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The Blood–Epididymis Barrier: Morphological, Physiological, Immunological, and Seasonal Aspects, and the Impact of Destabilizing Factors

Marat F. Ryskulov, Nicolai N. Shevlyuk

Orenburg state medical university, Orenburg, Russia

ABSTRACT

Spermatozoa entering the epididymis from the testis are unable to actively move and do not possess fertilizing ability. These functions are acquired within the lumen of the epididymal ducts, where the components of the blood–epididymis barrier create a specialized environment. The blood–epididymis barrier restricts paracellular transport and stimulates receptor-mediated transport of macromolecules across the epididymal epithelium. The blood–epididymis barrier consists of a pseudostratified columnar epithelium resting on a basement membrane, loose connective tissue of the lamina propria, and capillary endothelium located on its own basement membrane. Apical tight junctions and adherens junctions between adjacent principal cells of the pseudostratified epithelium play a key role in the blood–epididymis barrier's function. Tight junctions are composed of various families of transmembrane proteins. The vascular component of the blood–epididymis barrier features continuous endothelium on an uninterrupted basement membrane. Alongside the epithelial and vascular components, interactions among dendritic cells, macrophages, and lymphocytes are critical in regulating blood–epididymis barrier permeability. In many species, the epididymis consists of 5 to 9 segments, each with distinct morphofunctional and biochemical characteristics. It has been shown that the barrier function becomes progressively more pronounced from the caput toward the cauda of the epididymis. Impaired function of intercellular junctions in the blood–epididymis barrier is considered a factor contributing to male infertility.

This review aimed to analyze the data on the morphofunctional organization of the blood–epididymis barrier.

Keywords: reproductive system; epididymis; epithelium; blood–epididymis barrier.

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Гематоэпидидимальный барьер: морфологические, физиологические, иммунологические и сезонные аспекты, воздействие дестабилизирующих факторов

М.Ф. Рыскулов, Н.Н. Шевлюк

Оренбургский государственный медицинский университет, Оренбург, Россия

АННОТАЦИЯ

Попадающие из семенника (яичка) в его придаток (эпидидимис) сперматозоиды не могут активно перемещаться и не обладают способностью к оплодотворению. Эти функции сперматозоиды приобретают в просвете канальцев придатка, где компоненты гематоэпидидимального барьера формируют особую среду. Гематоэпидидимальный барьер ограничивает парацеллюлярный транспорт и стимулирует рецептор-опосредованный транспорт макромолекул через эпителий придатка. Гематоэпидидимальный барьер включает псевдомногослойный столбчатый эпителий, лежащий на базальной мембране, рыхлую соединительную ткань собственной пластинки слизистой и эндотелий капилляров, расположенный на базальной мембране. Ведущую роль в функционировании гематоэпидидимального барьера играют апикальные плотные контакты и адгезивные контакты между соседними главными клетками псевдомногослойного эпителия. Составными компонентами плотных контактов являются трансмембранные белки, включающие несколько семейств. Сосудистая часть гематоэпидидимального барьера представлена непрерывным эндотелием, лежащим на непрерывной базальной мембране. Важную роль в регуляции проницаемости гематоэпидидимального барьера наряду с эпителиальным и сосудистым компонентами играют взаимодействия дендритных клеток, макрофагов и лимфоцитов. У особей разных видов в придатке семенника можно выделить от 5 до 9 отделов, различающихся по морфофункциональным и биохимическим характеристикам. Установлено, что выраженность барьерной функции в придатке возрастает от головки к хвосту. Нарушение функций клеточных контактов в гематоэпидидимальном барьере является одним из факторов мужского бесплодия.

Цель настоящего обзора — проанализировать данные литературы о морфофункциональной организации гематоэпидидимального барьера.

Ключевые слова: репродуктивная система; придаток семенника (яичка); эпителий; гематоэпидидимальный барьер.

