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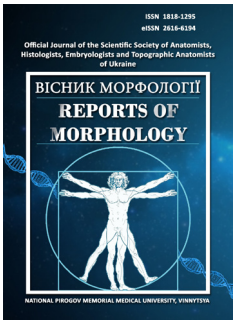

Ultrastructural patterns of formation of transendothelial transport pathways in the prenatal period of ontogeny

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The transport function of the cardiovascular system is realized at the level of the vessels of the hemomicrocirculatory system through the transvascular transport pathways. Normal functioning of the transvascular transport system ensures adequate functioning of the body. This issue is quite relevant, because the study of the structural pathways of transvascular and, especially, transendothelial transport in the norm opens up prospects for pharmacological correction of its disorders in various pathological conditions. The aim of this study is to investigate the formation of structural pathways of transendothelial transport of different types of endothelium in the early periods of human prenatal ontogeny. The structural features of the formation of the transendothelial transport system in the process of link differentiation and specialization of somatic, phenerated and sinusoidal endothelial cells of functionally different organs in the early stages of human prenatal ontogeny were studied by transmission electron microscopy and cryofractography. It has been determined that in the endothelial cells of blood capillaries developing in the direction of somatic capillaries, the main pathways of transendothelial transport are the system of micropinocytic vesicles. In the endothelium of blood exchange microvessels, which gradually develop into capillaries of the phenester type, the pathways of transendothelial transport are represented by a system of micropinocytic vesicles, diaphragmatic phenesters and interendothelial adhesive and gap contacts, which provide a fairly active two-way metabolism at the blood-working cells interface. According to the ultrastructural analysis, the most active transendothelial transport is carried out in endothelial cells that develop into sinusoidal endothelium, which lines the sinusoidal capillaries of the liver lobules. The pathways of transendothelial transport of sinusoidal endothelial cells include a system of micropinocytic vesicles, a system of diaphragmatic fenestrae arranged in clusters and open interendothelial contacts, which creates a morphological basis for active transendothelial transport of substances from the blood to hepatocytes. Thus, in the early periods of prenatal ontogeny, the systems of transendothelial transport of capillary endothelial cells of functionally different organs are formed.

Key words: *prenatal period of ontogeny, endothelium, capillaries, micropinocytic vesicles, interendothelial contacts.*

Introduction

The transport function of the cardiovascular system is realized at the level of blood capillaries of the hemomicrocirculatory system – through the blood-cellular barrier by transvascular transport, bilateral transport of substances occurs, which is necessary to maintain constant homeostasis parameters [6, 11, 15] and normal functioning of each organ and the body as a whole [9, 12, 13, 24]. The pathogenesis of many pathological conditions, such as inflammation [1, 19, 23], trauma [20], infectious diseases [14, 16, 18, 26], hypertension [24], atherosclerosis [4, 22, 29], diabetes mellitus [8], is based on the dysfunction of transvascular transport pathways, which leads to changes in the degree of vascular wall permeability and the onset of clinical symptoms [3, 5] and endothelial dysfunction [17, 25].

In the prenatal period of ontogenesis, the role of the intra-organic bloodstream increases significantly, because the

