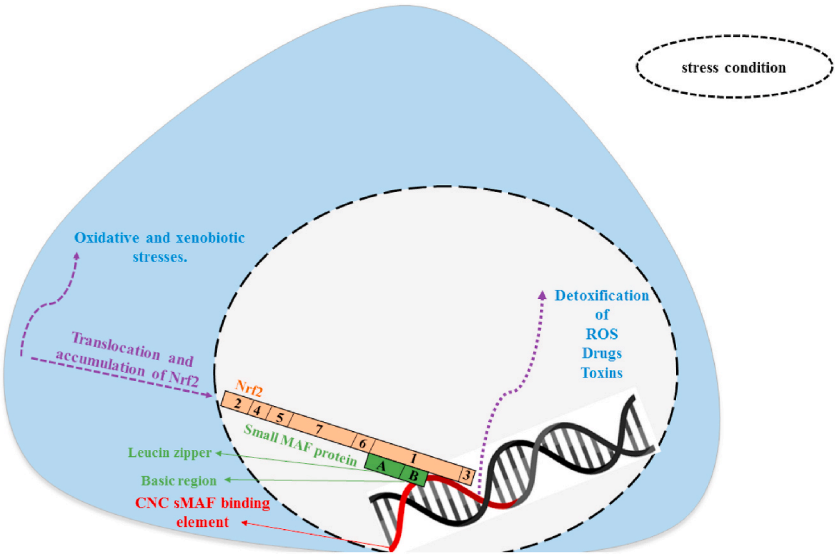

Fig. 3. Accumulation of Nrf2 in nuclei. Under stress condition, transmission and accumulation of Nrf2 takes place in nuclei and binding to CNC sMaf binding element through heterodimerization with sMaf and finally activation of cytoprotective genes, thereby detoxification of ROS, Toxins, and some Drugs.

should be initiated to struggle against the increased level of ROS in order to save the body from oxidative injury. Nrf2 is a master regulator of cellular redox balance and cell protective antioxidants. The correlation between Keap1/Nrf2/ARE and female and male reproductive disorders are discussed next [59–61].

3.1. Female infertility disorders

3.1.1. Polycystic ovarian syndrome (PCOS)

PCOS is considered as the most widespread endocrine and metabolic disorder in women of childbearing age, affecting about 6–15 % of them [62–64]. Although PCOS has drawn researches' attention, the exact cause of its pathophysiology is complex and remain unclear [64]. Some investigations have revealed that oxidative stress acts as major factor in the pathogenesis of PCOS [65,66]. Nrf2 accumulation increases in the early stage of OS in PCOS because of attempting to preserve the purposely removal of ROS. Nevertheless, the sustained OS causes antioxidant dysfunction, eventually leading to a decrease in the Nrf2 expression [66]. Meantime, the use of antioxidants with therapeutic potential, e.g., humanin and carnosol, can attenuate the OS activated by the PCOS through the activation of Nrf2 and its downstream genes, like HO-1 and NOQ1 [66]. Endocrine reticulum-Nrf2-Foxo1-ROS is one of the most famous pathways in PCOS, which is triggered by the therapeutic potential of Genistein to attenuate the OS and its detrimental effect [67,68]. It has been revealed that the induction of AMPK/AKT/Nrf2 pathway has a diminishing impact on the pathogenic events caused by the OS in the PCOS [69]. Subfertility rates are often higher in PCOS patients with obesity, which may be due to the reduction in the induction of Nrf2/HO-1/Cyp1b1 pathway. Some investigations have shown the role of therapeutic agents in preserving the adipose cells under PCOS through the promotion of Nrf2/HO-1/Cyp1b1 [70]. The level of GSSG and Keap1 protein concentrations shows a higher positive correlation between PCOS patients and low concentration of Keap1 in the visceral fat surface compared to the subcutaneous fat surface, which may also lead to the activation of the Nrf2 and its downstream genes [71]. There are strong beliefs that claim PCOS can lead to not only infertility but also some other induced behaviors such as short-term memory impairment, depression, and anxiety. Currently, studies have shown that these behaviors can be modified by ameliorating Nrf2 and acetylcholine esterase (AchE) gene expression [72]. Using a supplement like luteolin can inhibit insulin resistance by PI3/AKT in the PCOS patients and ameliorate anti-oxidative reactions through the restoration of Nrf2 and downstream genes like NQO1 and Hmox1 [73](Fig. 4)(Table 1).