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血附睾屏障：形态学、生理学、免疫学和季节性特征及其不稳定因素的影响

Marat F. Ryskulov, Nicolai N. Shevlyuk

Orenburg state medical university, Orenburg, Russia

摘要

来自睾丸的精子在进入附睾时尚不具备主动运动能力及受精能力。这些功能是在附睾小管腔内逐步获得的，在该部位，血附睾屏障的各组成成分共同形成了特有的微环境。血附睾屏障限制旁细胞运输，并促进大分子通过附睾上皮的受体介导运输。血附睾屏障包括：位于基底膜上的假复层柱状上皮、固有层内的疏松结缔组织，以及位于自身基底膜上的毛细血管内皮。假复层上皮相邻主细胞之间的顶端紧密连接和黏附连接在血附睾屏障功能中发挥主导作用。紧密连接由多个跨膜蛋白家族构成。血附睾屏障的血管部分由连续性内皮细胞构成，其位于连续的基底膜之上。除上皮与血管结构外，树突状细胞、巨噬细胞和淋巴细胞之间的相互作用在调控血附睾屏障通透性方面也具有重要作用。在不同物种中，附睾可划分为5至9个结构区段，其在形态和生化特性上存在差异。研究显示，附睾的屏障功能从头部至尾部逐渐增强。血附睾屏障中细胞连接功能的破坏是导致男性不育的因素之一。

本综述旨在分析文献中关于血附睾屏障形态与功能组织的研究资料。

关键词：生殖系统；附睾；上皮；血附睾屏障。

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INTRODUCTION

Histohematic barriers regulate metabolic processes between the bloodstream and tissues, ensuring the selective passage of substances into specific, closed spaces within organs. These barriers include the blood-brain barrier (BBB), glomerular filtration barrier (GFB), blood-air barrier (BAB), and blood–testis barrier (BTB), among others [1–4]. The blood–testis and blood-epididymis (BEB) barriers are crucial for ensuring complete spermatogenesis in the male reproductive system.

Spermatozoa entering the epididymis from the testicles are unable to move actively or fertilize. These functions are acquired within the epididymal lumen, where the BEB components create a special environment. The BEB restricts paracellular transport while stimulating receptor-mediated transport of macromolecules across the epididymal epithelium. Barrier interactions in the epididymis ensure that maturing germ cells are isolated from immunocompetent cells and circulating antibodies [5–8]. Dysfunction of the intercellular junctions in the BEB is considered a contributing factor to male infertility.

This issue can be thoroughly investigated *in vivo* using rat and other animal models of the epididymis, without involving sexually mature infertile men. Therefore, it is crucial to evaluate morphology and functional activity of the BEB in animals, both in laboratories and in their natural biological communities, to better understand its characteristics in humans. This knowledge can contribute to the development of new infertility treatment options.

Notably, despite the numerous papers on various BEB issues in animals and humans, many questions about morphology and functional activity of the BEB remain controversial. This is especially true for the mechanisms that regulate the functions and structural patterns of BEBs in mammals within natural and anthropogenically altered ecosystems [9–11].

This review **aimed** to analyze published data on the morphology and functional activity of the BEB.

MORPHOLOGY AND FUNCTIONAL ACTIVITY OF THE BLOOD-EPIDIDYMIS BARRIER

The epididymis is part of the male reproductive tract, formed by a system of tubules, which includes the efferent ducts and the epididymal duct. The epididymis has three segments: the caput, corpus, and cauda. The caput is formed by the efferent ducts, the corpus and cauda are formed by the epididymis duct.

Any histohematic barrier consists of capillary endothelial cells, endothelial basement membranes, interstitial matrices, basement membranes, and overlying organ epithelia. The BEB consists of a pseudostratified columnar epithelium resting on a basement membrane, loose connective tissues of the lamina propria, and the capillary endothelium resting on its own basement membrane. Morphologically, the BEB is characterized by apical intercellular junctions and adhesive junctions between the adjacent primary cells of pseudostratified columnar epithelium [1, 5, 8, 12–17].

Differences in tight junction have been revealed in various regions of the epididymal epithelium. In the caput epididymis, a significant part of the apical surface of the primary cells is covered by tight junctions, while desmosomes are present in small quantities. In contrast, other segments of the epididymis have smaller areas of tight junctions. The apical surface of primary cells has numerous desmosomes and invaginations of the lateral plasma membrane of one cell into another [17].

