Biochemistry and Biophysics Reports 38 (2024) 101698

Contents lists available at ScienceDirect

Biochemistry and Biophysics Reports

journal homepage: www.elsevier.com/locate/bbrep

Mitophagy and spermatogenesis: Role and mechanisms

Damilare Emmanuel Rotimi [a,c,**], Matthew Iyobhebhe [a,c], Elizabeth Temidayo Oluwayemi [a,c], Ikponmwosa Owen Evbuomwan [b], Rotdelmwa Maimako Asaleye [a,c], Oluwafemi Adeleke Ojo [d,*], Oluyomi Stephen Adeyemi [d]

[a] Department of Biochemistry, Landmark University, Omu-Aran 251101, Kwara State, Nigeria
[b] Department of Microbiology, Landmark University, PMB 1001, Omu-Aran-251101, Nigeria
[c] SDG 3, Good Health & Well-being, Landmark University, Nigeria
[d] Department of Biochemistry, Bowen University, Iwo, Osun State, Nigeria

ARTICLE INFO

Keywords:
Autophagy
Male infertility
Reproductive health
Spermatogenesis

ABSTRACT

The mitophagy process, a type of macroautophagy, is the targeted removal of mitochondria. It is a type of autophagy exclusive to mitochondria, as the process removes defective mitochondria one by one. Mitophagy serves as an additional level of quality control by using autophagy to remove superfluous mitochondria or mitochondria that are irreparably damaged. During spermatogenesis, mitophagy can influence cell homeostasis and participates in a variety of membrane trafficking activities. Crucially, it has been demonstrated that defective mitophagy can impede spermatogenesis. Despite an increasing amount of evidence suggesting that mitophagy and mitochondrial dynamics preserve the fundamental level of cellular homeostasis, little is known about their role in developmentally controlled metabolic transitions and differentiation. It has been observed that male infertility is a result of mitophagy's impact on sperm motility. Furthermore, certain proteins related to autophagy have been shown to be present in mammalian spermatozoa. The mitochondria are the only organelle in sperm that can produce reactive oxygen species and finally provide energy for sperm movement. Furthermore, studies have shown that inhibited autophagy-infected spermatozoa had reduced motility and increased amounts of phosphorylated PINK1, TOM20, caspase 3/7, and AMPK. Therefore, in terms of reproductive physiology, mitophagy is the removal of mitochondria derived from sperm and the following preservation of mitochondria that are exclusively maternal.

1. Introduction

Protein aggregates of undesirable, outdated, or damaged cellular components are transferred to lysosomes in eukaryotic cells by the catabolic process known as autophagy. In lysosomes, damaged cell components can undergo lysosome-mediated destruction and turnover [1]. After digestion, double-membrane vesicles called autophagosomes must sequester the cellular contents. Once the autophagosomes fuse with the lysosomes, the autophagy process is completed. Lysosomal enzymes will subsequently degrade autophagosomes [2]. Selective autophagy is primarily mediated by autophagy receptors and adaptor proteins that connect substrates to the autophagy apparatus [3]. Based on the various substrates, selective autophagy can be further classified into numerous subcategories, including pathogens (xenophagy), peroxisomes (pexophagy), aggregated proteins (aggrephagy), mitochondria (mitophagy), liposomes (lipophagy), endoplasmic reticulum (reticulophagy) and ribosomes (ribophagy) [4].

A type of exclusive mitochondrial autophagy is called mitophagy, which is responsible for eliminating defective mitochondria one by one [5]. Mitochondria are vital organelles that supply energy to the cell and also produce reactive oxygen species, control regulated cell death, and are necessary for healthy spermatogenesis. One form of cell defense mechanism is called mitophagy, which has the potential to protect the quantity and quality of cell mitochondria. Numerous human diseases, such as Parkinson's disease, neuroprotection, chronic obstructive pulmonary disease, cardiac ischemia–reperfusion damage, and diabetic kidney disease, have been associated with mitophagy dysregulation [6].

To ensure that spermatogenesis is successful, mitophagy is crucial for

* Corresponding author.
** Corresponding author.
E-mail addresses: rotimidamilare1@gmail.com (D.E. Rotimi), oluwafemiadeleke08@gmail.com (O.A. Ojo).

https://doi.org/10.1016/j.bbrep.2024.101698
Received 8 March 2024; Received in revised form 25 March 2024; Accepted 26 March 2024

a number of physiological activities, such as breakdown and recycling of cellular components [7]. During spermatogenesis, mitophagy can maintain cellular homeostasis and participates in a variety of membrane trafficking activities [4]. Despite research that has demonstrated a substantial link between mitophagy and spermatogenesis, a timely and efficient summary of the function of selective autophagy in spermatogenesis and male fertility is lacking. This is true, even though there have been descriptions of this link in the literature. In this review, we will discuss the latest findings, underlying processes, and the roles that mitophagy plays in spermatogenesis and male fertility.

2. Mitophagy

The lysosome-mediated breakdown mechanism of cellular contents, known as autophagy, is necessary for protein turnover and organelle quality control [8]. Cellular stressors include starvation, oxidative damage, infection, and inflammatory stimulation that trigger the start of autophagy. There are three main subtypes of autophagy that can be differentiated from each other: macroautophagy, microautophagy, and chaperone-mediated autophagy. The macroautophagy mechanism, also known as mitophagy, includes the selective removal of mitochondria [9]. Cells employ a variety of intricate pathways, including mitophagy, mitochondrial fusion and fission, and mitochondrial biosynthesis, to control the efficiency of their mitochondria and preserve the integrity of the mitochondrial network [10].

Mitochondrial homeostasis is crucial for cellular health. Therefore, mitophagy is the process by which the cell uses autophagy to specifically enclose and eliminate defective or extra mitochondria. This helps to maintain the cell's mitochondria in the right balance [3]. Furthermore, the emergence of neurodegenerative diseases and cardiovascular diseases has been associated with mitophagy [11,12]. When mitochondria are destroyed, they will divide and compromised mitochondrion will be removed by mitophagy, preserving mitochondria's normal function [13]. Consequently, mitophagy can aid in the creation of a fresh, more compact, and robust mitochondrion, a prerequisite for the ability of mitochondria to recycle energy.

