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ADVANCES IN SOCIAL HUMANITIES RESEARCH

The Role of Epididymis and "Bio-Active Cargo" Exosome in Sperm Cells Maturation

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Abstract

Male infertility may result from impaired posttesticular sperm maturation, a process in which the epididymis provides a specialized luminal microenvironment essential for sperm development and functional competence. This narrative literature review examined the anatomical and physiological roles of the epididymis and the potential contributions of epididymosome-associated bioactive cargo to sperm maturation. Relevant literature published between 2015 and 2025 was identified through PubMed, ScienceDirect, and other scientific sources and synthesized according to epididymal structure, epithelial cell functions, extracellular vesicle biology, and the transfer of proteins and small regulatory RNAs. The reviewed evidence indicated that epididymosomes, a heterogeneous population of extracellular vesicles released into the epididymal lumen, participate in intercellular communication and may transfer bioactive molecules to spermatozoa during epididymal transit. These molecular interactions have been associated with sperm plasma membrane remodeling, acquisition of motility, protection against oxidative stress, and other posttesticular modifications essential for sperm functional maturation. Experimental studies further suggested that epididymosome-mediated cargo transfer contributes to molecular communication between the epididymal epithelium and developing spermatozoa. However, much of the mechanistic evidence was derived from animal models and in vitro experiments, limiting its direct applicability to human reproductive physiology. Furthermore, the clinical relevance of specific epididymosomal cargo molecules in human infertility remains insufficiently established. Overall, this review highlighted the potential of epididymosomes as sources of reproductive biomarkers and targets for future investigations rather than validated diagnostic or therapeutic tools. Further research should clarify cargo-specific mechanisms in humans and distinguish molecular changes acquired during epididymal maturation from those associated with subsequent sperm capacitation in the female reproductive tract.

INTRODUCTION

Infertility is a reproductive health condition associated with significant medical, psychological, and economic consequences for individuals and couples. It is generally defined as the failure to achieve pregnancy after 12 months of regular, unprotected sexual intercourse, although clinical evaluation may be initiated earlier depending on individual circumstances (Eisenberg et al., 2023; World Health Organization, 2023). Male reproductive factors

contribute substantially to the global burden of infertility, highlighting the importance of evaluating sperm quality and function beyond conventional measures such as sperm concentration (Diaz et al., 2022; Vander Borght & Wyns, 2018). Understanding the biological mechanisms through which spermatozoa acquire functional competence after leaving the testes is therefore essential for explaining reproductive dysfunction that may occur despite apparently normal sperm production.

Spermatogenesis produces highly differentiated male germ cells; however, spermatozoa released from the testes have not yet acquired all the functional characteristics required for successful fertilization. During epididymal transit, spermatozoa undergo physiological and molecular modifications involving plasma membrane composition, protein distribution, motility acquisition, and interactions with the surrounding luminal microenvironment (James et al., 2020). These changes occur progressively across distinct epididymal regions, each characterized by specialized epithelial structures and functions. Consequently, understanding male infertility requires consideration of both testicular sperm production and posttesticular maturation processes that contribute to sperm functional competence and fertilizing potential.

The epididymal epithelium regulates the luminal microenvironment through coordinated secretory and absorptive activities involving principal cells, clear cells, narrow cells, and other specialized epithelial cell populations. Previous studies have demonstrated the importance of region-specific epithelial functions in maintaining luminal pH, regulating molecular composition, and supporting sperm maturation and quality control (Leir et al., 2020; Liu et al., 2024). Within this regulatory system, epididymosomes represent a heterogeneous population of extracellular vesicles released into the epididymal lumen that facilitate molecular communication between the epididymal epithelium and spermatozoa. Their lipid bilayer membranes protect bioactive molecular cargo, including proteins, lipids, and small regulatory RNAs, and may facilitate the transfer of selected molecules to spermatozoa during epididymal transit (Ali et al., 2023).

Recent investigations have provided further insights into the molecular mechanisms underlying epididymosome-mediated sperm maturation. James et al. (2020) reviewed the contributions of epididymosomes to mammalian reproductive physiology, while Barrachina et al. (2022) investigated the acquisition of epididymis-derived proteins by spermatozoa through extracellular vesicle-mediated transfer. Ali et al. (2023) examined the potential roles of nanoscale bioactive cargo in sperm maturation, whereas Méar et al. (2024) explored epididymosome composition and biological functions. Collectively, these studies supported the involvement of epididymosomes in molecular exchange, sperm membrane remodeling, and the acquisition of functional characteristics associated with reproductive competence. Nevertheless, differences in experimental models, biological specimens, and analytical approaches limit the direct generalizability of these findings to human reproductive physiology.