The BEB's functional activity is directly dependent on the activity of spermatogenesis. In most animals living in natural ecosystems, spermatogenesis is only active during the reproductive season. For mammals without apparent seasonal reproduction, such as many primates (including humans) and laboratory animals, the activity of spermatogenesis and the functional state of the barrier remain virtually unchanged throughout the year. In cases of seasonal reproduction, the barrier function decreases sharply during reproductive dormancy. This has been demonstrated in mink [13], moles [14], Winkelmann mice [15], and Indian hedgehogs [16]. During active spermatogenesis in the epididymis, the height of the epithelial cells, the length of the stereocilia, the lumen area, and the tubule diameter increase [15].

A comparative analysis of the epididymis in various mammals reveals parallelism in the morphology and functional activity of the BEB.

The BEB system demonstrates reversible regressive processes during seasonal inhibition of the reproductive activity, that are not accompanied by inflammatory responses. Before the start of the reproductive season, spermatogenesis is activated, and the integrity of the BTB and BEB is restored.

Barrier permeability markers reveal the apparent barrier properties of the BEB in various species under normal conditions. For example, horseradish peroxidase was not detected on the luminal surface of the epithelium when it was used as a BEB permeability marker during the reproductive period [13]. Tritium-labeled inulin also showed the apparent barrier properties of the BEB during the reproductive season [18].

The compartmentalization of the epididymis should be mentioned. Some authors suppose that the epididymis of different species contains 5–9 segments that differ in morphological, functional, and biochemical characteristics. The barrier function becomes more apparent from the caput to the cauda [15, 19].

During the reproductive season, when intercellular junctions strengthen, primary cells in the epididymal tubules of various mammals, such as a Winckelmann mouse (*Peromyscus winkelmanni (Carleton))* [15],

a hedgehog *(Paraechinus micropus)* [16], a mole *(Talpa europaea)* [14], a mink *(Mustela vison)* [13], a camel *(Camelus dromedarius)* [20], a donkey *(Equus asinus)* [21], and a horse *(Equus caballus)* [19], include a mature Golgi apparatus, smooth and rough endoplasmic reticulum, secretory vesicles, and lipid granules. All of these organelles essentially disappear during the regression period. The only exceptions are a minimally developed Golgi apparatus and moderately developed rough endoplasmic reticulum. During reproductive dormancy, the basal cells of hedgehogs contain large amounts of lipids and well-developed organelles. However, in reproductive active animals, organelles are poorly expressed [16].

During reproductive dormancy, multiple autophagic vacuoles were observed in primary cells that transformed into lipofuscin pigment granules [14].

MOLECULAR AND BIOLOGICAL CHARACTERISTICS OF THE BLOOD-EPIDIDYMIS BARRIER

Proteins that form the adhesive and tight junctions between epithelial cells play a crucial role in maintaining the morphological integrity of the BEB [8, 22–25].

Tight junctions are composed of three families of transmembrane proteins: claudins (Cldns), MARVEL proteins (e.g., occludin, tricellulin, and marvelD3), and junctional adhesion molecules (JAMs) [24].

The expression levels of claudins 1, 3, 4, 8, and 10 indicates the presence of these proteins at tight junctions throughout the human epididymis. These proteins are found along the lateral borders of primary cells and at the interfaces between primary and basal cells [26]. Claudins 1, 3, and 4 had the highest expression levels. The expression levels of occludin were detected exclusively at the tight junction sites between the primary cells in all three epididymis segments [26, 27]. These data suggest that the epididymis demonstrates a complex gene expression pattern that includes genes involved in forming the BEB. This indicates that the permeability of the BEB is subject to complex regulation.

Occludin immunoreactivity was detected at the lateral and apical junctions of the primary cells in the efferent tubules of the caput of wild rabbits *(Lepus sinensis coreanus)*. In the corpus, occludin is similarly located in both the basolateral and apical junctions of primary cells. In the cauda, occludin immunoreactivity is detected in the cytoplasm of the primary cells [28].

