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Review Article

# Potential role of autophagy in the male reproductive system

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## Abstract

Autophagy is a highly controlled cellular mechanism that maintains cellular homeostasis by degrading and recycling cellular components. In recent years, there has been a greater concentration on understanding the role of autophagy in the male reproductive system. This review addresses the potential importance of autophagy in many aspects of male reproductive physiology, such as spermatogenesis, sperm maturation, and testicular function. The role of autophagy in male fertility, sperm quality, and response to environmental stressors is explored. Insights into the molecular mechanisms driving autophagy in male reproductive cells cover the groundwork for future research targeted at understanding the complex relationship between autophagy and male reproductive health.

## Introduction

Autophagy, a conserved catabolic mechanism necessary for the maintenance of cellular equilibrium, has emerged as an important factor in a variety of physiological and pathological conditions [1,2]. While autophagy has been extensively investigated in the context of cellular maintenance and stress response, it has recently received a lot of attention for its role in the male reproductive system [3,4]. Understanding the complex connection between autophagy and male reproductive systems holds the prospect of yielding new insights into fertility, sperm production, and testicular health.

Spermatogenesis, the complex process of male germ cell differentiation, entails several carefully regulated events such as mitosis, meiosis, and spermiogenesis [5,6]. Recent research indicates that autophagy is critical in controlling these processes, impacting the destiny of germ cells and total sperm quality [7]. Furthermore, autophagy appears to help remove defective or superfluous organelles, resulting in the generation of functionally competent spermatozoa [8].

Autophagy has a role in cellular remodeling, energy balancing, and environmental cue response in the male reproductive tract, which includes the testes and epididymis [9,10]. The dynamic nature of autophagy enables cells to adapt to changing environments, ensuring optimal function even in stressful situations. Furthermore, autophagy may alter sperm maturation and storage in the epididymis (Figure 1), hence affecting spermatozoa's functional capability [11,12]. Despite these intriguing correlations, much about autophagy's potential role in the male reproductive system remains unknown. Understanding the molecular processes and signaling pathways that drive autophagy in male reproductive cells is critical for understanding its impact on fertility, sperm quality, and responses to diverse stresses [13,14]. This review will delve into the available literature, offering a detailed overview of autophagy's possible significance in male reproductive biology as well as emphasizing future research opportunities in this quickly expanding question.

Apoptosis, also known as programmed cell death, is a controlled process of cell suicide that occurs in response to various stimuli, such as DNA damage, cellular stress, or developmental signals. Apoptosis plays an important role in tissue development, immune response, and the elimination of



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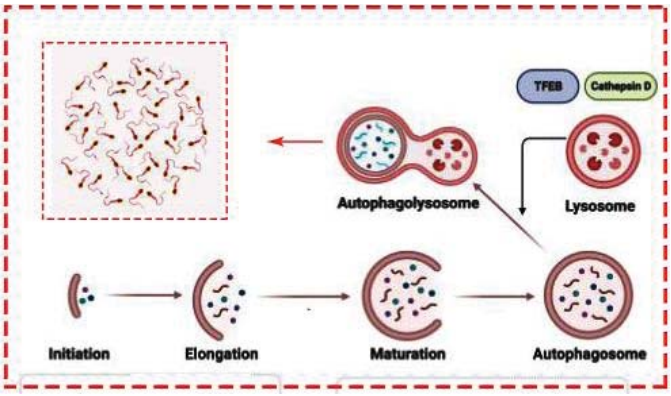


**Figure 1:** Autophagy plays an essential role in sperm production and maturation [56].

damaged or infected cells. Unlike necrosis, which is a form of cell death associated with trauma or injury and often results in inflammation, apoptosis is a highly regulated process that does not trigger an inflammatory response [15].

### Senescence

Cellular senescence refers to a state of irreversible cell cycle arrest that cells enter into in response to various stressors, such as DNA damage, telomere shortening, or oncogene activation. Senescent cells remain metabolically active but are unable to proliferate. Senescence is believed to be a protective mechanism against the proliferation of damaged or potentially harmful cells, such as those with oncogenic mutations [16]. However, senescent cells can also contribute to age-related diseases and tissue dysfunction through the secretion of pro-inflammatory molecules and the disruption of tissue homeostasis. The relationship between autophagy, apoptosis, and senescence is complex and interconnected. Autophagy can play a dual role in regulating apoptosis and senescence. On one hand, autophagy can promote cell survival by removing damaged components and preventing apoptosis or senescence induction under stress conditions. On the other hand, autophagy can also promote apoptosis or senescence by selectively degrading anti-apoptotic proteins or by regulating signaling pathways involved in cell cycle control [17-19].

