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ROLE OF MITOCHONDRIAL DYNAMICS IN MALE INFERTILITY

ERKEK İNFERTİLİTESİNDE MİTOKONDRİ DİNAMİĞİNİN ROLÜ

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ABSTRACT

Objective: *Mitochondria supply most cellular energy, and their dysfunction particularly affects high energy demand tissues, including the reproductive system. This study aims to evaluate the role of mitochondrial dynamics in male infertility and spermatogenesis.*
Result and Discussion: *Mitochondria are dynamic organelles undergoing continuous fusion, fission, and mitophagy, which are essential for maintaining cellular homeostasis and function. Fusion and fission regulate mitochondrial morphology and ensure the distribution and integrity of mitochondrial contents, while mitophagy removes damaged mitochondria. Disruption of these processes leads to mitochondrial heterogeneity and impaired cellular function. Spermatogenesis involves significant metabolic transitions and morphological changes in mitochondria, particularly during germ cell differentiation into mature spermatozoa. Sertoli cells provide structural and metabolic support throughout this process. Although key regulators of mitochondrial dynamics have been identified in mammals, their roles in human spermatogenesis remain insufficiently understood. Studies suggest that mitochondrial dynamics are critical for meiosis and germ cell differentiation. These processes may act as regulatory checkpoints in spermatogenesis and contribute to the pathogenesis of male infertility. Altered expression of mitochondrial dynamics-related markers in infertile men may provide insight into disease mechanisms and support the development of diagnostic and therapeutic strategies.*
Keywords: *Mitochondrial dynamics, male infertility, Sertoli cells*

ÖZ

Giriş: *Mitokondriler hücresel enerjinin büyük kısmını sağlar ve bu organellerdeki işlev bozuklukları, özellikle üreme sistemi gibi yüksek enerji gereksinimi olan dokuları etkilemektedir. Bu çalışmanın amacı, mitokondriyal dinamiklerin erkek infertilitesi ve spermatogenezdeki rolünü değerlendirmektir.*
Sonuç ve Tartışma: *Mitokondriler, hücresel homeostazın ve fonksiyonların sürdürülmesi açısından kritik öneme sahip olan füzyon, fisyon ve mitofaji süreçlerinden sürekli olarak geçen dinamik organellerdir. Füzyon ve fisyon süreçleri mitokondriyal morfolojiyi düzenlerken, mitokondriyal içeriklerin dengeli dağılımını ve bütünlüğünü sağlar; mitofaji ise hasarlı mitokondrilerin seçici olarak uzaklaştırılmasında rol oynar. Bu süreçlerde meydana gelen aksaklıklar, mitokondriyal heterojenitenin artmasına ve hücresel fonksiyonların bozulmasına yol açabilmektedir. Spermatogenez süreci, özellikle germ hücrelerinin olgun spermatozoalara farklılaşması sırasında, belirgin metabolik geçişler ve mitokondriyal morfolojik değişiklikler ile karakterizedir. Bu süreçte Sertoli hücreleri, gelişen germ hücrelerine yapısal ve metabolik destek sağlamaktadır.*

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Memelilerde mitokondriyal dinamikleri düzenleyen temel mekanizmalar büyük ölçüde tanımlanmış olmakla birlikte, bu süreçlerin insan spermatogenezi üzerindeki etkileri henüz tam olarak aydınlatılamamıştır. Çalışmalar, mitokondriyal dinamiklerin mayoz ve germ hücre farklılaşması açısından kritik rol oynadığını göstermektedir. Bu bağlamda, söz konusu süreçlerin spermatogenezde düzenleyici kontrol noktaları olarak işlev görebileceği ve erkek infertilitesinin patogenezine katkıda bulunabileceği düşünülmektedir. Mitokondriyal dinamiklerle ilişkili belirteçlerin infertil erkeklerde değişen ekspresyon profilleri, hastalık mekanizmalarının anlaşılmasına katkı sağlayabilir ve yeni tanısal ile terapötik yaklaşımların geliştirilmesine zemin hazırlayabilir.
Anahtar Kelimeler: *Mitokondriyal dinamik, erkek infertilitesi, Sertoli hücreleri*

INTRODUCTION

Mitochondria are highly dynamic organelles present in all eukaryotic cells, because of their crucial role in energy production, they are frequently known as the "cell's powerhouses" [1]. They consist of two membranes: the inner mitochondrial membrane (IMM), which is selectively impermeable and contains the oxidative phosphorylation (OXPHOS) complexes, and the outer mitochondrial membrane (OMM), which envelops the organelle and is semi-permeable. These membranes create distinct compartments, including the intermembrane space and the mitochondrial matrix, separating them from the cytoplasm. Mitochondria not only generate ATP (adenosine triphosphate) through oxidative phosphorylation but also serve as the primary intracellular source of reactive oxygen species (ROS), which are byproducts of these processes [2]. The number of mitochondria in a cell can range from one to hundreds, and each one has a genome made up of mitochondrial DNA (mtDNA) [3].