Epithelial cadherin, a calcium-dependent cell adhesion protein, is found in primary cells in various segments of the epididymis. Its presence has been demonstrated at the tight junctions between the lateral plasma membranes of adjacent primary cells [29].

Some substances have been found to play a crucial role in regulating BEB permeability. For example, transforming growth factor beta (TGF-β) isoforms affect BEB permeability and regulate growth of tubular epithelial cells. In addition, TGF-β seems to inhibit sperm differentiation and activate T cells [30]. TGF-β is present in the epididymis of many species. For example, latent TGF-β1 is found in the epididymis of rats, whereas active TGF-β3 is found in the corpus. No active TGF-β2 was detected in any segment of the epididymis. Mice also have high levels of TGF-β1 mRNA in both the caput and corpus of the epididymis. In addition, TGF-β1 and its receptors are found in the apical regions of primary cells in the caput and corpus of the epididymis, which suggests a paracrine process [30].

A study of seasonal fluctuations in oxytocin and oxytocin receptor levels in the epididymis components of muskrat *(Ondatra zibethicus)* showed that their concentrations in the epithelial and smooth muscle cell cytoplasms significantly increases during the reproductive season. The authors suggest that the epididymis is a direct target organ of oxytocin, which can regulate BEB functions through endocrine, autocrine, and paracrine mechanisms [31].

Similar data were obtained in a study of the seasonal activity of oxytocin and its receptors in the epididymis of ground squirrels *(Citellus dauricus Brandt)* [32]. The expression levels of oxytocin and its receptors in epithelial and muscle cells increase during the reproductive season, despite low levels of serum oxytocin. The authors suggest that the epididymis may be a source of oxytocin, which regulates the BEB permeability via oxytocin receptors.

IMMUNOLOGICAL CHARACTERISTICS OF THE BLOOD-EPIDIDYMIS BARRIER

The epididymis performs two opposing immunological functions: maintaining tolerance of immune cells to spermatozoa and responding to pathogens [33].

Approximately 1000 genes in the mouse genome have been found to be active, primarily in developing germ cells in the testes. In addition, many of the proteins encoded by these genes are potential antigens. Immune cells that attack antigens on the sperm membrane can cause immunological infertility. However, the BTB and BEB prevent such damaging effects from the immune system [34].

A peritubular space and the epithelium of the caput epididymis contain a large number of all types of immunocytes, the number of which decreases progressively closer to the sperm duct [35]. The caput epididymis demonstrates high activity of genes that encode immunomodulatory factors such as β-defensins, the bactericidal permeability-increasing protein, and indoleamine 2,3-dioxygenase 1. In contrast, the cauda epididymis demonstrates high expression levels of genes encoding proinflammatory mediators, including proinflammatory cytokines (e.g., IL-1α, IL-6, and IL-17) and chemoattractants (e.g., CCL2, CCL3, CCL4, and CXCL2 and CXCL5), as well as inflammasome-associated transcripts (e.g., NLRP3 and IL-1β). In addition, this segment of the epididymis expresses higher levels of genes associated

with fibrous tissue remodeling and proinflammatory immune responses. These genes are involved in the positive regulation of the nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), collagen fibril arrangement, and the positive regulation of the cascade of extracellular signal-regulated kinases 1 and 2 (ERK1 and ERK2). The closest interactions between epididymal epithelial cells and macrophages are typically observed in the caput epididymis [36–42].

No publications provide a convincing explanation for the distribution of immune cells in various segments of the epididymis. Further research is required to understand the progressive decrease in the number of immunocytes from the caput epididymis to the sperm duct. The high levels of gene expression that encode proinflammatory proteins, as well as the increased number of immune cells in the cauda epididymis, most likely serve to protect against ascending infections.

Voisin et al. [43] reported that the expression of TGF-β in dendritic cells is the most important mechanism of epididymal tolerance to spermatozoa. They demonstrated that immune and non-immune epididymal cells produce both TGF-β ligands and receptors, regardless of the mice's age.