## Autophagic role during spermatogenesis

The complex interplay between autophagy and male reproductive processes reveals an intriguing view of molecular events that have a substantial impact on fertility, spermatogenesis, and general reproductive health. As indicated by an increasing amount of literature, autophagy emerges as a multidimensional regulator in the male reproductive system, influencing germ cell growth, sperm quality, and reproductive organs' adaptive responses to various environmental signals (47 & 57). Regarding autophagy in Leydig cells, Leydig cells are a type of cell found in the testes that are responsible for producing testosterone, the primary male sex hormone. Autophagy has been shown to play a crucial role in regulating Leydig cell function and testosterone production. One study, titled "Autophagy in Leydig Cells of the Testis. Autophagy is involved in maintaining Leydig cell homeostasis and testosterone production, and dysregulation of autophagy may contribute to testicular dysfunction and male infertility [20,21].

Autophagosomes play a pivotal role in cellular homeostasis by digesting cellular components and enzymatically regenerating them into essential nutrients such as lipids, sugars, nucleosides, and amino acids. This process facilitates intracellular nutrient recycling and serves as a mechanism for energy replacement [22,23]. The balance of energy is a crucial component in the production of spermatozoa in the testis. A reduction in dietary energy has been linked to diminished testicular weight and a decrease in the number of spermatids within the seminiferous tubules, a phenomenon attributed to the activation of autophagy [24]. Additionally, supplementation with amino acids has proven to be a successful and effective strategy for enhancing spermatozoa quality, a response that is intricately linked to the activation of autophagy [25]. Furthermore, conditions such as elevated scrotal temperature, which induces testicular heat stress, have been shown to promote autophagy, leading to spermatogenic arrest [26]. This emphasizes the intricate relationship between autophagy and various factors influencing male reproductive health. Understanding these connections provides valuable insights into potential interventions to modulate autophagy for optimizing sperm production and quality [27]. Therefore, energy disorders, hyperthermia, and hypoxia all promote autophagy during spermatogenesis. Pharmacological inhibitors are often employed to achieve autophagy inhibition. The physiological function of Sertoli Cells is crucial for the success of spermatogenesis [28]. The number of Sertoli Cells influences the testis size and the number of mature spermatozoa, while they also form the blood-testis barrier, creating a conducive environment for germ cell growth through their close relationship. The blood-testis barrier, determining the polarity of Sertoli Cells, physically divides the seminiferous epithelium into basal and apical sections and is essential for spermatogenesis. Endoplasmic specialization, a testis-specific actin-based hybrid anchoring and tight junction, encompasses both basal and apical endoplasmic specialization [29,30]. The basal endoplasmic specialization forms the blood-testis barrier and links it to the actin cytoskeleton, while the apical endoplasmic specialization is crucial for spermatid development and maturation [31,32]. Autophagy-deficient Atg7-/- mice exhibited disorganized F-actin. Notably, when vital proteins required for autophagy initiation (Atg5 and Atg7) were knocked out in animal Sertoli Cells, both apical and basal endoplasmic specialization was disrupted, leading to a chaotic cytoskeleton structure, deformed spermatozoa heads, and reduced motility [33]. This disruption resulted in autophagy impairment, inefficient degradation of PDZ and LIM domain protein 1, and increased PDLIM1, leading to ineffective cytoplasm clearance during spermatogenesis and the breakdown of cytoskeletal components of spermatozoa [31]. During spermatogenesis, each diploid primary spermatocyte undergoes meiosis, developing into four haploid round spermatids, each occupying a specific nuclear location. Chromatoid bodies, distinctive ribonucleoprotein (RNP) granules, are common cytoplasmic characteristics of haploid round spermatids [31,34,35]. Autophagy agonists and antagonists exacerbate cellular defects