3.1.2. Endometriosis

Endometriosis is a common estrogen-dependent pelvic benign disorder characterized by the existence of endometrial tissue extra-pelvic sites. This disorder affects about 10 % of women in their reproductive age [78–80]. ROS and inflammation are two of the most important hallmarks of endometriosis [81]. ROS production can improve both nuclear factor kappa B (NF-kB) and vascular endothelial growth factor (VEGF), which play a key role in the induction of endometriosis [74]. Studies have recommended the use of antioxidants as a therapeutic strategy to control the early stages of endometriosis [82]. The link between Nrf2 and endometriosis has not been studied yet enough. But for the first time, Marcellin et al. revealed the correlation between Nrf2 and Glutamate Cysteine Ligase (GCL) expression and endometriotic lesion growth. A decrease in Nrf2 expression along with a decrease in one of its downstream genes, GCL, has been observed in women with endometriosis [75]. Unexpectedly, based on the research conducted by Kapoor et al. [76], on the one hand, the expression level of Nrf2 and its downstream genes, e.g., HO-1 and NQO1, increased in the ectopic lesion. On the other hand, endometriosis has shown a low level of Nrf2 inhibitor, Keap1, which could introduce Nrf2 as a key factor in the development of endometriosis (Fig. 4) (Table 1)

3.1.3. Primary ovarian insufficiency (POI)

POI is a disorder characterized by a lack of ovarian sex hormones and a decrease in residual follicles following ovarian dysfunction in women under 40 years of age and is associated with hypogonadism, oligo/amenorrhea, and subfertility/infertility [77,83]. Recent studies have shown that in POI mouse model, the GSH- and SOD-related activity of ovarian oxidation markers decreases, while the

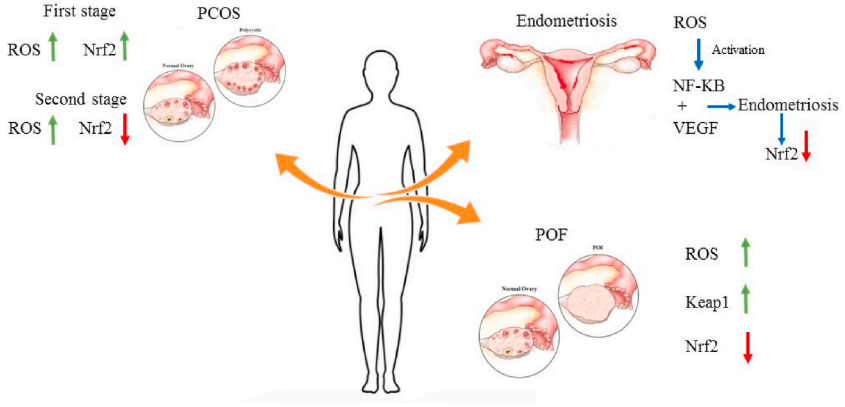

Fig. 4. Nrf2 and female fertility disorders. Schematic representation of female infertility disorders and Nrf2.

Table 1
Summary of female infertility disorders, Nrf2 and its downstream genes.

Female infertility disorders	Type of study	Models of disorder	Outcomes	References
PCOS	In Vivo (most of them) In Vitro	Animal (rat and mice) and Human models	The use of different antioxidant compounds can modulate the decrease in the expression of Nrf2 and its downstream genes, including HO-1 and NQO1, which is caused by oxidative stress in PCOS.	[65–73]
Endometriosis	In Vitro In vivo	Animal (Rat and Mice) and human model	Endometriotic ectopic lesions show a decrease in Nrf2, GCL (an enzyme involved in glutathione synthesis) and its downstream molecules (NQO1, HO-1) compared to eutopic endometria	[74,75,76]
POF (POI)	In Vivo	Animal (Rat and Mice) models	Oxidative stress is manifested by the decrease of ovarian oxidation markers such as SOD- and GSH- and the increase of MDA in the ovarian tissue of POI models, consequently, the expression level of Keap-1 in the ovarian tissue is increased, while the expression level of Nrf2/HO-1 and other downstream genes including GCLC and NQO1 decreases. In this regard, the use of different antioxidant compounds by activating Nrf2/ARE signaling pathway leads to the improvement of antioxidant activity and the enhancement of ovarian reserve in POI.	[77]