The mechanisms of bulk autophagy and mitophagy are distinct, notwithstanding the observation that the latter process may break down mitochondria. There are two types of pathways that the LC3 adaptor uses to identify mitochondrial proteins and initiate mitophagy: ubiquitin-dependent activities and ubiquitin-independent activities. There exist two methods that can significantly trigger mitophagy through ubiquitin-dependent processes: the PINK1-dependent, Parkin-independent pathway, which involves the mitochondrial serine/threonine protein kinase, and the Parkin-dependent, cytosolic E3 ligase pathway. Both mechanisms are based on the ubiquitin pathway [14]. Initially, scientists found a link between Parkinson's disease and Parkin and PINK [15]. Protease presenilin-associated rhomboid-like protein (PARL) on the inner mitochondrial membrane degrades the PINK1 protein after mitochondrial processing peptidase in the matrix cleaves its mitochondrial targeting sequence (IMM). To explain in more detail, under typical circumstances, PINK1 can enter mitochondria through the outer membrane translocase (TOM) [16]. However, only when mitochondria are destroyed does PINK1 pass through the outer mitochondrial membrane (OMM) due to reduction in potential and depolarization of the mitochondrial membrane. PINK1 cannot enter the mitochondria as a result. At this point, PINK1 starts to attach itself to OMM and is phosphorylated to activate it [17]. When ubiquitin is phosphorylated at the Ser65 site by active PINK1, PARKIN ubiquitin ligase activity is attracted and triggered. Next, PARKIN produces polyubiquitin chains that autophagy receptors P62, OPTN, NDP52, TAX1BP1, and NBR1 recognize as their own [18]. Therefore, in order for mitochondria to be degraded, they must be recruited to the forming autophagosomes by receptor proteins. By enlisting ULK1, DFCP1, and WIPI1, PINK1 can also trigger the Parkin-independent mitophagy pathway in addition to the PINK1/Parkin-dependent one. Furthermore, even when Parkin is absent, PINK1 can attract NDP52 and OPTN to mitochondria [19]. Furthermore, several proteins found in the mitochondrial membrane, including NIX, BNIP3, FUNDC1, BCL2L13, FKBP8, and NLRX1, can directly recognize LC3 and induce mitochondrial autophagy [20]. Under hypoxic conditions, FUNDC1 initiates mitochondrial autophagy by directly binding to LC3. Among these proteins, BNIP3 and NIX interact with LC3 through their BH3 domains, which further promote mitophagy [21–23]. Because BCL2L13, FKBP8, and NLRX1 have LIR motifs that allow them to bind to LC3 directly, they can trigger mitophagy [21,24].

2.1. Pathways

The most extensively researched and examined mitophagy model is the phosphatase and tensin homolog (PTEN) induced kinase I (PINK1)–Parkin pathway. The serine/threonine kinase known as PINK1 is degraded by proteases upon import into the mitochondrial matrix, maintaining a low, typical level of activity. Cellular stressors that interfere with the potential of the mitochondrial membrane prevent PINK1 from being imported and degraded; keeping it stable on the outer membrane of the mitochondria. The degradation pathway requires both import and degradation of PINK1 [25]. Parkin's E3 ubiquitin ligase is attracted to the injured mitochondrial surface where PINK1 phosphorylates ubiquitin. Parkin recruits more ubiquitin molecules to the outer membrane proteins of mitochondria. As PINK1 phosphorylates these ubiquitin chains, it creates a positive feedback loop that draws more Parkin. This loop attracts mitophagosomes and initiates the ubiquitin proteasome system (UPS) [26–28].

When mitochondria undergo depolarization, metabolic stress or hypoxic conditions arise, and mitophagy is initiated [29,30]. Similarly to autophagy, mitophagy is characterized by a series of steps that start with the synthesis of autophagosomes and end with the degradation of the autophagolysosomal material. In mammalian cells, several different mitophagic pathways may be activated. These pathways depend on the kind of stimulation that initiates mitophagy and the specific receptor. It is possible to differentiate between canonical and noncanonical travel routes [31]. The canonical pathway mediated by PINK1 and Parkin 2 is the best understood [32]. The protein associated with presenilin rhomboid-like (PARL) will normally cleave PINK1 as it reaches the inner mitochondrial membrane, after which the proteasome will break it down. Following mitochondrial polarization, PINK1 cleavage and translocation are inhibited and PARL is phosphorylated. Furthermore, PARL becomes increasingly stable [33]. As a result, on the outer mitochondrial membrane, PINK1 can gather and recruit Parkin 2, an E3 ubiquitin ligase [34]. Furthermore, PINK1-mediated phosphorylation can activate Parkin 2 [35]. To prevent mitochondria from fusion and from attaching to microtubules, Parkin 2 ubiquitinates mitochondrial proteins such as MFN1, MFN2, and Miro1 [36,37]. p62, OPTN, TAX1BP1, NBR1, and NDP52 are examples of adaptor proteins that can recognize polyubiquitylated MOM proteins. Subsequently, mitochondria are guided toward the breakdown machinery by these adaptor proteins and LC3 [35]. The LIR domains in OPTN and NDP52 have recently been shown to be not necessary for the recruitment of ATG8s proteins; nonetheless, they may still make it possible for the ATG8s proteins to enter autophagosomal assembly without the need for ubiquitin [38]. Prohibitin2 (PHB2), an inner mitochondrial membrane, participates in the mitophagy process, which is mediated by Parkin 2 [39]. The exposed PHB2 LIR motifs can interact exclusively with LC3 once the proteasome has disrupted the outer mitochondrial membrane; this starts the production of autophagosomes [39]. Parkin-induced mitophagy is mediated by GTPases, such as Rab7 and Rab5[40]. They are transported to mitochondria by RABGEF1, where they are involved in the growth of phagophores and the creation of ATG9 vesicles [40]. In recent studies, Rab5 now has a distinct function in the endosomal sorting complexes needed for the clearance of mitochondria mediated by the transport machinery (ESCRT). Regardless of the mitophagic process, the mechanism involves encapsulation of mitochondria in Rab5

positive endosomes and their subsequent transport to lysosomes for destruction. Several mitophagic pathways that do not need Parkin have also been discovered. Certain receptors function as mediators in these pathways, including AMBRA1, BNIP3 (BCL2/adenovirus E1B 19 kDa interacting protein 3), BNIP3L/NIX, FUNDC1 (FUN14 domain-containing protein 1) and BNIP3L/NIX. BNIP3, NIX, and FUNDC1 must all participate in hypoxic mitophagy [37]. They are able to find themselves in the OMM by binding LC3 through their LIR domain. Rheb is a GTP-binding protein that is known to activate mTOR; both BNIP3 and NIX can interact with it. The interaction between BNIP3 and Rheb causes Rheb levels to decrease, which in turn inhibits mTOR activation and reduces autophagy and mitophagy [35]. Instead, neither the binding of NIX and Rheb nor its impact on the mitophagy process can be attributed to mTOR [41]. Rheb is brought to the OMM just after stimulation of oxidative phosphorylation to promote mitophagy and preserve the effectiveness of mitochondrial energy production. This is made possible via Rheb's NIX binding [41]. FUNDC1 has an interaction with syntaxin 17 (Stx17), a SNARE protein that controls where the mitochondrial protease PGAM5 is located [42]. Furthermore, there is a positive correlation between LC3 binding to syntaxin 17 (Stx17) and FUNDC1 dephosphorylation in serine 13 [43].

Mitophagy is an additional quality control mechanism that uses autophagy to eliminate unnecessary mitochondria or damaged mitochondria [44]. The microtubule-associated protein 1A/1B light chain 3 (also known as MAP1LC3A, MAP1LC3B and MAP1LC3C) is recruited to the autophagosomal membrane during mitophagy and binds to mitochondria that express mitophagy receptors on their outer membrane selectively. This process is collectively referred to as LC3. Through molecular identification, damaged mitochondria are identified as cargo for autophagosomes. The resulting mitophagosomes combine with the lysosomes to break down and recycle ingested organelles. Many of the molecular mechanisms of mitophagy have been studied in cultured cells, and new developments in mice models allow us to study mitophagy in live organisms [45,46]. Although an increasing body of data suggests that mitophagy and mitochondrial dynamics preserve the fundamental level of cellular homeostasis, little is understood about how these processes function during differentiation and developmentally regulated metabolic changes. Mammalian spermatogenesis is a great model for tackling this knowledge gap, since it comprises many transitions of this type (see Fig. 1).