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in haploid round spermatids, leading to Chromatoid bodies fragmentations [15]. Autophagy is involved in clearing CB materials and maintaining CB homeostasis, acting as a double-edged sword [36,37]. In recent decades, connections between autophagy-related proteins and meiosis have slowly been postulated. Autophagy-related proteins, including LC3, Beclin 1, p62, Atg5, Atg7, Atg16, m-TOR, AMPKα 1/2, and PINK1, along with their upstream regulators, have been observed to interact with meiosis in male spermatozoa [38-41]. Autophagy activation substantially boosts motility, and the expression of LC3 and Atg7 significantly rises from round to elongated spermatids. Importantly, spermatozoa, highly differentiated cells, can be eliminated within Sertoli Cells by autophagy in live animals, ensuring the initiation of the next reproductive cycle [8,42-44].

Spermatogenesis is a highly controlled process that includes mitotic divisions, meiotic processes, and spermiogenesis, ending in the formation of differentiated spermatozoa [5,45]. Autophagy, a cellular quality control system, plays a role in the removal of faulty germ cells and the clearance of cytoplasmic components during sperm formation [36,46]. This ensures the creation of functionally competent spermatozoa that are devoid of cellular detritus and potential genetic defects. Furthermore, the dynamic nature of autophagy enables male reproductive cells to react to numerous stresses, ensuring cellular homeostasis even under difficult situations. Environmental factors such as toxin exposure, nutritional availability, and oxidative stress can all have an impact on male fertility [47-49]. Autophagy is an important adaptive mechanism that helps cells deal with stresses and maintain reproductive function [50,51]. Understanding the particular autophagic responses to various stressors in the male reproductive system sheds light on prospective therapeutic techniques for reducing the negative effects of environmental insults on fertility. The male reproductive system, which includes the testes and epididymis, is a dynamic environment in which autophagy helps to regulate cellular remodeling and energy balance [3,52,53]. Autophagy in the testes helps to remove damaged or extra organelles, allowing for the creation of high-quality sperm. Furthermore, autophagy's role in the epididymis is receiving study because it may influence sperm maturation and storage. Further research into the molecular processes that drive autophagy in these reproductive organs is required for a complete knowledge of its impact on male reproductive physiology [14,54,55]. While the present literature emphasizes the possible role of autophagy in male reproduction, significant knowledge gaps and areas for further investigation remain. Understanding the complex signaling pathways, molecular actors, and interaction between autophagy and other cellular processes in the male reproductive system remains a difficult but critical job. Furthermore, more research is needed to investigate the translational potential of autophagy modulation for therapeutic approaches in male infertility.

In summary, the potential role of autophagy in the male reproductive system is a fascinating field of study with far-reaching implications for understanding fertility, sperm quality, and environmental reactions. As our understanding grows, clarifying the complexity of autophagy in male reproduction holds the potential for finding novel approaches to improve reproductive health and address male infertility.

## Conclusion

Autophagy emerges as a meticulously regulated cellular mechanism crucial for maintaining cellular homeostasis through the degradation and recycling of cellular components. The increasing focus on unraveling the intricacies of autophagy in the male reproductive system has revealed its potential significance in various facets of male reproductive physiology, including spermatogenesis, sperm maturation, and overall testicular function. This review delves into the multifaceted role of autophagy in male fertility, sperm quality, and the response to environmental stressors. The elucidation of molecular mechanisms governing autophagy in male reproductive cells lays the foundation for future research aimed at comprehending the intricate interplay between autophagy and male reproductive health. The insights gained from these studies hold promise for advancing our understanding and potential interventions in the complex relationship between autophagy and male reproductive well-being.

Future directions in the context of clinical treatments of various diseases of the male reproductive system with autophagy hold significant promise for advancing therapeutic strategies. Further research efforts should aim to elucidate the specific role of autophagy in the pathogenesis of different male reproductive system disorders, such as infertility, erectile dysfunction, and testicular disorders. Additionally, there is a need to explore the potential of autophagy modulation as a therapeutic target for these conditions.

### Declarations

**Authors contribution:** Conception – MAM, WA; Design – MBA, ASK; Supervision -MKV; Materials –CK, SB, SAP Data Collection and/or Processing – MBA, SA, IR; Analysis and/or Interpretation – MAM, MBA Literature Search – SA, SAP, SA; Writing Manuscript – MBA, AWO; Critical Review – WA.

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