Despite advances in understanding epididymosome biology, important knowledge gaps remain concerning the functional significance and clinical applicability of their molecular cargo. Epididymosomal composition may vary across epididymal regions, species, and experimental conditions, complicating the identification of molecular components consistently involved in sperm maturation. Furthermore, experimental evidence demonstrating protein or

RNA transfer does not necessarily establish improvements in sperm fertilizing capacity or clinical fertility outcomes. An additional distinction concerns the relationship between epididymal sperm maturation and subsequent capacitation, a physiological process that occurs primarily within the female reproductive tract and enables spermatozoa to acquire fertilization-related capabilities. Clarifying these mechanisms is essential for accurately interpreting the biological significance of epididymosome-associated molecular changes without overstating their potential clinical applications.

Further investigation of epididymosome-mediated sperm maturation is particularly important for advancing the biological understanding of male infertility and identifying potential molecular biomarkers of reproductive dysfunction. Although epididymosomal proteins and regulatory RNAs have attracted increasing interest as candidate indicators of sperm quality and functional competence, their diagnostic and therapeutic applications require rigorous experimental validation and clinically relevant evidence. The novelty of the present review lies in its integrated synthesis of epididymal anatomy, epithelial regulation, extracellular vesicle composition, and bioactive cargo transfer in relation to sperm functional maturation. By distinguishing established physiological mechanisms from emerging experimental findings and unvalidated clinical applications, this review provides a comprehensive perspective on the potential contributions of epididymosomes to male reproductive health.

Accordingly, this narrative literature review aimed to synthesize current scientific evidence concerning the anatomical and physiological roles of the epididymis and the contributions of epididymosome-associated bioactive cargo to sperm maturation. Specifically, it sought to identify the principal molecular components involved in epididymosome-mediated communication, examine their potential roles in sperm membrane remodeling and functional development, and evaluate the limitations of existing experimental and clinical evidence. The review was expected to contribute to reproductive biology by providing an integrated understanding of posttesticular sperm maturation and identifying priorities for future investigations into extracellular vesicle characterization, molecular cargo transfer, and sperm functional competence. Furthermore, the synthesis offers a conceptual foundation for developing and validating potential biomarkers of male reproductive dysfunction while recognizing that epididymosome-based diagnostic and therapeutic applications remain investigational.

METHOD

This study employed a narrative literature review to examine the anatomical and physiological roles of the epididymis and the contributions of epididymosome-associated bioactive cargo to sperm maturation. Relevant scientific publications published between 2015 and 2025 were identified through PubMed, ScienceDirect, and other scholarly sources. The literature selection focused on studies addressing epididymal anatomy, epithelial cell functions, extracellular vesicle biology, epididymosome composition, and the molecular mechanisms underlying posttesticular sperm maturation. Publications were included in the synthesis based on their relevance to the research objectives and their contributions to understanding the anatomical, physiological, and molecular processes involved in sperm functional development.

Data were collected through a literature search and critical examination of relevant scientific publications. The selected articles were reviewed to identify findings concerning epididymal structure, epithelial regulation, extracellular vesicle formation, and the transfer of bioactive molecules to spermatozoa. Information was extracted from the reviewed publications and organized according to the principal research themes. The credibility of the synthesis was strengthened by comparing findings across multiple studies, examining the consistency of reported mechanisms, and considering differences in experimental approaches and biological models. Particular attention was given to distinguishing evidence obtained from human studies, animal models, and in vitro experiments to ensure appropriate interpretation of the findings.

The collected literature was analyzed using a qualitative narrative synthesis approach. The analysis focused on three principal themes: epididymal anatomy and epithelial cell functions, epididymosome biogenesis and molecular composition, and the roles of epididymosome-associated proteins, lipids, and small regulatory RNAs in sperm maturation. Findings from the selected publications were compared to identify recurring biological mechanisms, differences in experimental observations, and unresolved research questions. The synthesis also examined the potential implications of epididymosome-mediated molecular transfer for sperm membrane remodeling, motility acquisition, oxidative stress protection, and reproductive competence. Conclusions were formulated by integrating the available evidence while distinguishing experimentally supported physiological mechanisms from proposed clinical applications that require further validation.