expression of MDA increases [84]. These findings indicate the role of oxidative stress as one of the underlying etiology of POI [85]. In ovarian cells, Nrf2 is known as a substantial sensor and modulator of chemical homeostasis, which protects these cells against invasion by metabolic detoxification and endogenous antioxidant effects [86]. Experimental studies show that Nrf2 knockout remarkably damages the ovarian function and antioxidant capacity of POF mice [87]. In the POI following the oxidative stress, we see a moderate increase in Nrf2 and Bach 1 mRNA levels as a self-defense mechanism. However, this self-defense mechanism is not able to entirely impede oxidative damage. On the other hand, the total protein expression of Nrf2 and Bach 1 does not increase significantly [88]. This increase in Nrf2 mRNA expression along with a significant decrease in Nrf2 protein expression ultimately leads to the depletion of ovarian reserves [89]. In addition, the expression of Keap-1 protein in ovarian tissue increases, while the expression of downstream proteins of Nrf2, including GCLC, HO-1, and NQO1, decreases [84,87]. Therefore, by inhibiting the Nrf2/Keap1 signaling pathway, the antioxidant capacity is weakened in the POI [90]. In this regard, it seems that related antioxidant treatment can ameliorate ovarian oxidative stress status by modulating the Nrf2 pathway, making it an effective treatment for improving the POI symptoms [91]. For example, IN vitro experiments showed that antioxidants such as epicatechin, Bu Shen Huo Xue Tang (BSHXT), and curcumin can protect granulosa cells from oxidative damages by activating the Nrf2/Keap1 signaling pathway and increasing the expressions of SOD, NQO1, and HO-1 in POI mice [90,92,93](Fig. 4)(Table 1).

3.2. Male infertility disorders

3.2.1. Varicocele

Varicocele, as the most common modifiable cause of male infertility, is a vascular disease that is defined by abnormally dilated and twisted veins in the pampiniform plexus of the spermatic cord and leads to negative effects on sperm function, semen quality, and

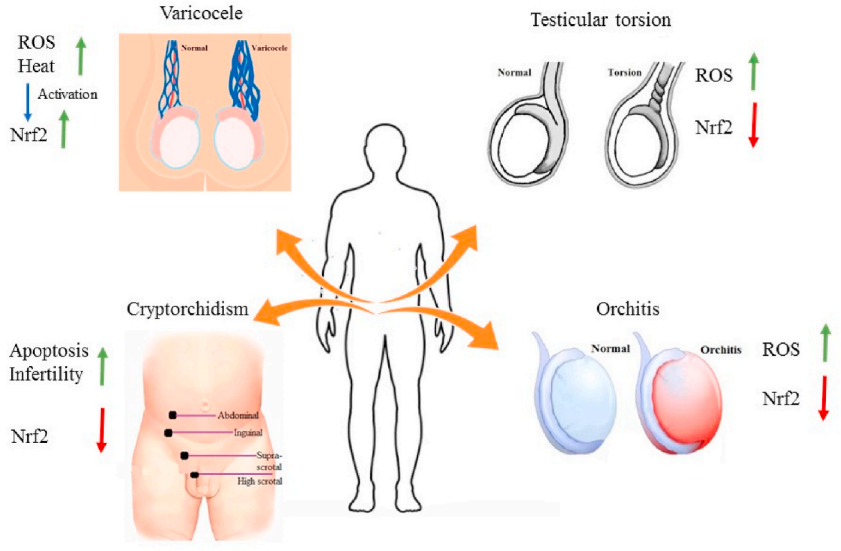

Fig. 5. Nrf2 and male fertility disorders. Schematic representation of male infertility disorders and Nrf2.

reproductive hormones [94,95] Although the exact mechanism of infertility following varicocele is still unclear, oxidative stress is considered to be one of its primary etiological causes [96]. An increase in oxidative stress occurs as a result of an increase in ROS (as a result of testicular heat stress) and a decrease in TAC [97]. In varicocele, due to the high temperature of the testis and as a result of an increase in the level of oxidative stress, antioxidant genes such as Nrf2 are activated to deal with the increase in oxidative stress and lipid peroxidation in sperm. Since Nrf2, as a transcription factor, can only exert its function upon entering the nucleus, examining the nuclear expression of Nrf2 shows the higher expression of Nrf2 and its downstream gene HO-1 in the interstitial cells of patients with varicocele. However, with the progress of the disease, persistent oxidative stress leads to a decrease in the expression of Nrf2 and its downstream genes [98,99]. Meanwhile, the use of antioxidants such as grape seed proanthocyanidin extract (GSPE) and alpha-lipoic acid (ALA) can reduce the oxidative stress and apoptosis triggered by varicocele by imposing a sustained effect on the Nrf2 expression [99–101]. On the other hand, ROS can trigger ferroptosis cell death pathways [102]. In varicocele, due to the decreased blood flow and increased testicular temperature, excessive deposition of iron in the testicles can activate ferroptosis [103]. However, an increase in the Nrf2 expression stimulates the transcription of antioxidants such as Slc7a11 and Gpx-4 (glutathione peroxidase 4) and thus acts as an anti-ferroptosis factor [101](Fig. 5)(Table 2).