As a key factor in cellular health, malfunctioning mitochondria disrupt energy production, elevate ROS levels, and initiate apoptotic signaling, resulting in tissue damage and dysfunction, which ultimately contribute to disease progression. Many studies show that mitochondrial dysfunction has been recognized as a key pathogenic mechanism contributing to the onset and progression of a growing number of diseases [4].

Mitochondria undergo constant structural changes through a process known as mitochondrial dynamics, which is required for maintaining cellular homeostasis and adapting to cellular needs. These dynamics include the ongoing processes of mitophagy, fission, and mitochondrial fusion, which work together to ensure proper mitochondrial function and maintenance. Mitochondrial dynamics is a highly intricate and regulated process. To sustain their structural and functional homeostasis, mitochondria constantly undergo fusion and fission. This dynamic balance is influenced by various environmental stressors, including energy depletion, hypoxia, and oxidative stress, which trigger adaptive modifications in mitochondrial function and morphology [5] (Figure 1).

Mitochondrial Fusion

Because mitochondria have two membranes, fusion occurs by first fusing the OMM and then the IMM. GTP hydrolyzing enzymes from the superfamily of dynamin are part of a particular mechanism involved in each of these two distinct fusion events in mitochondrial fusion. The dynamin-like Optic Atrophy 1 (Opa1) protein facilitates inner membrane fusion, which comes after outer membrane fusion, which is mediated by mitofusins (Mfn1 and Mfn2) located on the mitochondrial outer membrane [6]. Fusion events in both mitochondrial membranes occur sequentially; however, there can sometimes be a temporal distinction between these two processes. In the final stage of membrane fusion, the contents of the mitochondria mix, and matrix components spread throughout the newly formed mitochondrion. Two mitochondria collide end to end in a mitochondrial fusion, and the membrane merging event occurs at the collision site. Fusion can also take place within a single mitochondrion or in an end-to-end manner, forming ring-like structures [7].

Mitofusins

Mitofusins are essential protein involved in mitochondrial fusion. Mitofusin (MFN1/2) proteins play a major role in keeping mitochondrial function and morphology, as well as ensuring the proper distribution of mitochondrial content. They are localized in the outer mitochondrial membrane and are

key players in the fusion process, specifically mediating the merging of two mitochondrial membranes. Mitofusins are homologous proteins belonging to a large family of mitochondrial transmembrane GTPases, which are encoded by the MFN1 and MFN2 genes located on the outer mitochondrial membrane [8]. MFN1 and MFN2 are highly similar proteins, consisting of 737 and 757 amino acids, respectively (approximately 80% similarity in humans). These proteins contain a large, cytosolic N-terminal GTPase domain, a C-terminal coiled-coil domain (heptad repeat HR1), two C-terminal transmembrane regions (TM), and a second C-terminal coiled-coil domain (heptad repeat HR2). Mitofusin 2 (Mfn2) shows approximately 82% similarity and 66% identity with Mitofusin 1 (Mfn1), and their most comprehensive homology is found in the same functional domains. The main difference between MFN1 and MFN2 is that MFN2 contains a proline-rich region between the HR1 and TM domains, which is closely associated with protein-protein interactions [9]. In mice with knock-out of MFN1 and MFN2, which play a crucial role in the mitochondrial fusion process, these mutations can lead to embryonic lethality and cause organ-specific mitochondrial dynamic dysfunctions in tissues disrupting homeostasis [10].

Key Role of OPA1 in Mitochondrial Fusion

Mitochondrial fusion is a crucial process for maintaining mitochondrial morphology and function. One of the key proteins involved in this process is OPA1, a mitochondrial dynamin-like GTPase located on the inner mitochondrial membrane. It was first discovered through mutation screening in autosomal dominant optic atrophy. Through alternative splicing of the OPA1 gene, at least eight mRNA variants produce both long and short isoforms. The long forms of OPA1 are processed in the matrix to generate the short forms, and both long and short isoforms work together to restore mitochondrial fusion activity [11].