RESULTS AND DISCUSSION

Epididymis And Its Structure

Epididymis is one of male reproductive tracts, which male reproductive tracts consist of: seminiferous tubules, rete-testis, efferent duct, deferens duct, ejaculatory duct and urethra. Based on its organogenesis, epididymis is a derivative of Wolffian duct (Akmal et al., 2015). Epididymis can be distinguished into four anatomical segments: initial segment, caput, corpus and cauda (James et al., 2020). Each segment has its own specialized function and characteristic.

In the epididymis, there are six types of cells that constitute the epididymal epithelium that can be found in all areas of the epididymis, while some other cells are located specifically in some parts of the epididymis (Leir et al., 2020). Cells in the epididymis have high secretory, endocytic and metabolic activity regulated by androgen (James et al., 2020). The cells in the epididymis consist of principal cells, apical cells, narrow cells, clear cells, basal cells, and halo cells (Akmal et al., 2015).

Principal cells in the epididymis are cells subject to the process absorption and secretion of materials to the epididymal lumen, hence principal cells have high secretory and endocytic activity (Zhou et al., 2018). These cells are characterized by long stereocilia extended from the apical surface (Hassan & Holtz, 2024). Principal cells also synthesize numbers of proteins that will be stored in cells or actively secreted to lumen compartment. Additionally, principal cells synthesize and release cargo containing epididymosomes (Faisal & Akbarsha, 2021). Principal cells constitute approximately 80% epithelium in the epididymis duct (Akmal et al., 2015).

Principal cells are characterized by more developed and rich presence of secretory apparatuses, such as Golgi complex (Martínez-Martínez et al., 2017).

In the epididymis, there are cells that secrete H+ ion to epididymal lumen and are subject to the process of endocytosis, known as apical cells and narrow cells (Liu et al., 2024). Apical cells can be found in the initial epithelial segment of the epididymis and have endocytic properties, while narrow cells are located in the initial segment too, but these cells have more narrowed structures compared to the surrounding principal cells (James et al., 2020). There are cells found concentrated in the caput, corpus and cauda segment of the epididymis, which are clear cells that are responsible for engulfing the cytoplasmic droplets released by sperm cells in the epididymal lumen during the process of maturation (James et al., 2020). Synergy between clear cells and narrow cells responsible in maintaining and regulating the epididymal pH.

Basal cells are located at the basal membrane of the epididymis. These cells are integral parts of tubular structure and suggested these cells indirectly alter the lumen environment by regulating some functions of the principal and clear cells (Zhao et al., 2020). As someone ages, the number of principal cells and basal cells declines in every part of the epididymis, narrow cells in caput segment and clear cells in the corpus segment of the epididymis.

Halo cells are found in all areas of epididymal epithelial and are main immune cells in the epididymis, since halo cells are rich of monocytes, T helper lymphocytes and cytotoxic T lymphocytes (Zhao et al., 2020). Epididymal epithelial is surrounded with smooth muscle which has the thinnest structure in the caput segment and gradually thicken up to cauda in the epididymis (James et al., 2020). Halo cells number increases significantly along with the humans age in all epididymal area.

Spermatogenesis: From Primordial Germ Cells To Sperm Cells

The development of primordial germ cells into spermatogonia stem cells is the first step in the formation of male gametes (James et al., 2020). Population of spermatogonia stem cells must have the capacity to self-regenerate to maintain the stem cells population and to produce progenitor cells that will continue into the process of spermatogenesis to produce sperm cells. The synthesis of BMP8B by spermatogenic germinal cells, or spermatogonia, may influence the initiation of spermatogenesis during adolescence. When BMP8B is essential, germinal cells will begin the differentiation process (Wu et al., 2017). After the cell becomes spermatogonia, spermatogenesis will next take place in the seminiferous tubules. Spermatogenesis at first starts in basal membrane, the most outer area of Sertoli cells aligned in seminiferous tubules towards the lumen of the tubule. Activation and support to the process of spermatogenesis requires important factors which is vitamin A (Griswold, 2016).

The process of spermatogenesis started after birth. After birth, prospermatogonia start to develop, this marks the beginning of spermatogenesis, then prospermatogonia will differentiate into spermatogonia together with the migration to the periphery of testis (Ibtisham et al., 2017). Two types of spermatogonia are Aundiff known as undifferentiated spermatogonia and also B known as differentiating spermatogonia (Yoshida, 2019). Within the Aundiff there is spermatogenic stem cells, which is the most primitive spermatogonia in the testis, which is important to maintain the process of spermatogenesis (Kubota & Brinster, 2018). The spermatogenic stem cells may undergo differentiation to form Apr spermatogonia, which subsequently will generate Aal spermatogonia and will eventually lead to the

differentiation to form A1 spermatogonia (Kubota & Brinster, 2018). The A1 cells will divide through the process of mitosis to form A2, which will divide into A3, and eventually form A4 spermatogonia, then type B spermatogonia. The B spermatogonia will undergo the process of meiosis to produce spermatids.