microcirculation system not only ensures the implementation of the transport function of the cardiovascular system, but also contributes to normal processes of organ and histogenesis, and determines the performance of organ-specific functions of developing organs. Disturbances in the transvascular transport system during the prenatal period of ontogeny can lead to abnormal developmental processes, which causes degenerative phenomena in developing organs. Violation of their functions often leads to the formation of various malformations, sometimes incompatible with life [2]. The intensity of transvascular transport processes is determined by the type of blood capillaries in the hemomicrocirculatory bed. It is generally accepted to define the following types of blood capillaries by the structure of endothelial cells; capillaries of somatic, fenestrated and sinusoidal types [10]. Somatic capillaries are characterized by high selectivity of transvascular permeability. This type of capillaries is the most common and is found in organs that do not require intensive bilateral transport of substances to perform their organ-specific functions, but ensure the preservation of the parameters of the organ microregions [10]. Skeletal muscle vessels are a classic model for studying somatic capillaries. Fenestrated capillaries are inherent in organs with a high intensity of transcapillary metabolism at the blood-working elements of the organ, which is necessary for the performance of their organ-specific functions, for example, blood capillaries of the small intestine mucosa, endocrine organs. Sinusoidal capillaries are found only in liver lobules. Their structure promotes maximum contact between blood and hepatocytes, which is the structural basis for the liver's detoxification function. Transvascular transport pathways are determined by the structure of the wall of the corresponding blood capillary, where endothelial cells play a leading role [18, 20]. The transendothelial transport pathways include the system of micropinocytic vesicles, their derivatives, and interendothelial contacts [7, 17, 30]. The structure of transendothelial transport pathways in the normal postnatal period of ontogeny has been studied in detail [3, 28]. However, the issues of formation of transendothelial transport pathways in the prenatal period of ontogeny, when the processes of histo- and organogenesis determine the normal development of individual organs and the organism as a whole, are still insufficiently covered. The knowledge of the structure of transport pathways through the vascular wall in the normal state opens up wide opportunities to study the factors that affect the structure and function of transvascular and transendothelial pathways and is promising for the development of pharmacological effects on this process.

The aim of this study is to investigate the formation of structural pathways of transendothelial transport of different types of endothelium in the early periods of human prenatal ontogeny at the ultrastructural level.

Materials and methods

The work was performed on 12 human embryos and fetuses aged 4-5 to 16 weeks of prenatal ontogeny. The cadaveric material was obtained from obstetric and gynecological departments of Kyiv hospitals after spontaneous abortions, as a result of mental or mechanical trauma, therapeutic abortions, and preterm births. The material for the study does not contradict the basic bioethical standards of the Helsinki Declaration of the World Medical Association "Ethical Principles for Medical Research Involving Human Subjects", which was adopted by the 18th General Assembly of the WMA in Helsinki in 1964 and revised by the 59th General Assembly of the WMA in Seoul in 2008. The work was approved at the meeting of the Bioethics Commission of Bogomolets National Medical University on April 2, 2024 (Protocol No. 2).

The age of the embryos and fetuses was determined by measuring the parieto-coccygeal and parieto-calcaneal sizes. In determining the age of the embryo and fetus, the data of the mother's history and medical examination were also taken into account.

In accordance with the purpose of the study, blood microvessels of functionally different organs (skeletal muscle, small intestine and liver) were studied.

The material was processed by transmission electron microscopy and cryofractography, which allow visualization of transendothelial transport pathways. The material for transmission electron microscopy was processed according to the conventional method. Ultrathin sections were contrasted with uranyl acetate and lead citrate. The preparations were examined and photographed using UEMV-100 AK and JEM-100B electron microscopes. For the cryofractor study, the tissue blocks were fixed in 2.5 % glutaraldehyde solution, impregnated in 25 % glycerol solution, successively frozen in liquid Freon-22 and liquid nitrogen, and sectioned with subsequent preparation of carbon-platinum replicas in the BALZERS BAF-301 apparatus. The resulting preparations were examined in a JEM-100B electron microscope.

Results

At 4-5 weeks of embryogenesis, the metabolic needs of the cells of the forming organs are met by the pre-vascular microcirculation pathways formed by interstitial compartments of various shapes and sizes, which are limited by the processes and bodies of mesenchymal cells and by channels and gaps between the working cells of the organ. Primary blood microvessels (protocapillary type vessels) begin to form at 4-5 weeks of embryonic development due to the expansion of intercellular channels and gaps in the areas of aggregation of spindle-shaped mesenchymal cells. In the lumen of many intercellular gaps, blood cells are detected, resulting in the formation of blood islets (Fig. 1).