2.2. Role of mitophagy/autophagy in spermatogenesis and male infertility

Sperm transformation, sometimes referred to as spermiogenesis, is a process that must be finished at the last stage of spermiogenesis. This process includes the formation of flagella, the production of acrosomes, and the elongation and condensation of the sperm nucleus. The formation of individual spermatozoa and proper mitochondrial rearrangement during this phase depend on the elimination of surplus mitochondria from residual bodies through a process called mitophagy [46].

For example, FBXO7 is a target for the SCF-type ubiquitin E3 ligase complex and functions in the PINK1 and Parkin-dependent mitophagy pathway. To trigger mitophagy in spermatids, FBXO7 operates downstream of PINK1, and its ability to cooperatively recruit Parkin to mitochondria is dependent on the phosphorylation of PINK1 [47]. Similarly to this, FBXO7 expression is required for both the translocation of Parkin to mitochondria and the mitophagy process [47]. In Fbxo7-deficient spermatids (Fbxo7LacZ/LacZ mice), nuclear elongation and histone substitution by transition proteins remain normal. However, incorrect phagocytotic cell activities lead to spermatid mortality due to the inability to modify and remove undesirable cellular contents [48]. Similarly to this, null homozygous spermatids for Nutcracker, the homolog of Fbxo7 in Drosophila, are unable to complete the individualization pathway of sperm [49]. Furthermore, spermatid

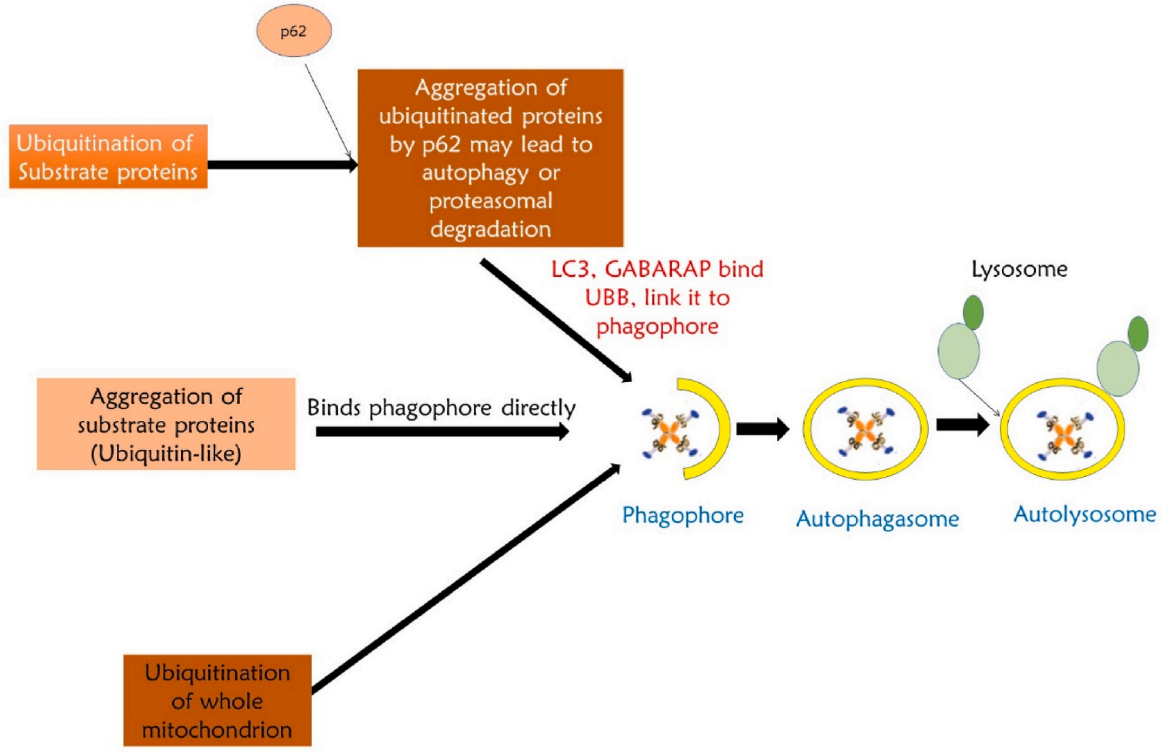

Fig. 1. Diagram of candidate pathways leading to sperm mitophagy by autophagy and ubiquitin proteasome system. Autophagy begins with the aggregation and ubiquitination of proteins or organelles that require recycling. Multiubiquitin chains on these aggregates are recognized by ubiquitin-binding autophagy receptors and are brought to phagophore, a membranous organelle that eventually closes around the protein aggregate to form an autophagosome. Finally, autophagosome fuses with a lysosome that contains proteases able to degrade the protein cargo.

individualization failed in the Parkin mutant Drosophila due to a distinct lack of abnormal mitochondrial derivatives, which prevented late spermiogenesis from occurring. The end of late spermiogenesis was caused by this abnormality [50]. Similar to this, male sterility resulted from the deletion of pacrg in mice, a homolog of the human PARKIN-coregulated gene, due to improper formation of sperm flagellum and incorrect elimination of extraneous cytoplasm [51]. Mice with a disease known as male germ cell conditional knockout Atg7 had badly curled sperm flagella, poorly compacted, and mislocalized mitochondria. This resulted in a disruption of mitochondrial rearrangement, which in turn decreased sperm mobility and ultimately caused male infertility [52]. Likewise, aberrant sperm differentiation and male is associated with ATG5 deficiency in male germ cells. Among these anomalies were larger residual bodies, incorrect acrosome biogenesis, and mitochondrial rearrangement. The reason for these symptoms was an interruption in the autophagic process [53]. Furthermore, the enzyme of AMP-activated protein kinase AMPK (5′-AMP-activated protein kinase catalytic subunit 2) must be active in order for sperm motility, sperm membrane stability, and mitochondrial membrane potential (m) to occur [54]. On their midpiece, mammalian sperm have a cluster of AMPK proteins [54,55]. The mitochondrial membrane potential of the sperm, a crucial signal for mitophagy, would decrease as a result of sperm AMPK dysfunction, which will also affect sperm motility [54].

From a medical perspective, mitophagy is closely linked to the disorders cryptorchidism, and asthenozoospermia. Not too long ago, a study was published which demonstrated that elevated body temperature causes mitochondrial destruction and initiates the mechanism of mitophagy in addition to stopping spermatogenesis, leading to cryptorchidism [56]. Sperm are carried to the epididymis as the outer mitochondrial membrane grows, the mitochondria become onion-shaped, and they undergo a number of changes that impact their location within the cell, as well as their structure. Ultimately, mitochondria start to supply energy for sperm motility. This therapy is not effective because people with cryptorchidism also have epididyma abnormalities, which cause the development of asthenozoospermia. Furthermore, the only organelle in sperm that can produce reactive oxygen species is mitochondria [57]. Production of reactive oxygen species can cause damage and induce mitophagy. It can also cause a phenotype in male gametes that is comparable to apoptosis [56]. Furthermore, rats' Sertoli cells exposed to acute ethanol administration could undergo mitophagy, which is crucial in keeping Sertoli cells from apoptosis and causing these cells to become activated [58]. The findings suggest that the processes governing Sertoli cell mitophagy may have therapeutic implications for male infertility. Furthermore, a thorough examination of the connection between spermatogenesis-related diseases and mitophagy can prove to be extremely beneficial in the future for the diagnosis and treatment of male infertility.