3.2.2. Cryptorchidism

Cryptorchidism (undescended testis, testis maldescendus), as a congenital anomaly, is a condition where one or both testicles do not descend properly into the scrotum and is known as one of the most common causes of non-obstructive azoospermia in men [104, 105]. In cryptorchidism, the oxidative stress that occurs in response to testicular hyperthermia ultimately leads to the induction of germ cell apoptosis, increasing sperm damage and reducing male fertility [106,107]. The results of studies on the genes involved in cryptorchidism show that the Nrf2/Keap1 antioxidant pathway is not induced in the testis tissue, while in the epididymis, the expression of Nrf2 signaling decreases over time [108]. Also, the expressions of HO1 and NQO1 (2 mechanisms of heat tolerance to protect germ cells against oxidative stress), which are controlled by Nrf2, decrease gradually in the epididymis of cryptorchid mice [109]. On the other hand, Nrf2-knockout in the epididymis of male mice can lead to an increase in lipid peroxidation and a decrease in the expression of GST, SOD2; moreover, it can decrease the enzyme activities of glutathione reductase and glutathione peroxidase, leading to spermatogenesis disorders [14]. These results indicate the prominent role of the epididymis against oxidative stress in the male reproductive system. Researchers show that the use of Nrf2 inducers, e.g., curcumin, ethanol extract of Cuscuta chinensis seeds, and decursin extracted from Angelica gigas in animal experimental models of cryptorchidism, can improve the expression of Nrf2/HO-1 signaling pathway in the testis and epididymis and reduce the complications of cryptorchidism [13,110,111](Fig. 5)(Table 2.

3.2.3. Spermatic cord torsion

Testicular torsion, as a common urological emergency, occurs when the spermatic cord is twisted, which is followed by a blood flow obstruction and testicular ischemia, and ultimately leads to male infertility or subfertility by disrupting the process of spermatogenesis [112,113] Ischemia and reperfusion (I/R) are among the main pathophysiological consequences of spermatic cord torsion, leading to excessive production of reactive oxygen species that disrupt the seminiferous epithelium [114]. Studies show that the Nrf2 expression and NQO-1 and HO-1 levels decrease in animal models of I/R [114]. Previous studies show the undeniable therapeutic role of HO-1 overexpression (e.g., following the use of Hemin as the strongest inducer of heme oxygenase-1) in I/R injury following the activation of the Nrf2 pathway [115,116]. Research findings show that activation of the PI3K/AKT signaling pathway can activate the Nrf2 antioxidant pathway by the phosphorylation of glycogen synthase kinase 3β (GSK-3β) [117]. In this regard, it has been stated that treatment with low-energy shock wave (LESW) can improve testicular IR injury in rats by activating the PI3K/AKT/Nrf2 pathway [118]. The octamer-binding transcription factor 4 (Oct4)-cancerous inhibitors of protein phosphatase 2A (CIP2A) axis are considered to be another pathway that increases the antioxidant defense system in spermatic cord torsion/detorsion by activating the

Table 2
Summary of male infertility disorders, Nrf2 and its downstream genes.