Mitosis of spindle cells is detected in some areas. Spindle cells, which line the primary blood vessels, gradually differentiate into stromal cells. One of the earliest signs of spindle cell differentiation into stromal cells is the formation of dense intercellular contacts between individual cells. However, the primary protocapillaries at this stage of development are not yet closed and freely communicate with

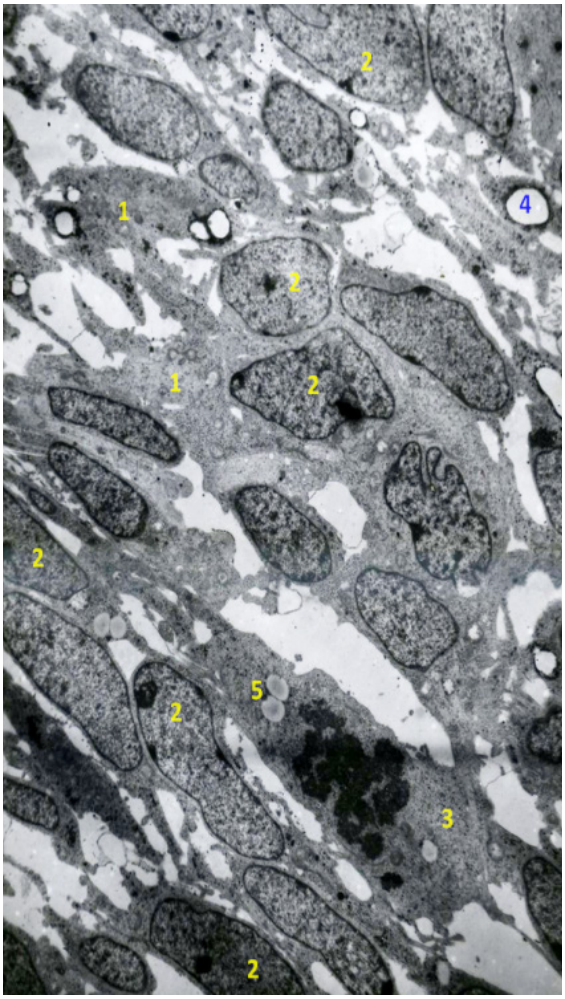

Fig. 1. Spindle-shaped mesenchymal cells of the small intestine of a human embryo of 4-5 weeks of prenatal ontogeny: 1 – mesenchymal cell cytoplasm; 2 – mesenchymal cell nucleus; 3 – mesenchymal cell mitosis; 4 – glycogen granules; 5 – lipid droplet. ×2000.

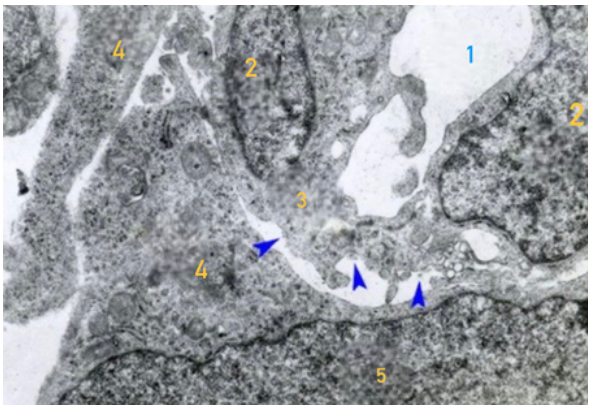

Fig. 2. Primary microvessel of the protocapillary type in the skeletal muscle of the human embryo at 4-5 weeks of prenatal ontogeny: 1 – protocapillary lumen; 2 – primordial endothelial cell nucleus; 3 – primordial endothelial cell cytoplasm; 4 – mesenchymal cell cytoplasm; 5 – mesenchymal cell nucleus. Arrows indicate clusters of electron-dense material on the basal surface of the endothelial cell. ×6600.

the interstitial space through intercellular gaps. Gradually, the coastal cells differentiate into primordial endothelial cells that line the primary protocapillaries. One of the signs of structural differentiation of the primordial endothelial cells is the appearance in their cytoplasm of single large micropinocytic vesicles, which are prone to fusion to form multivesicular complexes (Fig. 2).