2.3. Autophagy and mitophagy during spermatogenesis

Male subfertile spermatozoa frequently exhibit DNA destruction and other defects, which can have detrimental clinical effects, including impeded fertilization and disturbed preimplantation embryonic maturation [59]. Human sperm include proteins that regulate the autophagy process, as well as those required for the production of autophagolysosomes, including Atg 5, 16, and LC3 (mTOR, beclin 1, AMPK, etc.).

Aparicio et al. [60] showed that human sperm contain a variety of autophagy and mitophagy-related proteins. Furthermore, the same authors demonstrated a link between decreased expression of PINK1, TOM20, and caspase 3/7 and enhanced sperm motility resulting from autophagy activation. They showed that sperm with autophagy inhibition have reduced motility and increased levels of phosphorylated PINK1, TOM20, caspase 3/7, and AMPK. Collectively, the findings unequivocally demonstrate that autophagy is involved in sperm physiological activities [60]. Researchers have previously shown that rat and mouse spermatogenic cells possess LC3-II and autophagosomes. Mice and rats were used in these researches. More LC3-II/LC3-I ratios have been observed in culture and after heat treatment [61,62]. Spermatozoa were incubated for 2 h at 37 °C, resulting in an increase in the LC3-II/LC3-I ratio. The increase was further induced by bafilomycin A1, which inhibits the union of autophagosome and lysosome [60]. In reproductive physiology, the term "mitophagy" refers to the elimination of mitochondria originating from sperm and the subsequent retention of mitochondria that are exclusively maternal. Many proteins linked to the autophagy process have been found in mammalian spermatozoa. Because the sperm core region contains mitochondria and can be eaten by them, mitophagy may occur. Following fertilization, the bulk of the sperm organelles are consumed by the egg rather than being carried on to the child. Mitophagy ensures that only maternal mitochondrial DNA is inherited from the fertilized egg by removing mitochondria that came from sperm [63,64]. Studies have shown that the *Caenorhabditis elegans* egg starts an autophagic process minutes after fertilization to disintegrate the components of the sperm, including mitochondria. This takes place within the *C.* elegans oocyte [63,65].

According to recent studies, autophagy is crucial for the cellular remodeling that occurs in post-meiotic spermatids [52]. Given that autophagy eliminates extraneous cellular elements during spermiogenesis, its involvement in this process should not be surprising. The scientists were able to decrease the amount of autophagic flux in spermatids and stop the development of acrosomes by eliminating the essential autophagy gene Atg7 from primordial germ cells [66,67]. More recently, Atg7 has been shown to be essential for spermatid polarization and removal of cytoplasm during spermiogenesis [52].

The breakdown of PDLIM1, a regulator of cytoskeletal dynamics, in spermatozoa during elongation required autophagy.

The fact that the deletion of Atg7 did not affect the maturation of early germ cell types indicates that autophagy is not readily active in these cells [52]. A recent study supporting this view discovered that spermatids contain the maximum number of autophagosomes per cell [68].

Collectively, these results imply that autophagy is involved in spermatid polarization, maintenance of the acrosome and degradation of cytoplasmic components during spermiogenesis. Furthermore, excess mitochondria are eliminated during spermiogenesis, raising the question of whether mitophagy plays a role. Spermatids of flies carrying a mutation in the pink1 gene have abnormal mitochondria and problems with customization [69].

Furthermore, during mammalian spermiogenesis, UPS is very active and drives Parkin-mediated mitophagy [27,70,71]. These findings imply that the mitochondrial breakdown process that takes place during spermiogenesis may be related to Parkin-mediated mitophagy. Extra mitochondria and other components of the cell will group shortly before spermiation or the release of sperm. These leftover bodies will subsequently be phagocytosed and broken down by Sertoli cells. Therefore, it is unclear whether a non-selective or selective mechanism is used to remove mitochondria during spermiogenesis. Future research should investigate whether mitophagy aids in the removal of mitochondria from residual bodies and/or germ cells, which are notable for having lysosomes. A crucial step in the maturation of sperm is the formation of the acrosome. The acrosome has historically been thought to be an organelle that originates in the Golgi apparatus and is linked to the lysosome [72]. When vesicles that have arisen from the *trans*-Golgi network fuse with one another to form the granule, a massive proacrosomal granule is created. The granule then fuses with the nucleus of the spermatid. The process of vesicle fusion leads to the growth and flattening of the acrosomal granule surrounding the spermatid nucleus, ultimately encompassing the majority of the nucleus's surface. Vesicle transport has been shown to be essential for the process of acrosome biogenesis [72,73]. In addition to the Golgi apparatus, other membrane sources can also aid in the development of acrosomes. Recent studies have demonstrated the presence of mitochondrial cardiolipin in the

acrosome, supporting the theory that mitochondria may also supply membranes to the acrosome [74]. More evidence has confirmed that mitochondria are involved in the formation of acrosomes. As mentioned previously in relation to cultured cells, FIS1 interacts with TBC1D15, a RabGAP for RAB7A, to enable mitophagy. The testes have high expression levels of TBC1D15 and other proteins containing the TBC domain, and some of these proteins are believed to be involved in the development of acrosomes [75]. For example, it has been demonstrated that RAB3A and the Rab GTPase-activating protein (MgcRabGap), which is exclusive to male germ cells located in the testis, colocalize in the acrosome. The Tbc1d21 gene produces this protein (MgcRabGap) [76]. Furthermore, sperm produce a broad range of Rab proteins, while sperm produce the TBC1D9 protein [77,78]. Therefore, more studies are required to determine whether mitochondrial FIS1 influences mitophagy and vesicular trafficking in post-meiotic spermatids.

2.4. Environmental toxicants and possible treatment

Autophagy may also be triggered in germ cells or somatic cells due to cellular stress imposed by environmental contaminants. People may bioaccumulate some heavy metals and metalloids, which are harmful to cells [79]. Caspases are activated, and arsenic substances, including arsenic oxide, have anticancer effects. They also damage mitochondria and produce reactive oxygen species. However, by lowering gene expression levels in the pathway leading to testosterone production, arsenic compounds can also have an impact on spermatogenesis [79,80]. Commonly used in plastics manufacturing, bisphenol-A (BPA) has the ability to down-regulate mTOR activity, which could improve LC3-II and autophagy [81].