Many studies have shown that, in addition to its role in IMM fusion, OPA1 is involved in maintaining cristae organization, respiratory chain function, and the integrity of mitochondrial DNA [12]. In mouse embryonic fibroblasts, the complete loss of OPA1 leads to fragmentation of the mitochondrial network, a significant reduction in mtDNA copy number, and major disorganization of cristae structure, accompanied by decreased respiratory capacity. OPA1 oligomerization is essential for apoptosis regulation by tightening cristae junctions, preserving cytochrome c within the cristae, and controlling its release [13]. OPA1 independently plays a critical role in maintaining cristae structure in the inner mitochondrial membrane. In the absence of OPA1, the cristae structure is severely disrupted, and respiratory chain supercomplexes are significantly reduced [14].

In cells deficient in OPA1, mitochondrial outer membrane fusion occurs, but inner membrane fusion never takes place. The resulting failed fusion intermediates are then fragmented by fission. Unlike mitofusins, OPA1 only needs to be present in one of the two mitochondria's membranes undergoing fusion to mediate inner membrane fusion [15].

Mitochondrial fusion is tightly regulated for cellular energy homeostasis and the maintenance of mitochondrial functions. Although Mfn1, Mfn2, and OPA1 are all required to control mitochondrial fusion, excessive expression of OPA1 can counteract the effects of Mfn2 knockout. However, it cannot rescue the impact of Mfn1 loss on mitochondrial morphology [16].

Mitochondrial Fission

Mitochondrial fission is a multistep process involving the division of mitochondria into smaller and spherical organelles to ensure the elimination of damaged mitochondria to keep quality control. It is mainly regulated by a large GTPase, Drp1, and other adaptor proteins. Mitochondrial fission is usually triggered during mitochondrial dysfunction associated with high stress levels and apoptosis. Mitochondrial fusion is regulated by fission. This balance is achieved by appropriate organelle size and morphology to facilitate mitochondrial distribution and transport throughout the cell [17]. Fission is mediated by Drp1 (dynamin-related protein 1 = DRP1; encoded by the DNM1L gene) and the interaction between mitochondria and the endoplasmic reticulum (ER). In mitochondria, at marked fission sites, actin filaments and the endoplasmic reticulum (ER) perform the first steps of fission by wrapping and constricting the mitochondria. Then, receptors on the OMM recruit cytosolic DRP1 into the fission site. DRP1 is a mechanochemical enzyme that assembles into ring-like structures to further constrict and

separate mitochondrial tubules [18].

DRP1 Function at the Mitochondrial Fission Region

Mitochondrial fission is supported by the activity of DRP1, a cytosolic protein that translocates to the mitochondrial membrane to initiate fission. Structurally, DRP1 is composed of an N-terminal GTPase domain, a middle domain, and a C-terminal GTPase Effector Domain (GED) [18]. Beyond its role in mitochondrial dynamics, DRP1 is crucial for cell cycle progression, cardiac and muscle differentiation, and the regulation of apoptosis. By increasing the permeability of the mitochondrial outer membrane, DRP1 facilitates cytochrome c release, thereby amplifying apoptotic signaling pathways. Dysfunctional DRP1 activity has been associated with mitochondrial impairment and neuronal damage in diseases such as Parkinson's and Alzheimer's [7].

Since DRP1 lacks a domain that directly binds to membrane phospholipids, adaptor proteins are required for its recruitment to the outer mitochondrial membrane. The translocation of DRP1 from the cytosol to the mitochondrial surface depends on the action of specific receptors located on the mitochondrial outer membrane, namely FIS1, MFF, MID49, and MID51 [19]. These receptor proteins in mammals facilitate the transfer of cytosolic DRP1 to the mitochondrial outer membrane: mitochondrial fission factor (MFF), mitochondrial dynamics proteins of 49 and 51 kDa (MID49 and MID51, encoded by MIEF2 and MIEF1 genes, respectively), and mitochondrial fission 1 protein (FIS1) [20]. In the absence of these adaptors, DRP1 remains in the cytosol. In mammals, FIS1 is involved not only in DRP1 recruitment but also in mitochondrial fission and mitophagy. Each DRP1 receptor plays a distinct yet complementary role. MID49 and MID51 capture GTP-bound DRP1 to promote oligomerization, whereas MFF selectively recruits the oligomeric, active forms of DRP1 [18].