Also, the primordial endothelial cells are interconnected by dense interendothelial contacts, forming a continuous cell layer. Morphologically, primordial endothelial cells are continuous endothelial cells. Gradually, discretely formed primary microvessels such as protocapillaries are widely anastomosed to each other, forming a primary diffuse protocapillary bed.

At 5-6 weeks of embryonic development, the diffuse intra-organic protocapillary bed of the organ is connected to the fetal main bloodstream, which is the beginning of the circulatory phase of the development of the intra-organic microcirculatory bed. Morphologic evidence of this process is the appearance of adventitious and outflow vessels in the diffuse protocapillary bed. The beginning of the circulatory phase of the intra-organic microcirculatory bed development causes the processes of link differentiation of the vessels of the diffuse protocapillary bed. The supply vessels gradually differentiate into arterioles and precapillary arterioles. Drainage vessels give rise to the venular link of the hemomicrocirculatory system and lymphatic microvessels. The metabolic microvessels develop into blood capillaries, the main metabolic link of the hemomicrocirculatory system.

In the endothelial cells of metabolic microvessels, in parallel to the processes of link differentiation, structural signs of specialization are revealed, which are due to the peculiarities of the functional activity of the organ. The main structural manifestation of endothelial cell specialization is the restructuring of the micropinocytic vesicle system and its derivatives, as well as changes in the morphology of interendothelial contacts.

In skeletal muscle, as a result of the process of specialization, continuous endothelial cells lining the metabolic microvessels of the primary protocapillary bed develop in the direction of somatic endothelial cells, which are inherent in the blood capillaries of the secondary hemomicrocirculatory bed. The formation of endothelial cytoplasm zonation occurs – the perikaryon zone and peripheral cytoplasmic compartments are determined, which gradually become thinner and longer. In the process of formation of endothelial cell zonation, redistribution of synthetic apparatus organelles, which are concentrated in the perikaryon zone, is determined. All classes of micropinocytic vesicles are located in the peripheral cytoplasmic compartments. Free micropinocytic vesicles dominate, their number increasing with fetal growth. Gradually, free micropinocytic vesicles decrease in diameter. Free large micropinocytic vesicles almost disappear and the population of micropinocytic vesicles becomes more homogeneous in size. On the luminal and basal surfaces of the endothelial lining, diaphragmatic micropinocytic vesicles

are detected, the cells of which are blocked by a single-layer diaphragm. These vesicles are filled with medium electron density content. The diameter of micropinocytic vesicles attached to the luminal surface of the endothelial lining is smaller than the diameter of micropinocytic vesicles associated with the basal surface. According to the data of cryofractography, micropinocytic vesicles attached to the luminal and basal surfaces of endothelial cells have a flask-shaped shape with an elongated elongated neck, which open into the lumen of the vessel or the abluminal surface of the endothelial cell, respectively (Fig. 3).

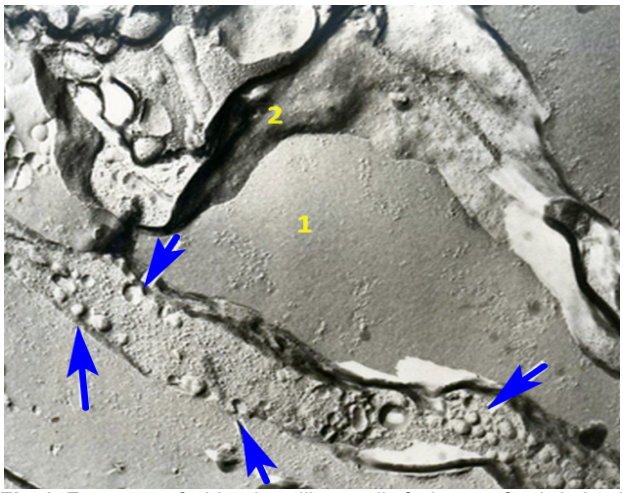

Fig. 3. Fragment of a blood capillary wall of a human fetal skeletal muscle at 16 weeks of prenatal ontogeny: 1 – capillary lumen; 2 – endothelial cell cytoplasm. Arrows indicate micropinocytic vesicles. Cryofractography, ×10000.