The differentiation of spermatid into spermatozoa happens through a process called spermiogenesis. During spermiogenesis, there are significant changes in the nucleus which become compact and elongated (Dunleavy et al., 2019). The cytoplasm forms an acrosome and a flagellum; mitochondria are localized at the first segment of the spermatozoon tail; and unused cytoplasm is phagocytized by Sertoli cells (Teves & Roldan, 2022).

Epididymosomes

Extracellular vesicles are mediators in cell-to-cell communication (Kowalczyk et al., 2022), therefore nucleic acid, protein and small size molecules between donor cells and recipient cells will be made possible (Devhare & Ray, 2018; O'Brien et al., 2020). There are three types of extracellular vesicles, namely exosomes, micro vesicles, and apoptotic bodies, each of which have differences in density, size, biological function, formation process and secretion products (Dickhout & Koenen, 2018; Tarique et al., 2019; Vistro et al., 2019). Extracellular vesicles undergo budding from a cell or tissue's plasma membranes as well as through the endosomal system (Stahl & Raposo, 2019). Exosomes represent specific subtypes of derivative vesicles secreted defined as homogenous vesicles, sized 30-100 nm consisted of lipid bilayer, contain specific set of fat, nucleic acid and protein (Frydrychowicz et al., 2015). Extracellular vesicles have an important role in reproduction, but further researches still required to explain the source, mechanism of synthetize, secretion products, the targets and the fates (Höög & Lötvall, 2015).

Environmental conditions in epididymis is a quality control system to ensure the sperm cells have a good survival rate to external environmental conditions and to eliminate damaged cells. Epididymosomes released by epididymal epithelium affect the epididymal environments. Epididymosomes suggested to have an important role in this mechanism on rodents, cattle, and humans (Ali et al., 2023).

Epididymosome is a homogeneous extracellular vesicle measuring 30-150 nm (Alzahrani & Saadeldin, 2021). Epididymosomes are secreted by principal cells of the epididymis via apocrine secretion (Foot & Kumar, 2021; Machtinger et al., 2016). Apocrine secretion from main cells in the epididymal epithelium causes the development of projecting apical blebs into the epididymal lumen (James et al., 2020). Epididymal corpuscle freely interacts with the other cells, such as sperm cells and epithelial cells.

Epididymosomes can interact with neighboring cells to alter one sort of paracrine control, which indirectly affects the sperm maturation process by maintaining a complex epididymal lumen environment (Barrachina et al., 2022). Encapsulation capability of epididymosomes to bring molecules in lipid bilayer protective layer on epididymal lumen shows epididymosomes' role to bring sRNA to spermatozoa inside the epididymis (Ali et al., 2023). Analysis of epididymosomes taken from certain segments all over the epididymis shows significant changes in sRNA content, which is followed by changes in the spermatozoa. This phenomenon gives significant evidence to the role of vesicles in affecting the epigenome of spermatozoa during the transit in the epididymis (Hutcheon et al., 2017). miRNA cargo in

epididymosomes partially isolated from certain segments of epididymis indicate miRNA expression pattern on epithelial cells from the same segments (James et al., 2020). Evidence shows that epididymosomes have the capability to bind in vitro with epithelial cells, therefore it is made possible that transport from sRNA cargo to epithelial cells by epididymosomes in vivo can functionally regulate gene expression pattern in cells.

Sperm cells entering the epididymis are immature and not ready to fertilize ovum. In the epididymis, maturation and capacitation of sperm needed for sperm cells to be able to withstand the external environment and ready to fertilize. In the process to become mature sperm, sperm cells go through changes in protein, cholesterol, phospholipid content and also sncRNA load all along inside the epididymis (Ali et al., 2023). These changes affected by microenvironment in the epididymis influenced by epididymosomes to the sperm cells.