Male infertility disorders	Type of study	Models of disorder	Outcomes	References
Varicocele	In Vivo	Animal (Rat)	The use of antioxidant compounds by activating the Nrf2 pathway can lead to the reduction of abnormal spermatogenesis and testicular injury in varicocele models by increasing the expression of Nrf2, NQO1and HO-1.	[95–99]
Cryptorchidism	In vivo (most of them) In Vitro	Animal (Rat and Mice) model	The expression of genes involved in Nrf2/Keap1 pathway such as Nrf2, HO-1 and NQO1 declines in the epididymis of cryptorchid models more than testis. So, treatment with Nrf2 inducer could improve cryptorchidism-induced infertility.	(13,14, 104–107)
spermatic cord torsion	In vivo (the most) In vitro	Animal (Rat) model	Excessive oxidative stress attenuates Nrf2 signaling pathway in testicular T/D injury. Using compounds which benefits detoxification and antioxidant defense through activation of Keap1-Nrf2 pathway by increasing the expression of Nrf2 and its target genes HO-1 and NQO1 protected testes from torsion-detorsion injury	(110–121)
Orchitis	In Vivo In vitro	Animal (Mice and sheep) model	The increase in oxidative stress in the orchitis models inhibits the Nrf2 signaling pathway and thus plays a role in the occurrence of infertility. An activated Keap1-Nrf2 axis, reduces ROS production and upregulated expression of HO-1 and antioxidant genes	(112, 121,122)

Nrf2-HO-1-NQO1 pathway [119]. Overexpression of the transcription factor Oct4 increases the expression of its downstream gene CIP2A in Leydig, Sertoli, and germ cells, leading to the activation Nrf2 [120]. Examining microRNAs expression in the testicular tissue of rats with testicular I/R injury shows the upregulated level of miR-101-3p, leading to the downregulation of Nrf2, GST, NQO1, and HO-1 levels. Therefore, miR-101-3p directly targets Nrf2 and is known as a negative factor in testicular I/R injury [121]. The use of an antioxidant, e.g., Zinc, can lead to the activation of the Nrf2 pathway in rats with testicular I/R damage by reducing the expression of miR-101-3p [122]. The findings show that the use of antioxidants such as Idebenone (IDE), selenium (Se), and MitoQ, in spermatic cord torsion/detorsion models can improve Nrf2/Keap1 signaling translocation from the cytoplasm to the nucleus and regulate the Nrf2 levels to counteract with oxidative stress [123–125](Fig. 5)(Table 2).

3.2.4. Orchitis

Orchitis is defined as an acute unilateral or bilateral inflammatory reaction of the testicle following a bacterial or viral infection. Inflammation causes an over-expression of ROS, thereby increasing cellular oxidation, which damages cellular components [126]. In the induced infertility following orchitis, not only the number of macrophages with strong phagocytic activity in the testicular interstitial tissue decreases, but also the number of macrophages that secrete abundant inflammatory cytokines increases [126]. The increased activity of HO-1 in the p38MAPK/Nrf2/HO-1 signaling pathway, as an important anti-inflammatory pathway in macrophages, reduces oxidative damage in testicular inflammation [127]. The cell-based experiments on the lipopolysaccharide (LPS)-induced orchitis mouse model show the inhibition of OCT4-CIP2A pathway expression in Leydig, Sertoli, and germ cells, leading to the suppression of the Keap1-Nrf2 pathway activation, the increased ROS production, and the inhibition of the antioxidant activity. These findings support the importance of the OCT4-CIP2A axis as two potential therapeutic targets of orchitis following the mediation of the Keap1-Nrf2-HO-1 signaling pathway [119](Fig. 5)(Table 2).

4. Conclusion and recommendation

Nrf2 acts as a main key in the pathogenesis of female and male reproductive disorders. Numerous pieces of evidences indicate that Nrf2 activation can be a safe and productive factor in treating reproductive disorders. However, Conflicting studies propose that if may act as disease inducer. Therefore, Nrf2 holds promise as a target for future research on the progression and treatment of female and male infertility, potentially influencing the development of new therapies. Additionally, the use of Nrf2 activator compounds could play a crucial role in preserving fertility in patients experiencing reproductive disorders. These findings should be further assessed through original studies involving both females and males facing infertility in various related diseases. Particular focus on Nrf2/Keap1/ARE pathway is recommendable, to specify accurate mechanism of Nrf2 in females and males reproductive disorders.

5. Limitation

Fertility is a complex process influenced by various factors such as genetics, lifestyle, and the environment. On the other hand, several diseases contribute to infertility in both men and women, and the undeniable role of oxidative stress in the occurrence of these diseases is evident. Since the activation of the Nrf2 pathway can significantly reduce the effects of oxidative stress and reactive oxygen species, it may lead to improved fertility outcomes. However, only a limited number of in vitro and in vivo studies have addressed the role of Nrf2 in infertility. This study attempts to compile these existing studies, highlighting the need for further research in this field.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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