Unlike yeast Fis1, mammalian FIS1 does not serve a central role in mitochondrial fission, as cells deficient in FIS1 display only minimal fission defects. Instead, FIS1 is more critical for mitophagy in certain mammalian cells [21]. In mammals, the other three outer membrane proteins MFF, MID49, and MID51are more crucial for efficient DRP1 recruitment to mitochondria. Alterations in the expression levels of any of these receptor proteins can lead to defects in mitochondrial fission. For instance, deletion of MFF impairs the recruitment of DRP1 and disrupts normal fission dynamics [22].

While each receptor can independently recruit DRP1, evidence suggests that physical interactions among these receptors may help coordinate the modulation of mitochondrial fission. However, the precise mechanisms by which these interactions regulate division remain to be fully elucidated [23].

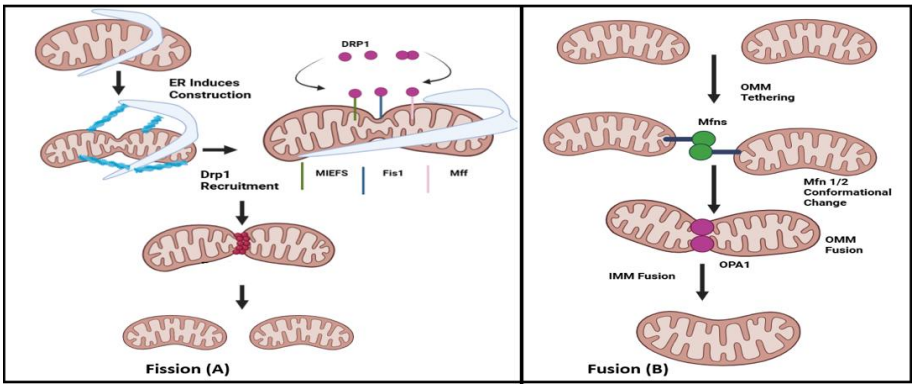

Figure 1. Mitochondrial fission and fusion in response to cellular stress. Mitochondria continuously undergo two opposing processes, fission and fusion, to maintain cellular homeostasis. A. Fission is primarily triggered by mild mitochondrial damage and involves proteins such as Drp1, Fis1, Mff, MIEFS (MiD49, and MiD51). This process helps segregate damaged regions and facilitates mitophagy. B. Fusion, on the other hand, becomes critical during severe damage and is mediated by Mfn1, Mfn2, and OPA1, promoting the mixing of mitochondrial contents to maintain mitochondrial integrity and compensate for stress. This dynamic balance ensures adaptation to metabolic demands and preservation of mitochondrial quality (Created with BioRender.com)

Mitochondrial Quality Control Through Mitophagy

Mitophagy is a critical component of mitochondrial quality control, facilitating the degradation of damaged mitochondria through lysosomal pathways. By selectively eliminating dysfunctional mitochondria, mitophagy preserves cellular energy balance, reduces oxidative stress, and plays an essential role in maintaining cellular homeostasis and survival. PTEN-induced kinase 1 (PINK1)-Parkin pathway in healthy mitochondria, PINK1 is imported into the inner mitochondrial membrane via the TOM complex and subsequently degraded by mitochondrial proteases. However, upon mitochondrial damage and loss of membrane potential, PINK1 import is arrested, leading to its accumulation on the outer mitochondrial membrane. PINK1, a serine/threonine kinase normally present at low levels, phosphorylates ubiquitin molecules on the OMM when mitochondrial damage occurs, triggering the recruitment and activation of the E3 ubiquitin ligase means Parkin [24]. Activated Parkin ubiquitinates various OMM proteins such as MFN1, MFN2, and VDAC, providing a signal for the recognition of mitochondria by the autophagosomal membrane. Additionally, PINK1-mediated phosphorylation of ubiquitin enhances Parkin recruitment, establishing a positive feedback loop that amplifies the mitophagic signal. The ubiquitin chains on OMM proteins serve as binding sites for mitophagy adaptor proteins, including p62/SQSTM1, NDP52, and optineurin, which link ubiquitinated mitochondria to the autophagosome through interactions with LC3, a protein associated with the autophagosomal membrane. Ultimately, mitochondria engulfed by the autophagosome fuse with lysosomes to form mito-lysosomes, where lysosomal enzymes degrade the damaged organelles, thus completing the mitophagic process [25] (Figure 2).