Macrophages play a key role in regulating the activity of circulating antigens in the epididymis [42, 44–45]. It has been demonstrated that epididymal macrophages respond to the apoptosis of epithelial cells induced by unilateral sperm duct ligation [42]. Most epithelial cells undergo apoptosis within 48 hours after dressing. Moreover, the rapid removal of apoptotic cells by macrophages helps maintain an epithelial balance between proliferative activity and apoptosis, thereby preserving the structure and integrity of the BEB.

Michel et al. [33] discovered that antigen-presenting dendritic cells in the epididymal tubules form a dense network in the basement membrane of the epithelium. The prosesses of these cells extend between epithelial cells and apical junctions. Dendritic cells are particularly active in the caput epididymis, where their processes reach the lumen of the tubules, expose antigens, and present them to CD4+ T lymphocytes. The researchers suggest that dendritic cells and macrophages have a dual function in the epididymal epithelium. Under normal conditions, these cells suppress responses to antigens, but when exposed to pathogens during infections, they activate these responses.

Dendritic cells and macrophages internalize and process alloantigenes and autoantigens. The resulting peptides are displayed on their surfaces alongside molecules of the major histocompatibility complex (MHC). MHC-antigen complexes stimulate the proliferation and differentiation of both effector and regulatory T cells by presenting themselves to naïve T cells [46]. Despite the large amount of data in scientific papers, the mechanisms of these interactions are not fully understood.

REACTIVE STRUCTURAL TRANSFORMATIONS OF THE BLOOD-EPIDIDYMIS BARRIER

Despite morphological, physiological, and immune structures and mechanisms that maintain its integrity, the BEB can be negatively affected by many factors.

During epididymitis (inflammation of the epididymis), the BEB is affected by released cytokines, which can result in the loss of its barrier function [47]. The development of a sperm granuloma is one possible mechanism of epididymitis [48].

Studies on the effects of the Zika virus on the BEB in mice showed that the virus replicates efficiently in the primary cells of the epididymal tubules. Apparent infiltration of immunocompetent cells was observed in the epididymis, accompanied by increased levels of IL-6 and IL-28, as well as disruption of tight junctions. These changes created a less favorable microenvironment for sperm maturation [49].

Dube et al. [50] reported that an inability of the epididymal tubule cells to form tight junctions, which constitute the basis of the BEB, was one of the causes of infertility in patients with obstructive azoospermia. This was associated with impaired expression of genes that regulate the synthesis of proteins that comprise tight junction structure (*CRISP1, SPINLW1, NPC2, CD52, DCXR, CDH1, CDH2, CLDN1, CLDN4, CLDN7, CLDN8*).

In mice deficient in cathepsin A, the junctions between the primary cells of the epididymal tubules were disrupted. These cells became vacuolated and demonstrated an increased number of lysosomes, with some of which reached to large sizes. A large number of macrophages were also found in the epithelium and interstitium [51].

Exposure to bisphenol, an organic synthetic compound used in the production of certain plastics, decreases the number of macrophages in the epididymal tubules of mice, as well as the levels of anti-inflammatory and pro-inflammatory cytokines, such as IL-10, IL-6, IL-7, and interferon gamma. At the same time, the levels of the chemotaxis-associated cytokines CCL12, CCL17, CXCL16, and MCP-1 increase. This suggests that bisphenol may affect immune homeostasis and lead to a collapse of macrophage phagocytic activity by inhibiting the production of pro-inflammatory cytokines. These factors contribute to the disruption of the BEB's barrier properties and the development of autoimmune disorders, such as epididymitis and orchitis [52].

Similar changes were reported during the experimental infection of mice with *Trypanosoma equiperdum*, a parasite that disrupts the synthesis of proteins comprising tight junctions in the epithelial tubule cells of the epididymis, leading to the destruction of the basement membrane. The presence of trypanosomes in the epididymal interstitium activates macrophages, which secrete tumor necrosis factor that can disrupt tight junctions between epithelial cells and initiate apoptosis [53].