Developing somatic-type endothelial cells are characterized by complicated interendothelial contacts. The junctions between adjacent endothelial cells lengthen and acquire a complex configuration. The interendothelial gaps are narrow and virtually no dilatation is detected. Interendothelial gaps are filled with a substance of medium electron density. Within one interendothelial junction, the membranes of neighboring endothelial cells approach, followed by their fusion and formation of dense contacts such as obliteration zones. Within one interendothelial gap, 5-10 obliteration zones are formed. According to cryofractography, the variability of the relationship between the membranes of neighboring endothelial cells is determined within one interendothelial gap. Tight contacts alternate with gap (communication) contacts. A dense interendothelial contact is formed by a contact strip or fibre, which on the P-surface of the chip is formed by a comb consisting of globular lobules, and on the E-surface - by complementary grooves. Dense contact is interrupted by gap contact, which is formed by a miniature plaque of intramembrane particles, which are formed by globules on the P-surface of the chip and complementary dimples on the E-surface. Thus, according to the data of cryofractography, different types of relationships between the intramembrane components of the membranes of contacting endothelial cells are determined along one interendothelial junction.

The exchange microvessels of the primary protocapillary bed of the small intestine gradually differentiate into fenestrated blood capillaries. In the endothelial cells lining the metabolic microvessels of the primary protocapillary bed, the processes of specialization are determined in parallel with the processes of link differentiation, which leads to the formation of phenesterified endothelial cells. Intensive processes of cytoplasmic zonation are determined in the endothelial cells of the small intestine microvasculature: a small perikaryon zone and long, thinned peripheral cytoplasmic compartments are determined. At the early stages of link differentiation, the peripheral cytoplasmic compartments are uneven in thickness: alternation of thicker cytoplasmic islands and thinned areas is determined. With the growth of the fetus, the length of the thinned peripheral areas of endothelial cells gradually increases. Organelles of the synthetic apparatus are concentrated in the perikaryon zone. Structural manifestations of specialization processes are transformation of inter-endothelial contacts, qualitative and quantitative changes in the micropinocytic transport system and the appearance of diaphragmatic fenestrae. Developing endothelial cells are characterized by polymorphism of interendothelial contacts. Long, complexly configured interendothelial gaps filled with a medium electron density substance are predominantly formed between neighboring endothelial cells. The interendothelial gap alternates between narrowed and dilated areas. In some places, the membranes of neighboring endothelial cells are quite tightly adjacent to each other, but a very narrow interendothelial gap is preserved between them. In some areas, neighboring endothelial cells approach each other at a short distance with their lateral surfaces and a short, straight, uneven interendothelial gap is formed between them. The micropinocytic transport system changes most intensively. With the growth of the fetus, a progressive increase in the population of free micropinocytic vesicles is determined, which are mainly concentrated in the peripheral cytoplasmic compartments. The size of micropinocytic vesicles gradually decreases. The population of free micropinocytic vesicles becomes more homogeneous in diameter. The micropinocytic vesicles attached to the luminal and basal surfaces of the endothelial lining look like rounded flasks with the neck covered by an electron-dense single-layer diaphragm. The size of attached vesicles also decreases with fetal age. The system of micropinocytic vesicles is characterized by dynamic transformations that lead to the appearance of diaphragmatic phenesters – derivatives of micropinocytic vesicles. In the thinned areas of the cytoplasm, a chain of several micropinocytic vesicles is detected, forming transendothelial channels that open both to the luminal and basal surfaces of the endothelium. Discrete micropinocytic vesicles occupying the entire thickness of the endothelial cytoplasm are detected in the thinnest peripheral areas of the endothelial cytoplasm. The micropinocytic vesicle cell is blocked by a single-layer diaphragm and opens onto the luminal or basal surface of the endothelial cell. In some areas, the micropinocytic vesicle has two cells,