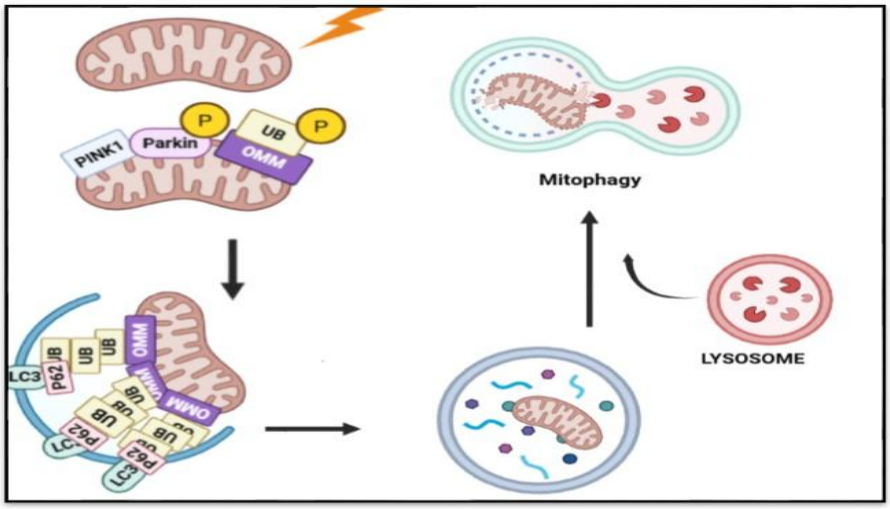

Figure 2. Mitophagy as a mitochondrial quality control mechanism. Mitophagy selectively eliminates damaged mitochondria through the PINK1/Parkin pathway. Upon loss of mitochondrial membrane potential, PINK1 accumulates on the outer mitochondrial membrane and recruits Parkin, which ubiquitinates mitochondrial surface proteins. Phosphorylated ubiquitin amplifies Parkin activation, triggering the recruitment of autophagosomes via LC3 binding to mitophagy receptors. The damaged mitochondria are subsequently engulfed into autophagosomes and degraded after fusion with lysosomes (Created with BioRender.com)

Male Infertility and Spermatogenesis

The inability to conceive naturally for 1 year despite unprotected intercourse is called infertility. Male infertility has become an important and widespread public health problem in recent years, and this situation has a strong social and economic impact in many countries [26]. Male infertility affects 10% to 15% of couples and is one of the serious health problems, among which the male factor plays a role in approximately 50% of all infertile couples [27-28]. Regenerative therapies may offer a potential

solution, but a detailed understanding of cell type-specific mechanisms is necessary to achieve this goal. Many factors have been identified regarding the mechanisms of dysfunction in testicular cells in male infertility. These mechanisms include somatic cell immaturity, abnormal growth factor signaling, increased inflammation, increased rates of cell death, and abnormal extracellular matrix regulation. In the future, more detailed investigations focusing on cellular transcription and translation modulators are needed to better understand spermatogenesis niche dysfunction in both somatic and germ cells [29].

The development of the male germ cell is a suitable system for studying mitochondrial dynamics and mitophagy because the shape, number, and distribution of mitochondria undergo major changes during spermatogenesis [6]. Spermatogenesis occurs in the seminiferous tubules of the testes in 3 stages: (1) Proliferation of spermatogonia by mitotic division, (2) Formation of round spermatids from primary spermatocytes by meiosis, and (3) Advanced differentiation of round spermatids into mature spermatozoa. Mitotically dividing spermatogonia are located near the basement membrane at the periphery of the tubule, and cells progressing through the differentiation stages migrate into the tubule lumen. This process is critically dependent on somatic Sertoli cells, which provide structural and metabolic support to developing germ cells and enable their differentiation. When undifferentiated spermatogonia receive certain signals from surrounding Sertoli cells, they begin to differentiate [30].

Mammalian spermatogenesis is one of the most complex and long differentiation processes in biology, which involves the formation of mature sperm cells from spermatogonial stem cells, in addition to the high energy demand, during these stages, thousands of genes and different cells are involved in the maturation of germ cells. This differentiation process requires several developmentally regulated mitochondrial and metabolic transitions, making the study of mitochondrial dynamics in spermatogenesis an attractive model system [6].