After BPA treatment, Rahman et al. [82] observed a statistically significant decrease in sperm motility. According to the results, sperm proteins' tyrosine residues may be more highly phosphorylated because of BPA, impairing the sperm's ability to fertilize eggs, and slowing down the development of the embryo. In addition to harming spermatogenesis, exposure to BPA has also been associated with increased levels of oxidative stress and endocrine problems, which can result in autophagy and death in testicular cells [83]. Human sperm have been shown to have apoptotic markers by Ricci et al. [84]; however, it is unclear whether ejaculated sperm still retain the capacity to undergo apoptosis. Spermatozoa from normal fertile men had a lower rate of apoptosis than spermatozoa from male infertile men, as demonstrated by Gandini et al. [85]. Sperm can perish from necrosis rather than apoptosis in vitro, according to Lachaud et al. [86]. However, in sperm, apoptosis can occur extremely quickly. Because of this, it could be challenging to identify it in the early stages of spermatogenesis and could make them more vulnerable to a range of negative consequences from the environment.

Zhao et al. [87] conducted a study on the role of lycopene (LYC) in spermatogenic cell damage induced by di (2-ethylhexyl) phthalate (DEHP) and the underlying mechanism. The results showed that by activating UPRmt, LYC was able to reduce the mitochondrial stress that DEHP had generated in spermatogenic cells. It also has the ability to improve the decrease in mitochondrial membrane potential and volume density caused by DEHP. Furthermore, in spermatogenic cells, LYC was able to prevent DEHP from causing a decrease in mitochondrial biogenesis, which was mediated by PGC-1. LYC showed some promise as a preventive agent against the mitophagy that DEHP induced in spermatogenic cells, which was mediated by a disruption in mitochondrial dynamics. These results suggested a potential connection between the protective effect of LYC against DEHP-induced mitophagy in spermatogenic cells and mitochondrial quality control. LYC works to stop DEHP-induced mitophagy. By preserving a population of healthy mitochondria (UPRmt), mitochondrial quality control systems including mitochondrial biogenesis, mitochondrial dynamics, mitophagy, and the mitochondrial disordered protein reaction have developed to shield cells from harm [88]. The mechanism of presumed kinase protein 1 (Pink1) and Parkin-mediated mitophagy preferentially breakdowns malfunctioning mitochondria, which harm cell homeostasis and ultimately result in cell death [87].

Furthermore, Liang et al. [89] demonstrated a fluoride-induced mitophagy process in testicular tissues, especially in Leydig cells and the locations of the mitophagy receptor PHB2. The expressions of PINK1 and PHB2 were found to increase in TM3 Leydig cells after fluoride exposure. These results led to the discovery that NaF-treated TM3 Leydig cells had a lower mitochondrial membrane potential (MMP), a decreased amount of mitochondrial mass and an increased number of lysosomes [89]. Fluoride can also result in increased PINK1/Parkin-mediated mitophagy and mitochondrial dysfunction in testicular cells, especially Leydig cells. This may help clarify the mechanisms behind the harm caused by fluoride-induced male reproductive dysfunction. The research not only offers examples of the possible risk assessment of other chemicals, but also proposes a unique harmful mechanism of fluoride-induced reproductive consequences. This is because fluoride presents serious health dangers and is widely used in the domains of agriculture and food research. The results showed that fluoride exposure increased the amounts of proteins and transcripts for PINK1 and PHB2, both in vivo and in vitro [89].

In the testes, a new autophagy mediator called SPATA33 promotes mitophagy [6]. The VDAC2 protein, which is present on the outer membrane of mitochondria, interacts with the carboxyl terminus of the SPATA33 protein, causing it to concentrate in mitochondria. By attaching to the autophagy machinery ATG16L1 through its N-terminal, the protein SPATA33 is recruited to the autophagosome when starvation was induced. This happens at the same time that mitochondria degrade. Interestingly, deletion of SPATA33 resulted in suppression of autophagy, but overexpression of Spata33 promoted the generation of autophagosomes and mitochondrial sequestration. Consequently, in male germline cells, SPATA33 is responsible for promoting mitophagy and controlling the selectivity of mitochondrial degradation [6].

Furthermore, ethanol promotes mitophagy in Sertoli cells, and Eid et al. [58] clarified the role the PINK1-Parkin pathway plays in this process. Using transmission electron microscopy, the authors showed that skeletal muscle cells of rats treated with ethanol had higher levels of mitochondrial damage [58]. This was accompanied by a notable increase in the number of mitophagic vacuoles (mitophagosomes and autolysosomes), relative to the decreased levels found in the control group that received phosphate buffered saline treatment (PBS). The identification of imprisoned mitochondria inside LC3-labeled membranes, the increase in LC3 protein levels, the colocalization of LC3 with cytochrome *c*, and the reduction in the expression of mitochondrial proteins provided ultrastructural evidence for this enhancement. Crucially, Parkin expression was shown to increase in ETR SCs, namely, in mitochondria and mitophagosomes. Furthermore, colocalization was observed between PINK1 and pan-cathepsin, indicating an increase in mitophagy. The transcription factor EB, or TFEB, was demonstrated to be up-regulated in the ETR SC nucleus and this was related to higher expression of iNOS [58]. A transcription factor called TFEB regulates the synthesis of autophagy and mitophagy proteins. Elevated parkin-related mitophagy in ETR stem cells could be a therapeutically and protectively relevant mechanism. The authors do not know of any other publication that illustrates the molecular mechanisms and ultrastructural characteristics of Parkin-related mitophagy in ETR SC [58].

3. Conclusions and perspectives

It is now well known that mitochondrial dynamics play a crucial role in the maintenance of cellular homeostasis. However, little is now known about its role in controlling developmentally regulated metabolic transitions. Research in this area is fascinating considering the fact that mammalian spermatogenesis requires many metabolic transitions. Furthermore, during the course of germ cell development, the shape of the mitochondria changes dramatically, resulting in a highly

coordinated wrapping of the mitochondria around the sperm midpiece. The major components involved in mitochondrial fusion and fission are impacted by post-translational changes, but the regulatory networks in charge of coordinating the dynamics of mitochondria during spermatogenesis remain unknown. The alteration of the metabolic requirements of germ cells as they pass through the segmented seminiferous epithelium is likely to be reflected in these mitochondrial alterations. This is due to the close association between cellular metabolism and mitochondrial dynamics. OXPHOS is the primary enzyme responsible for spermatogenesis and, in particular, meiosis in mammalian animals.

Funding

None.

Conflicts of interest/Competing interests

None.

Availability of data and material (data transparency)

Not applicable.

Code availability (software application or custom code)

None.

Ethics approval

Not required.

Consent to participate

None.

Consent for publication

None.

CRediT authorship contribution statement

Damilare Emmanuel Rotimi: Writing – review & editing, Writing – original draft, Project administration, Methodology, Investigation, Funding acquisition, Conceptualization. **Matthew Iyobhebhe:** Writing – review & editing, Writing – original draft, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis. **Elizabeth Temidayo Oluwayemi:** Writing – original draft, Project administration, Methodology, Investigation, Formal analysis, Data curation. **Ikponmwosa Owen Evbuomwan:** Writing – original draft, Validation, Supervision, Resources, Project administration, Methodology, Funding acquisition, Formal analysis. **Rotdelmwa Maimako Asaleye:** Writing – original draft, Resources, Project administration, Methodology, Investigation, Formal analysis, Data curation. **Oluwafemi Adeleke Ojo:** Writing – review & editing, Writing – original draft, Supervision, Methodology, Investigation. **Oluyomi Stephen Adeyemi:** Writing – review & editing, Writing – original draft, Supervision, Project administration, Methodology, Data curation.