In vitro studies demonstrate that epididymosomes can temporarily merge and bind with sperm to facilitate protein transfer (Martin-Deleon, 2015). This cause epididymosomes related with the process of alteration in sperm proteome. It is known that epididymosome-derived proteomes differ greatly from luminal plasma proteomes and exhibit segment-specific protein profiles consistent with known sperm proteins. Through epididymosomes also brought proteins that when all of them are synergized can improve sperm motility, metabolism, oxidation reduction, acrosomal reaction, capacitation and fertilization (Gaikwad et al., 2020). For example, human epididymosomes are known to bring secretory protein rich with disulfide-isomerase A protein (PDIA), macrophage migration inhibitory factor (MIF), clusterin protein (CLU), cysteine (CRISP), and metalloprotease-disintegrins (ADAM) (Ali et al., 2023). Besides that, there are also other proteins related such as prominin-2 found in cauda epididymosomes (Nixon et al., 2019), lactadherine (MFGE8), endoplasmin (HSP90B1), cluster of differentiation (CD63), member of 26S proteasome non-ATPase regulatory subunits (PSMD), sorbitol dehydrogenase (SDH), aldehyde dehydrogenase (ALDH2), beta-1,4-galactocyltransferase (B4GALT), BAG6 protein rich with large proline (BAG6), Src kinase tyrosine-protein proto-oncogene (cSRC) and Tcomplex 1 protein subunit complex containing chaperonin (TCP1) are mediators found in epididymosome's proteome (Ali et al., 2023).

The mechanistic observations summarized above should not be treated as proof of equivalent effects in living human subjects. Cargo composition varies by epididymal segment and experimental preparation, while isolated-vesicle uptake and molecular transfer do not necessarily demonstrate improved fertility outcomes. Studies that directly connect specific cargo changes with standardized human sperm-function measurements are therefore needed.

In the maturation process after the sperm released from the epididymis, epididymosomes are suggested to have a role in the lipid remodeling process and changes in proteome environment (Angrimani et al., 2017). These changes are important in capacitation process when the sperm cells are in the female reproductive tract to maintain the capacity of sperm plasma membrane. Epididymosomes also have a role in miRNA and tRF transfer to sperm cells in the epididymis (Reilly, 2016; Rompala et al., 2018; R. Sharma et al., 2018; U. Sharma et al., 2016). Changes happened in this process positively affect in the produced sperm population functional capacity.

CONCLUSION

The findings of this narrative literature review indicated that the epididymis provided a specialized, region-specific luminal microenvironment that supported the functional maturation of spermatozoa following their release from the testes. Epididymal epithelial cells and epididymosomes contributed to this process through the secretion and transfer of bioactive molecular cargo, including proteins, lipids, and small regulatory RNAs, which were associated with sperm plasma membrane remodeling, motility acquisition, and other reproductive functions. These findings highlighted the biological importance of extracellular vesicle-mediated communication between the epididymal epithelium and spermatozoa during posttesticular maturation. Nevertheless, much of the mechanistic evidence was derived from animal models and in vitro experiments, limiting its direct applicability to human reproductive physiology. Furthermore, the detection or transfer of epididymosomal cargo did not independently establish improved fertilization outcomes or validate specific molecular components as clinically reliable biomarkers of male infertility. Overall, the review emphasized the potential significance of epididymosomes in understanding sperm maturation while recognizing the need for further experimental and clinical validation.

Future research should employ standardized and transparently reported procedures for epididymosome isolation, characterization, and molecular cargo analysis to improve the reproducibility and comparability of findings. Comparative investigations across different epididymal regions, species, and relevant human populations are recommended to identify molecular components consistently associated with sperm functional maturation. Further studies involving human biological samples, appropriate control groups, and validated assessments of sperm function are necessary to determine the diagnostic accuracy and clinical relevance of candidate epididymosomal biomarkers. Additionally, future investigations should distinguish molecular modifications acquired during epididymal transit from those associated with subsequent sperm capacitation and evaluate their relationships with clinically meaningful reproductive outcomes. Until sufficient evidence becomes available, epididymosome-associated bioactive cargo should be regarded as a promising subject for reproductive research and biomarker development rather than an established diagnostic tool or therapeutic intervention for male infertility.

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CONFLICT OF INTEREST

The author states that there is no conflict of interest in the preparation of this article.

AUTHOR CONTRIBUTION

All authors contributed to conceptualization, search and synthesis of literature, interpretation of results, manuscript preparation, and critical review of manuscripts. All authors have read and approved the final version of the manuscript.

GENERATIVE ARTIFICIAL INTELLIGENCE USAGE STATEMENT

The authors declare that Generative Artificial Intelligence (Generative AI) was used solely to assist with language refinement, grammatical correction, and improvement of manuscript readability. All scientific concepts, interpretations, literature synthesis, analyses, and conclusions were developed by the authors. All AI-assisted content was carefully reviewed, verified, and revised by the authors, who take full responsibility for the accuracy, integrity, and final content of the manuscript.

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