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In addition, mice with experimental diabetes have been shown to have structural abnormalities in the BEB, including those resulting from a zinc imbalance in the epididymis. A decrease in the expression levels of proteins associated with the morphology and functional activity has been reported in diabetes, including β-catenin, N-cadherin, and aquaporins (AQP3, AQP9, and AQP11) [54].

Treatment options for BEB damage in experimental diabetes are also being studied [55]. A combined treatment with zinc and selenium for eight weeks has been shown to reduce structural epididymal abnormalities and sperm damage in the lumen of epididymal tubules in diabetic rats.

All the evidence suggests that the BEB is extremely sensitive to various destabilizing factors. During seasonal inhibition of reproductive activity, the regression processes in the BEB are reversible, and the BEB fully restores its morphology and functional activity with a new reproductive season. However, under intense negative influences, destructive changes can become irreversible, contributing to infertility.

CONCLUSION

The epithelial part of the BEB functions primarily due to apical tight junctions and adhesive junctions between adjacent cells of the pseudostratified epithelium, as well as due to the vascular part of the BEB, which constitutes a continuous endothelium that rests on a continuous basement membrane. The BEB's functional activity is directly dependent on the activity of spermatogenesis.

Proteins that are part of the adhesive and tight junctions between epithelial cells play a key role in morphology and functional activity of the BEB.

Moreover, the interactions among dendritic cells, macrophages, and lymphocytes are crucial for regulating BEB permeability, along with the epithelial and vascular components. The complex mechanisms of interaction between the BEB components and immune cells are not well understood.

The BEB system demonstrates high plasticity in response to seasonal fluctuations in reproductive activity. A comparative analysis of the epididymis in various mammals reveals parallelism in the morphology and functional activity of the BEB.

ADDITIONAL INFORMATION

Author contributions: The primary contributions are as follows: M.F. Ryskulov, N.N. Shevlyuk: conceptualization, sources analysis, interpretation of results, writing—original draft, writing—review & editing. All the authors approved the version of the manuscript to be published and agreed to be accountable for all aspects of the work, ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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ДОПОЛНИТЕЛЬНАЯ ИНФОРМАЦИЯ

Вклад авторов. Наибольший вклад распределён следующим образом: М.Ф. Рыскулов, Н.Н. Шевлюк — концепция работы, анализ литературных данных, интерпретация результатов, написание и редактирование текста статьи. Все авторы одобрили рукопись (версию для публикации), а также согласились нести ответственность за все аспекты работы, гарантируя надлежащее рассмотрение и решение вопросов, связанных с точностью и добросовестностью любой её части.

Источники финансирования. Авторы заявляют об отсутствии внешнего финансирования при проведении поисково-аналитической работы.

Раскрытие интересов. Авторы заявляют об отсутствии отношений, деятельности и интересов за последние три года, связанных с третьими лицами (коммерческими и некоммерческими), интересы которых могут быть затронуты содержанием статьи.

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AUTHORS' INFO

***Marat F. Ryskulov,** Cand. Sci. (Biology),
Assistant Professor;
address: 6 Sovetskaya st, Orenburg, Russia, 460000;
ORCID: 0009-0002-9569-3585;
eLibrary SPIN: 4813-0330;
e-mail: mar-star89@yandex.ru

Nicolai N. Shevlyuk, Dr. Sci. (Biology), Professor;
ORCID: 0000-0001-9299-0571;
eLibrary SPIN: 6952-0466;
e-mail: k_histology@orgma.ru

ОБ АВТОРАХ

***Рыскулов Марат Фирдатович,** канд. биол. наук,
доцент;
адрес: Россия, 460000, Оренбург, ул. Советская, д. 6;
ORCID: 0009-0002-9569-3585;
eLibrary SPIN: 4813-0330;
e-mail: mar-star89@yandex.ru

Шевлюк Николай Николаевич, д-р биол. наук, профессор;
ORCID: 0000-0001-9299-0571;
eLibrary SPIN: 6952-0466;
e-mail: k_histology@orgma.ru

* Corresponding author / Автор, ответственный за переписку