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.

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

Data availability

Data will be made available on request.

Acknowledgement

None.

ABBREVIATIONS

AMBRA1	Activating Molecule in Beclin 1-regulated Autophagy
AMPK	AMP-activated protein kinase
ATG8s	Autophagy-related 8 Protein
BCL2L13	Bcl-2-like protein 13
BNIP3	BCL2/adenovirus e1B 19 kDa protein interaction protein 3
BPA	Bisphenol-A
DEHP	Di (2-ethylhexyl) phthalate
DFCP1	Double *FYVE containing* Protein 1
E3	Ubiquitin-protein Ligase
ESCRT	Endosomal *classification complex required* for Transport
FBXO7	F-box protein only 7
FIS1	Mitochondrial Fission 1 Protein
FKBP8	FK506 binding Protein 8
FUNDC1	FUN14 domain containing Protein 1
GTPases	Guanosine Triphosphatases
IMM	Inner Mitochondrial Membrane
LC3	Microtubule-associated protein-1 light chain 3
LC3-II	LC3-phosphatidylethanolamine Conjugate
LIR	LC3-interacting Region
LYC	Lycopene
MAP1LC3A	Microtubule Associated Protein 1 Light Chain 3 Alpha
MAP1LC3B	Microtubule-associated proteins 1A/1B light chain 3B
MFN1	Mitofusin 1
MFN2	Mitofusin 2
MMP	Mitochondrial Membrane Potential
mTOR	Mechanistic Target of Rapamycin
NBR1	Neighbor of BRCA1 gene 1
NBR1	Neighbor of BRCA1 Gene 1
NDP52	Nuclear Dot Protein 52
NDP52	Nuclear Dot Protein 52
NLRX1	NOD-like Receptor X1
OMM	Outer Mitochondrial Membrane
OPTN	Optineurin
OXPHOS	Oxidative Phosphorylation
P62	Tumor Protein 62
PARL	Presenilin-associated Rhomboid-like Protein
PBS	Phosphate-buffered Saline treatment
PDLIM1	PDZ and LIM domain Protein 1
PGAM5	Phosphoglycerate Mutase 5
PHB2	Prohibitin2
PINK1	PTEN-induced kinase 1
PTEN	Phosphatase and Tensin Homolog
Rab5	Rabaptin-5
Rab7	Rabaptin-7
RabGAP	Mitochondrial Rab GTPase-activating Protein
RABGEF1	Rab5 GDP/GTP Exchange Factor
SNARE	Soluble N-ethylmaleimide-sensitive Actor Activating Protein Receptor
Stx17	Syntaxin 17
TAX1BP1	Tax1 Binding Protein 1
TBC1D15	TBC domain family member 15
TOM	Translocase of the Outer Membrane
ULK1	UNC51-like Kinase-1
UPRmt	Mitochondrial Unfolded Protein Response
UPS	Ubiquitin Proteasome System
VDAC2	Voltage-dependent Anion Channels 2

WIPI1 WD-repeat Protein Interacting with Phosphoinositide;