which are covered by a diaphragm and open to the basal and luminal surface of the endothelium. Subsequently, the structural transformation of such micropinocytic vesicles leads to the appearance of diaphragmatic fenestrae. The first diaphragmatic fenestrae in endothelial cells that develop into fenestrated endothelial cells are detected at 8-12 weeks of fetal development (Fig. 4).

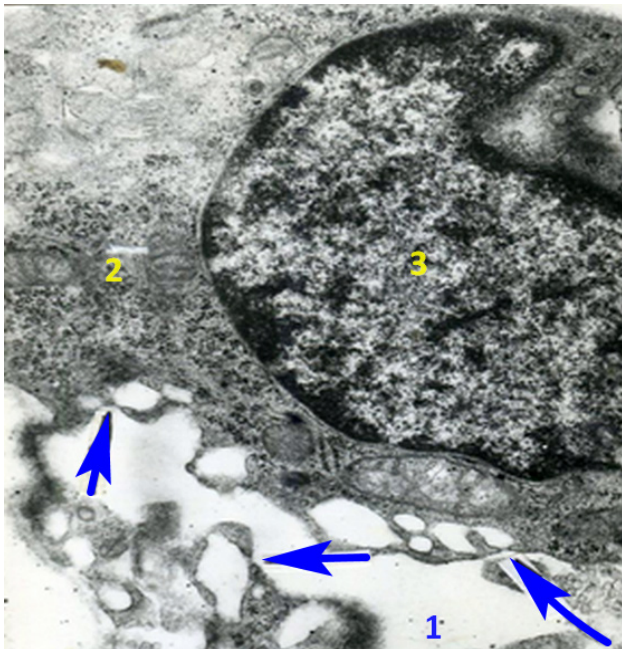

Fig. 4. Fragment of the wall of a blood capillary of the fetal small intestine of the human fetus at 11-12 weeks of prenatal ontogeny: 1 – capillary lumen; 2 – endothelial cytoplasm; 3 – endothelial nucleus. Arrows indicate diaphragmatic fenestrae. ×13300.

With the age of the fetus, the number of diaphragmatic fenestrae gradually increases.

The highest rates of linkage differentiation are determined in the exchange microvessels of the primary protocapillary liver bed. In parallel with the processes of link differentiation, the structural features of specialization are determined in the primordial endothelial cells of the continuous type, which are detected quite early - already at 5-6 weeks of embryogenesis. In the cytoplasm of endothelial cells lining the sinusoids of the liver lobule, the perikaryon zone and significantly thinned peripheral areas are clearly distinguished. Organelles of the synthetic apparatus are concentrated in the perikaryon zone, and all classes of micropinocytic vesicles are detected in the peripheral areas, which are significantly thinned. With the growth of the fetus, the number of micropinocytic vesicles increases and their size decreases. At early stages of development, diaphragmatic fenestrae are detected in the endothelial cells lining the sinusoids of the liver lobules. With the age of the fetus, the size of the diaphragmatic fenestrae decreases and their number increases. The dynamics of fenestrae distribution in the cytoplasm of endothelial cells was determined by cryofractography. At the early stages of development, a chaotic distribution of phenesters is determined. With the growth of the fetus, as the processes of specialization deepen, the topography of the fenestrae becomes more ordered – simultaneously with the chaotic arrangement of the fenestrae, clusters of fenestrae are already detected (Fig. 5).