Thousands of genes are estimated to be involved in the genetic control of human spermatogenesis, but the functional role of the majority of these genes in male infertility is still poorly understood. In infertile men, the expression of genes that play an important role in mitochondrial dynamics may differ, and these differences may contribute to the elucidation of the etiology of infertility, the identification of new biomarkers, and the development of treatment protocols for infertile patients with mitochondrial dynamic defects [31]. The importance of mitochondrial dynamics in many systems has been demonstrated by studies conducted in recent years. However, studies examining mitochondrial dynamics specifically in Sertoli cells in the context of male infertility are limited.

Key Functions of Sertoli Cells

Spermatogenesis occurs due to the functional interaction between somatic Sertoli cells and germ cells. Sertoli cells surround germ cells and provide support to these cells. Sertoli cells, defined as somatic components extending from the basement membrane of the seminiferous epithelium towards the lumen, are among the most imxiportant somatic cells that play a role in spermatogenesis. These cells provide functional and structural support for the differentiation of germ cells in response to external hormones such as FSH and testosterone, paracrine, and endocrine stimuli. The tight junctions between Sertoli cells located close to the basal part of the seminiferous tubule form the blood-testis barrier (BTB), which divides the epithelium into basal and adluminal compartments [32]. Cell-cell junctions between Sertoli and germ cells break and rejoin to ensure the passage of germ cells formed during spermatogenesis, which ensures the continuity of the highly specialized BTB formed by Sertoli cells. The mechanisms that are effective in this process have not yet been sufficiently elucidated. Spermatogonia in the basal compartment is in contact with blood-borne substances in the circulation. The adluminal compartment is connected to all other germ cells in an environment created by the secretory and endocytic activity of Sertoli cells [33].

Sertoli cells regulate the localization of germ cells and their movement toward the lumen during the differentiation process of spermatogenesis. These cells protect germ cells from autoimmunity by the defense cells in the blood by maintaining them with the tight junctions they make with each other. Sertoli cells produce many proteins such as growth factors, immunomodulatory factors (such as interleukins and cytokines), anti-apoptotic factors, hormones, extracellular matrix proteins, transferrin, erythropoietin, and the fluid in the seminiferous tubule. Sertoli cells phagocytose residual organelles and dysfunctional germ cells formed during the spermatogenesis process [34].

Mitochondrial Dynamics in Spermatogenesis and Male Infertility

Mitochondrial dynamics, encompassing the processes of fusion, fission, and mitophagy, represent essential quality control mechanisms that preserve cellular and tissue homeostasis. In the context of male germ cell development, these dynamic processes play a critical role in maintaining mitochondrial integrity, ensuring proper energy production, and supporting the differentiation of spermatogenic cells. Male germ cells exhibit distinct metabolic requirements depending on their stage of differentiation. Spermatogonia reside outside the blood testis barrier and can directly access glucose from the bloodstream, spermatocytes, and spermatids are located within the barrier, necessitating alternative and efficient energy supply mechanisms [35].

During spermatogenesis, a high number of germ cells undergo differentiation and transformation into mature spermatozoa within the seminiferous tubules. This process demands significant metabolic adaptation and precise mitochondrial regulation. Mitochondrial morphology undergoes dramatic remodeling throughout germ cell development, culminating in the highly organized mitochondrial sheath formation around the midpiece of mature spermatozoa, which is essential for motility and fertilization capability [36].

Sertoli cells are cells that play a very important role in the spermatogenesis process, support germ cells mechanically and metabolically, and are in close contact with germ cells [32]. There are many studies on mitochondrial dynamics in humans, such as neurodegenerative diseases, developmental delay, mitochondrial diseases, diabetes, cancer, and heart failure [23,37]. However, only limited data are available regarding the role of mitochondrial dynamics in Non-obstructive azoospermia (NOA), the leading cause of male infertility in humans, whose etiology remains incompletely understood and for which novel therapeutic approaches are urgently required.

Although key regulators of mitochondrial fusion and fission, such as MFN1, MFN2, OPA1 (fusion), and DRP1, FIS1 (fission), have been identified in mammals, the specific molecular factors governing mitochondrial dynamics during human spermatogenesis remain poorly understood [6]. Studies in murine models suggest that mitochondrial fusion and fission events are crucial during meiosis, orchestrating metabolic shifts that facilitate spermatogonial differentiation and successful progression through spermatogenesis. Disruptions in these processes can impair mitochondrial function, energy metabolism, and ultimately germ cell maturation, contributing to male infertility [38].