References

[1] G. Hewitt, V.I. Korolchuk, Repair, reuse, recycle: the expanding role of autophagy in genome maintenance, Trends Cell Biol. 27 (2017) 340–351.
[2] L. Yu, Y. Chen, S.A. Tooze, Autophagy pathway: cellular and molecular mechanisms, Autophagy 14 (2018) 207–215.
[3] C. Lv, X. Wang, Y. Guo, S. Yuan, Role of Selective Autophagy in Spermatogenesis and Male Fertility Cells, vol. 9, 2020, p. 2523.
[4] A. Stolz, A. Ernst, I. Dikic, Cargo recognition and trafficking in selective autophagy, Nat. Cell Biol. 16 (2014) 495–501.
[5] G. Ashrafi, T. Schwarz, The pathways of mitophagy for quality control and clearance of mitochondria Cell, Death & Differentiation 20 (2013) 31–42.
[6] Y. Zhang, X. Xu, M. Hu, X. Wang, H. Cheng, R. Zhou, SPATA33 is an autophagy mediator for cargo selectivity in germline mitophagy, Cell Death Differ. 28 (2021) 1076–1090.
[7] H. Gao, M.B. Khawar, W. Li, Autophagy in reproduction autophagy: biology and diseases, Basic Science (2019) 453–468.
[8] W. Xie, J. Zhou, Aberrant regulation of autophagy in mammalian diseases, Biol. Lett. 14 (2018) 20170540.
[9] A.H. Chourasia, M.L. Boland, K.F. Macleod, Mitophagy and Cancer Cancer & Metabolism, vol. 3, 2015, pp. 1–11.
[10] A.W. El-Hattab, J. Suleiman, M. Almannai, F. Scaglia, Mitochondrial dynamics: biological roles, molecular machinery, and related diseases, Mol. Genet. Metabol. 125 (2018) 315–321.
[11] M.B. Khawar, H. Gao, W. Li, Autophagy and lipid metabolism autophagy: biology and diseases, Basic Science (2019) 359–374.
[12] J. Liu, W. Liu, R. Li, H. Yang, Mitophagy in Parkinson's Disease: from Pathogenesis to Treatment Cells, vol. 8, 2019, p. 712.
[13] R. Wang, G. Wang, Autophagy in mitochondrial quality control autophagy: biology and diseases, Basic Science (2019) 421–434.
[14] G. Twig, O.S. Shirihai, The interplay between mitochondrial dynamics and mitophagy, Antioxidants Redox Signal. 14 (2011) 1939–1951.
[15] W.-X. Ding, X.-M. Yin, Mitophagy: mechanisms, pathophysiological roles, and analysis, Biol. Chem. 393 (2012) 547–564.
[16] N. Matsuda, et al., PINK1 stabilized by mitochondrial depolarization recruits Parkin to damaged mitochondria and activates latent Parkin for mitophagy, JCB (J. Cell Biol.) 189 (2010) 211–221.
[17] S. Park, S.-G. Choi, S.-M. Yoo, J. Nah, E. Jeong, H. Kim, Y.-K. Jung, Pyruvate stimulates mitophagy via PINK1 stabilization, Cell. Signal. 27 (2015) 1824–1830.
[18] T.N. Nguyen, B.S. Padman, M. Lazarou, Deciphering the molecular signals of PINK1/Parkin mitophagy, Trends Cell Biol. 26 (2016) 733–744.
[19] M. Lazarou, et al., The ubiquitin kinase PINK1 recruits autophagy receptors to induce mitophagy, Nature 524 (2015) 309–314.
[20] R.A. Hanna, M.N. Quinsay, A.M. Orogo, K. Giang, S. Rikka, Å.B. Gustafsson, Microtubule-associated protein 1 light chain 3 (LC3) interacts with Bnip3 protein to selectively remove endoplasmic reticulum and mitochondria via autophagy, J. Biol. Chem. 287 (2012) 19094–19104.
[21] G.G. Lim, K.L. Lim, Parkin-independent mitophagy—FKBP 8 takes the stage, EMBO Rep. 18 (2017) 864–865.
[22] L. Liu, et al., Mitochondrial outer-membrane protein FUNDC1 mediates hypoxia-induced mitophagy in mammalian cells, Nat. Cell Biol. 14 (2012) 177–185.
[23] I. Novak, et al., Nix is a selective autophagy receptor for mitochondrial clearance, EMBO Rep. 11 (2010) 45–51.
[24] Y. Zhang, et al., Listeria hijacks host mitophagy through a novel mitophagy receptor to evade killing, Nat. Immunol. 20 (2019) 433–446.
[25] D. Narendra, J.E. Walker, R. Youle, Mitochondrial quality control mediated by PINK1 and Parkin: links to parkinsonism, Cold Spring Harbor Perspect. Biol. 4 (2012) a011338.
[26] N.C. Chan, D.C. Chan, Parkin uses the UPS to ship off dysfunctional mitochondria, Autophagy 7 (2011) 771–772.
[27] A. Rakovic, et al., PINK1-dependent mitophagy is driven by the UPS and can occur independently of LC3 conversion, Cell Death Differ. 26 (2019) 1428–1441.
[28] S. Sekine, R.J. Youle, PINK1 import regulation; a fine system to convey mitochondrial stress to the cytosol, BMC Biol. 16 (2018) 1–12.
[29] L.E. Drake, M.Z. Springer, L.P. Poole, C.J. Kim, K.F. Macleod, Expanding perspectives on the significance of mitophagy in cancer, in: Seminars in Cancer Biology, Elsevier, 2017, pp. 110–124.
[30] D.F. Egan, et al., Phosphorylation of ULK1 (hATG1) by AMP-activated protein kinase connects energy sensing to mitophagy, Science 331 (2011) 456–461.
[31] A. Moyzis, Å.B. Gustafsson, Multiple recycling routes: canonical vs. non-canonical mitophagy in the heart, Biochim. Biophys. Acta, Mol. Basis Dis. 1865 (2019) 797–809.
[32] S. Sato, N. Furuya, Induction of PINK1/Parkin-mediated mitophagy mitophagy, Methods and Protocols (2018) 9–17.
[33] S.M. Jin, R.J. Youle, PINK1-and Parkin-mediated mitophagy at a glance, J. Cell Sci. 125 (2012) 795–799.
[34] C. Vives-Bauza, et al., PINK1-dependent recruitment of Parkin to mitochondria in mitophagy, Proc. Natl. Acad. Sci. USA 107 (2010) 378–383.
[35] R.J. Youle, D.P. Narendra, Mechanisms of mitophagy, Nat. Rev. Mol. Cell Biol. 12 (2011) 9–14.
[36] X. Wang, et al., PINK1 and Parkin target Miro for phosphorylation and degradation to arrest mitochondrial motility, Cell 147 (2011) 893–906.
[37] Y. Chen, G.W. Dorn, PINK1-phosphorylated mitofusin 2 is a Parkin receptor for culling damaged mitochondria, Science 340 (2013) 471–475.
[38] B.S. Padman, T.N. Nguyen, L. Uoselis, M. Skulsuppaisarn, L.K. Nguyen, M. Lazarou, LC3/GABARAPs drive ubiquitin-independent recruitment of Optineurin and NDP52 to amplify mitophagy, Nat. Commun. 10 (2019) 408.
[39] L. Wei, J. Wang, A. Chen, J. Liu, X. Feng, L. Shao, Involvement of PINK1/parkin-mediated mitophagy in ZnO nanoparticle-induced toxicity in BV-2 cells, Int. J. Nanomed. (2017) 1891–1903.
[40] K. Yamano, et al., Endosomal Rab cycles regulate Parkin-mediated mitophagy, Elife 7 (2018) e31326.
[41] S. Melser, et al., Rheb regulates mitophagy induced by mitochondrial energetic status, Cell Metabol. 17 (2013) 719–730.
[42] M. Sugo, et al., Syntaxin 17 regulates the localization and function of PGAM5 in mitochondrial division and mitophagy, EMBO J. 37 (2018) e98899.
[43] G. Chen, et al., A regulatory signaling loop comprising the PGAM5 phosphatase and CK2 controls receptor-mediated mitophagy, Mol. Cell 54 (2014) 362–377.
[44] S. Pickles, P. Vigié, R.J. Youle, Mitophagy and quality control mechanisms in mitochondrial maintenance, Curr. Biol. 28 (2018) R170–R185.
[45] A. Kuma, M. Komatsu, N. Mizushima, Autophagy-monitoring and autophagy-deficient mice, Autophagy 13 (2017) 1619–1628.
[46] T.G. McWilliams, et al., mito-QC illuminates mitophagy and mitochondrial architecture, in Vivo Journal of Cell Biology vol. 214 (2016) 333–345.
[47] V.S. Burchell, et al., The Parkinson's disease–linked proteins Fbxo7 and Parkin interact to mediate mitophagy, Nat. Neurosci. 16 (2013) 1257–1265.
[48] C.C. Rathje, et al., A conserved requirement for Fbxo7 during male germ cell cytoplasmic remodeling, Front. Physiol. 10 (2019) 1278.
[49] M. Bader, E. Arama, H. Steller, A novel F-box protein is required for caspase activation during cellular remodeling in Drosophila, Development 137 (2010) 1679–1688.
[50] J.C. Greene, A.J. Whitworth, I. Kuo, L.A. Andrews, M.B. Feany, L.J. Pallanck, Mitochondrial pathology and apoptotic muscle degeneration in Drosophila parkin mutants, Proc. Natl. Acad. Sci. USA 100 (2003) 4078–4083.
[51] G.R. Wilson, H.X. Wang, G.F. Egan, P.J. Robinson, M.B. Delatycki, M.K. O'Bryan, P. J. Lockhart, Deletion of the Parkin co-regulated gene causes defects in ependymal ciliary motility and hydrocephalus in the quaking viable mutant mouse, Hum. Mol. Genet. 19 (2010) 1593–1602.
[52] Y. Shang, et al., Autophagy Regulates Spermatid Differentiation via Degradation of PDLIM1 Autophagy, vol. 12, 2016, pp. 1575–1592.
[53] Q. Huang, et al., Autophagy core protein ATG5 is required for elongating spermatid development, sperm individualization and normal fertility in male mice, Autophagy 17 (2021) 1753–1767.
[54] D. Martin-Hidalgo, A. Hurtado de Llera, V. Calle-Guisado, L. Gonzalez-Fernandez, L. Garcia-Marin, M.J. Bragado, AMPK function in mammalian spermatozoa, Int. J. Mol. Sci. 19 (2018) 3293.
[55] V. Calle-Guisado, et al., AMP-activated kinase in human spermatozoa: identification, intracellular localization, and key function in the regulation of sperm motility, Asian J. Androl. 19 (2017) 707–714.
[56] M.G. Yefimova, et al., Autophagy is increased in cryptorchid testis resulting in abnormal spermatozoa, Asian J. Androl. 21 (2019) 570.
[57] A. Amaral, B. Lourenco, M. Marques, J. Ramalho-Santos, Mitochondria Functionality and Sperm Quality Reproduction, vol. 146, 2013, pp. R163–R174, https://doi.org/10.1530/REP-13-0178.
[58] N. Eid, Y. Ito, A. Horibe, Y. Otsuki, Y. Kondo, Ethanol-induced mitochondrial damage in sertoli cells is associated with parkin overexpression and activation of mitophagy, Cells 8 (2019) 283.
[59] R.J. Aitken, A.J. Koppers, Apoptosis and DNA damage in human spermatozoa, Asian J. Androl. 13 (2011) 36.
[60] I. Aparicio, et al., Autophagy-related proteins are functionally active in human spermatozoa and may be involved in the regulation of cell survival and motility, Sci. Rep. 6 (2016) 1–19.
[61] X. Bustamante-Marín, C. Quiroga, S. Lavandero, J.G. Reyes, R.D. Moreno, Apoptosis, necrosis and autophagy are influenced by metabolic energy sources in cultured rat spermatocytes, Apoptosis 17 (2012) 539–550.
[62] M. Zhang, M. Jiang, Y. Bi, H. Zhu, Z. Zhou, J. Sha, Autophagy and apoptosis act as partners to induce germ cell death after heat stress in mice, PLoS One 7 (2012) e41412.
[63] Rawi S. Al, et al., Postfertilization autophagy of sperm organelles prevents paternal mitochondrial DNA transmission, Science 334 (2011) 1144–1147.
[64] Q. Zhou, H. Li, D. Xue, Elimination of paternal mitochondria through the lysosomal degradation pathway in C, elegans Cell research 21 (2011) 1662–1669.
[65] M. Sato, K. Sato, Degradation of paternal mitochondria by fertilization-triggered autophagy in C, elegans embryos Science 334 (2011) 1141–1144.
[66] M. Komatsu, et al., Impairment of starvation-induced and constitutive autophagy in Atg7-deficient mice, J. Cell Biol. 169 (2005) 425–434.
[67] H. Wang, et al., Atg7 is required for acrosome biogenesis during spermatogenesis in mice, Cell Res. 24 (2014) 852–869.
[68] P. Yang, et al., In vivo autophagy and biogenesis of autophagosomes within male haploid cells during spermiogenesis, Oncotarget 8 (2017) 56791.
[69] I.E. Clark, et al., Drosophila pink1 is required for mitochondrial function and interacts genetically with parkin, Nature 441 (2006) 1162–1166.
[70] R. Bose, G. Manku, M. Culty, S.S. Wing, Ubiquitin–proteasome System in Spermatogenesis Posttranslational Protein Modifications in the Reproductive System, 2014, pp. 181–213.
[71] L. Hermo, R.M. Pelletier, D.G. Cyr, C.E. Smith, Surfing the wave, cycle, life history, and genes/proteins expressed by testicular germ cells. Part 4: intercellular bridges, mitochondria, nuclear envelope, apoptosis, ubiquitination, membrane/voltage-