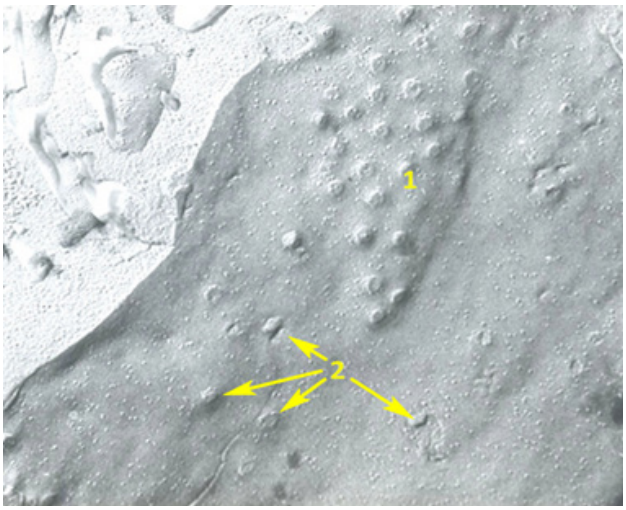

Fig. 5. Cluster arrangement of phenesters in the endotheliocyte of sinusoidal type of the exchange microvessel of the human fetal liver lobule at 7-8 weeks of prenatal ontogeny: 1 – phenester cluster; 2 – single phenesters. Cryofractography. ×18000.

Fenestrae clusters are of different shapes and are formed by 10-20 fenestrae. In the process of cytodifferentiation, the structure of interendothelial contacts increases. The interendothelial gap has a composite configuration that is uneven in width. Short dilated areas alternate with loci of fusion of neighboring membranes with the formation of spots and obliteration zones. Adhesive interendothelial contacts are more often detected. In some areas of the interendothelial junction, the membranes are approximated, but the interendothelial gap is not reduced. With the age of the fetus, few intercellular hatches are detected between adjacent endothelial cells – open intercellular contacts or open fenestrations.

Discussion

The intensity of bilateral transvascular transport is determined by the morphology of the blood-cellular barrier, the central role in the functioning of which belongs to the endothelial cells of blood vessels [21, 24, 27]. In the early stages of prenatal ontogeny, the primary protocapillary bed is not yet closed, which allows direct contact of blood with the interstitial environment. Gradually, the coastal cells differentiate into primordial endothelial cells that line the primary protocapillaries. Numerous, large micropinocytic vesicles are already detected in the cytoplasm of the primordial endothelial cells, and dense intercellular contacts are formed between neighboring endothelial cells. These structural features of the differentiation of primordial endothelial cells indicate a decrease in the intensity of bilateral circulation and the gradual formation of selectivity of transvascular transport due to the development of micropinocytic vesicles.

In the process of further specialization of endothelial cells of metabolic microvessels, transendothelial transport pathways are gradually formed and improved, which correlates with the data of the study on the gradual structural formation of the myocardial hemomicrocirculatory bed in the prenatal period of development [31].

In somatic-type endothelial cells, which are characterized by high selective permeability but not intense enough, the main pathways of transendothelial transport according to morphological studies are the system of micropinocytic vesicles. Gradually, with the age of the fetus, the number of all classes of micropinocytic vesicles increases, and their size decreases and becomes more homogeneous. Interendothelial contacts, among which dense contacts dominate, due to their structure, do not take an active part in metabolic processes between blood and the matrix of the interstitial space.

In phenesterified endothelial cells, which are found in organs with a high degree of transendothelial transport activity and its high selectivity, the main pathways of metabolism between blood and working cells of the organ are a system of micropinocytic vesicles and their derivatives – diaphragmatic phenesters. With the age of the fetus, the number of micropinocytic vesicles and diaphragmatic phenestra increases, which significantly increases the intensity of transendothelial transport. Among the interendothelial contacts, gap junctions and adhesive contacts dominate, which by their structure can also be permeable to certain substances.