RESULT AND DISCUSSION

Mitochondrial homeostasis is regulated by specific mechanisms that preserve organelle structure and function, with mitochondrial dynamics playing a central role. These dynamics include mitochondrial biogenesis, fission, fusion, and mitophagy a selective form of autophagy that degrades damaged mitochondria. Together, these processes ensure the proper functioning and maintenance of mitochondria, highlighting their critical role in cellular health and disease [39].

Mitochondrial fusion enables the dynamic repair of damaged mitochondrial regions, forming functional, elongated organelles. Conversely, when mitochondria are irreversibly damaged and pose a potential threat to the cell, mitochondrial fission takes place. This process involves the fragmentation of damaged mitochondria into smaller, spherical organelles, which are then recognized and degraded through mitophagy [25].

Mitophagy, another dynamic process in mitochondria, plays a crucial role in maintaining a healthy mitochondrial population by selectively removing dysfunctional mitochondria through autophagy. During mitophagy, damaged mitochondria are identified as cargo for autophagosomes, which subsequently fuse with lysosomes to degrade and recycle the engulfed organelles [24]. While extensive research has demonstrated that mitochondrial dynamics and mitophagy are essential for maintaining cellular homeostasis, the role of mitochondrial and metabolic transitions in differentiation and development remains poorly understood [23].

Mitochondrial dynamics act as a critical quality control mechanism for preserving cellular and tissue homeostasis. Under normal physiological conditions, mitochondria continuously undergo fusion and fission cycles, regulated by specific proteins. These organelles can adopt various morphologies, including small spheres, short or long tubular structures, and interconnected networks. The balance

between fusion and fission governs these morphological variations [23]. In addition to shaping mitochondrial structure, fusion, and fission facilitate the mixing and even distribution of mitochondrial contents within a cell, ensuring optimal mitochondrial function. In the absence of these processes, mitochondrial heterogeneity may increase, potentially leading to mitochondrial and cellular dysfunction [20].

Emerging evidence suggests that alterations in the expression of mitochondrial dynamic regulators may contribute to the etiology of male infertility. Infertile patients may exhibit dysregulation in key mitochondrial markers, leading to defective mitochondrial remodeling, impaired energy metabolism, and abnormal sperm development. Investigating these markers could not only shed light on the molecular mechanisms underlying defective spermatogenesis but also lead to the identification of novel biomarkers for diagnosis and the development of targeted therapeutic strategies for infertility associated with mitochondrial dynamic defects [31].

In conclusion, mitochondrial dynamics serve as a fundamental mechanism in maintaining cellular homeostasis and regulating developmental processes. The harmonious functioning of processes such as fusion, fission, and mitophagy is one of the vital elements of the mitochondrial quality control mechanism. Disorders in these processes have been shown by various studies to be associated with many pathological conditions such as neurological diseases and muscular dystrophies [25]. Moreover, disruption of these mechanisms can contribute to various pathological conditions, including male infertility. A better understanding of the biological and molecular basis of male infertility may contribute to the development of novel approaches for its treatment. Meeting the energy demands during spermatogenesis is closely associated with the regulation of mitochondrial dynamics. Germ cells undergo dynamic adaptations throughout their maturation to optimize both intracellular displacement and energy production. Within the seminiferous tubules of the testis, germ cells complete their differentiation steps while being supported structurally and metabolically by surrounding Sertoli cells through tight junctions [6]. Although limited studies exist, current evidence suggests that mitochondrial dysfunction in Sertoli cells may impair germ cell development and male fertility, and mitochondrial dynamics in Sertoli cells may contribute to idiopathic non-obstructive azoospermia [40].

Understanding the molecular regulation of mitochondrial dynamics is crucial for clarifying disease mechanisms and identifying potential therapeutic targets. In the context of male reproduction, further investigation of mitochondrial remodeling during spermatogenesis will enhance diagnostic and therapeutic strategies. Such insights may uncover the causes of male infertility and support the development of more effective treatments.

AUTHOR CONTRIBUTIONS

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CONFLICT OF INTEREST

The authors declare that there is no real, potential, or perceived conflict of interest for this article.

ETHICS COMMITTEE APPROVAL

The authors declare that the ethics committee approval is not required for this study.

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