gated channels, methylation/acetylation, and transcription factors, Microsc. Res. Tech. 73 (2010) 364–408.
[72] M.B. Khawar, H. Gao, W. Li, Mechanism of acrosome biogenesis in mammals, Front. Cell Dev. Biol. 7 (2019) 195.
[73] G. Berruti, C. Paiardi, Acrosome biogenesis: revisiting old questions to yield new insights, Spermatogenesis 1 (2011) 95–98.
[74] M. Ren, et al., Extramitochondrial cardiolipin suggests a novel function of mitochondria in spermatogenesis, JCB (J. Cell Biol.) 218 (2019) 1491–1502.
[75] X.-M. Zhang, B. Walsh, C.A. Mitchell, T. Rowe, TBC domain family, member 15 is a novel mammalian Rab GTPase-activating protein with substrate preference for Rab7, Biochem. Biophys. Res. Commun. 335 (2005) 154–161.
[76] Y.H. Lin, Y.M. Lin, Y.C. Kuo, Y.Y. Wang, P.L. Kuo, Identification and characterization of a novel Rab GTPase-activating protein in spermatids, Int. J. Androl. 34 (2011) e358–e367.
[77] J.-W. Bae, et al., Ras-related proteins (Rab) are key proteins related to male fertility following a unique activation mechanism Reproductive, Biology 19 (2019) 356–362.
[78] Y. Nakamura, A. Asano, Y. Hosaka, T. Takeuchi, T. Iwanaga, Y. Yamano, Expression and intracellular localization of TBC1D9, a Rab GTPase-accelerating protein, in: Mice Testes Experimental Animals, 2015, pp. 15–16.
[79] R. Chiarelli, M.C. Roccheri, Heavy metals and metalloids as autophagy inducing agents: focus on cadmium and arsenic, Cells 1 (2012) 597–616.
[80] T.-J. Chiou, S.-T. Chu, W.-F. Tzeng, Y.-C. Huang, C.-J. Liao, Arsenic trioxide impairs spermatogenesis via reducing gene expression levels in testosterone synthesis pathway, Chem. Res. Toxicol. 21 (2008) 1562–1569.
[81] S. Lee, et al., Neurotoxic effects of bisphenol AF on calcium-induced ROS and MAPKs, Neurotox. Res. 23 (2013) 249–259, 2013.
[82] M.S. Rahman, W.-S. Kwon, J.-S. Lee, S.-J. Yoon, B.-Y. Ryu, M.-G. Pang, Bisphenol-A affects male fertility via fertility-related proteins in spermatozoa, Sci. Rep. 5 (2015) 1–9.
[83] C. Quan, C. Wang, P. Duan, W. Huang, W. Chen, S. Tang, K. Yang, Bisphenol a induces autophagy and apoptosis concurrently involving the Akt/mTOR pathway in testes of pubertal SD rats, Environ. Toxicol. 32 (2017) 1977–1989.
[84] G. Ricci, et al., Apoptosis in human sperm: its correlation with semen quality and the presence of leukocytes, Hum. Reprod. 17 (2002) 2665–2672.
[85] L. Gandini, et al., Study of apoptotic DNA fragmentation in human spermatozoa, Hum. Reprod. 15 (2000) 830–839.
[86] C. Lachaud, J. Tesarik, M.L. Cañadas, C. Mendoza, Apoptosis and necrosis in human ejaculated spermatozoa, Hum. Reprod. 19 (2004) 607–610.
[87] Y. Zhao, M.-Z. Li, M. Talukder, Y. Luo, Y. Shen, H.-R. Wang, J.-L. Li, Effect of mitochondrial quality control on the lycopene antagonizing DEHP-induced mitophagy in spermatogenic cells, Food Funct. 11 (2020) 5815–5826.
[88] D. Liu, Y. Fan, X. Tao, W. Pan, Y. Wu, X. Wang, et al., Mitochondrial quality control in Sarcopenia: updated overview of mechanisms and interventions, Aging and Disease 12 (8) (2021) 2016.
[89] C. Liang, et al., Fluoride induced mitochondrial impairment and PINK1-mediated mitophagy in Leydig cells of mice: in vivo and in vitro studies, Environ. Pollut. 256 (2020) 113438.