The most intense bilateral metabolic processes are determined in sinusoidal endothelial cells of the metabolic microvessels of the liver lobules. In endothelial cells developing towards sinusoidal endothelial cells, the earliest processes of specialization are detected, which are quite intense. The cytoplasm of sinusoidal endothelial cells has a significantly developed micropinocytic transport system. Diaphragmatic fenestrae are formed, the number of which increases with fetal growth. The fenestrae are initially irregularly arranged and then form discrete clusters. Presumably, the clustering of the fenestrae is determined by the organization of the elements of the endothelial cytoskeleton. Other transendothelial transport pathways include open interendothelial contacts or hatches, or open fenestrations, which provide direct contact between blood and the space of Disse.

Thus, the relation of transendothelial transport pathways in different types of endothelium at the early stages of human development was described for the first time at the ultrastructural level. This study opens up the prospect of pharmacological control of transendothelial and transvascular transport processes in various pathological conditions.

Conclusions

1. In the early stages of prenatal ontogeny, structural processes of link differentiation and specialization of endothelial cells lining the metabolic microvessels determine the structural formation of transendothelial transport pathways.

2. In each type of endothelium, the structure of transendothelial transport components is determined by the peculiarities of the structure of the blood-cellular barrier and is determined by the degree of functional activity of the organ.

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УЛЬТРАСТРУКТУРНІ ЗАКОНОМІРНОСТІ ФОРМУВАННЯ ШЛЯХІВ ТРАНСЕНДОТЕЛІАЛЬНОГО ТРАНСПОРТУ В ПРЕНАТАЛЬНОМУ ПЕРІОДІ ОНТОГЕНЕЗУ

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Реалізація транспортної функції серцево-судинної системи відбувається на рівні судин гемомікроциркуляторного русла за допомогою шляхів транссудинного транспорту. Нормальне функціонування системи транссудинного транспорту забезпечує адекватне функціонування організму. Це питання є досить актуальним, тому що вивчення структурних шляхів транссудинного і, особливо, трансендотеліального транспорту в нормі відкриває перспективи фармакологічного корегування його порушень при різних патологічних станах. Метою даного дослідження є вивчення формування структурних шляхів трансендотеліального транспорту різних типів ендотелію в ранні періоди пренатального онтогенезу людини. Методами трансмісійної електронної мікроскопії та кріофрактографії вивчені структурні особливості становлення системи трансендотеліального транспорту в процесі ланкової диференціації та спеціалізації ендотеліоцитів соматичного, фенестрованого та синусоїдного типів функціонально різних органів на ранніх стадіях пренатального онтогенезу людини. Визначено, що в ендотеліоцитах кровоносних капілярів, які розвиваються у напрямку капілярів соматичного типу, основними шляхами трансендотеліального транспорту є система мікропіноцитозних везикул. В ендотелії кровоносних обмінних мікросудин, які поступово розвиваються у капіляри фенестрованого типу, шляхи трансендотеліального транспорту представлені системою мікропіноцитозних везикул, діафрагмованими фенестрами і міжендотеліальними адгезивними і щілинними контактами, що забезпечують досить активний двосторонній обмін речовин на межі кров-робочі клітини органу. За даними ультраструктурного аналізу найбільш активний трансендотеліальний транспорт здійснюється в ендотеліоцитах, що розвиваються в ендотелій синусоїдного типу, котрий вистеляє синусоїдні капіляри печінкових часточок. До шляхів трансендотеліального транспорту ендотеліоцитів синусоїдного типу відносять систему мікропіноцитозних везикул, систему діафрагмованих фенестр, котрі розташовані кластерами, і відкриті міжендотеліальні контакти. Це все створює морфологічний базис для активного трансендотеліального транспорту речовин із крові до гепатоцитів. Таким чином, в ранні періоди пренатального онтогенезу формуються системи трансендотеліального транспорта ендотеліоцитів капілярів функціонально різних органів.

Ключові слова: *пренатальний період онтогенезу, ендотелій, капіляри, мікропіноцитозні везикули, міжендотеліальні контакти.*

Author's contribution

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