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The topography of major salivary glands in human prenatal ontogenesis period

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The issues of salivary gland embryogenesis and perinatal diagnosis are poorly understood and ambiguous. Clarifying the features of the laying, development and formation of the topography of the salivary glands in the prenatal period of ontogenesis is important for a holistic understanding of the structural and functional organization of the salivary apparatus and the oral cavity, the interaction of organs and structures of the oral cavity.

Aim – to study the basic morphological processes of embryogenesis of the major human salivary glands, including the formation of rudiments of secretory and non-secretory acinar glands to assess the immune functions of the fetus and newborn.

Materials and methods. Material for the study of human salivary gland development in the prenatal period was obtained at the Ternopil Regional Pathological Bureau. The collected samples were fixed in 10% neutral formalin solution. From paraffin and epoxy blocks, we received thin slices. From epoxy blocks – cuts, painted with toluidine blue. On paraffin sections, general histological colorings were performed with hematoxylin-eosin, shik-alcian blue, shik-Alzianium blue + Bergan, immunohistochemical studies with grades CX-34, VEGF, and electron-microscopic studies.

Results. In the first stage of embryogenesis, the primary oral fossa was covered by a cuticle of peripheral epithelium. The determination of its immunohistochemical characteristics showed that it contained two varieties of epithelial cells that synthesize keratogialin. The germ of the salivary gland was formed as a result of the growth of the cuticular epithelium in the subjective mesenchyme. The immunohistochemical reaction to VEGF has shown that epithelial rudiments of mesenchyme gave enhanced expression of the marker. There was a phenomenon of vegetation because of the germic factor VEGF presence – the growth of the epithelium in subjective mesenchyme with the formation of primary excretory ducts. The third stage of gland embryogenesis was characterized by the appearance of inserted sections, as well as cross-strapped ducts, which had cells with Bergman-positive grains that formed the APUD system. The fourth stage was characterized by the formation of acinus rudiments, the epithelial cells of which had a shik-positive cytoplasm and a rounded nucleus, indicating a high synthetic activity of the cells.

Conclusion. The morphological study of large salivary glands during embryogenesis showed the stereotypical stages of morphogenesis: formation of a cuticle-peridermal epithelium in the primary oral fossa; its epithelial ingrowth into the underlying mesenchyme; formation of intercalated and striated ducts; formation of rudiments of secretive and non-secretive acinus glands.

The research was carried out in accordance with the principles of the Declaration of Helsinki. The study protocol was approved by the Local Bioethics Commission of an institution. For each fetus, informed consent from the mother to participate in the study was obtained.

The authors declare no conflict of interest.

Keywords: perinatal immunology, embryogenesis, salivary glands.

Топографія великих слинних залоз у пренатальному періоді онтогенезу людини

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Питання ембріогенезу слинних залоз та перинатальної діагностики є мало вивченими та неоднозначними. З'ясування особливостей закладки, розвитку і становлення топографії слинних залоз у пренатальному періоді онтогенезу має важливе значення для цілісного розуміння структурно-функціональної організації слиновидільного апарату та ротової порожнини, взаємодії органів та структур порожнини рота.

Мета – вивчити основні морфологічні процеси ембріогенезу великих слинних залоз людини, формування зачатків секретних і несекретних ацинусних залоз для оцінки імунних функцій плода і новонародженої дитини.

Матеріали і методи. Матеріал для дослідження розвитку слинних залоз людини у внутрішньоутробному періоді було отримано в Тернопільському обласному патологоанатомічному бюро. Відібрані зразки фіксували в 10% розчині нейтрального формаліну. З парафінових і епоксидних блоків ми отримали тонкі зрізи. З епоксидних блоків – вирізи, пофарбовані толуїдиновою синькою. На парафінових зрізах проводили загальне гістологічне фарбування гематоксилін-еозином, шик-альціановим синім, шик-альціановим синім + Бергана, імуногістохімічні дослідження класу CX-34, VEGF та електронно-мікроскопічні дослідження.

Результати. На першому етапі ембріогенезу первинна ротова ямка була вкрита кутикулою периферичного епітелію. Визначення його імуногістохімічних характеристик показало, що він містить два різновиди епітеліальних клітин, які синтезують кератогіалін. Зачаток слинної залози утворився внаслідок проростання кутикулярного епітелію в суб'єктивну мезенхіму. Імуногістохімічна реакція на VEGF показала, що епітеліальні зачатки мезенхіми забезпечували посилену експресію маркера. Простежувався феномен вегетації внаслідок наявності гермінального фактора VEGF – розростання епітелію суб'єктивної мезенхіми з утворенням первинних вивідних проток. Третій етап ембріогенезу залоз характеризувався появою вставних ділянок, а також переплетених проток, які мали клітини з Бергман-позитивними зернами, що утворювали систему APUD. Четверта стадія характеризувалася утворенням зачатків ацинусів, епітеліальні клітини яких мали шик-позитивну цитоплазму та округле ядро, що свідчить про високу синтетичну активність клітин.

Висновки. Морфологічне дослідження великих слинних залоз в ембріогенезі показало стереотипні етапи морфогенезу: утворення кутикуло-перидермального епітелію в первинній ротовій ямці; його епітеліальне вростання в підлеглу мезенхіму; формування вставних і поперечо-смугастих протоків; формування зачатків секретних і несекретних ацинусних залоз.

Дослідження виконані відповідно до принципів Гельсінської Декларації. Протокол дослідження ухвалено Локальною біоетичною комісією установи. Для кожного плода було отримано інформовану згоду матері на участь у дослідженні.

Автори заявляють про відсутність конфлікту інтересів.

Ключові слова: перинатальна імунологія, ембріогенез, слинні залози.

Introduction

Future health status and quality of human life are determined by the state of the intrauterine development period of the fetus and the course of the newborn period [10,15]. At the same time, the immune system of children in European countries is formed today under the influence of an adverse infectious situation caused by the extremely high risk of ante- and neonatal infections [10,11,13]. The urgency of studying the issues of perinatal immunology is indisputable, since fundamental research may be relevant in the study of immune response formation in ontogenesis. Taking into account the peculiarity of the child's immune system, which is in the stage of formation and development, it determines the peculiarity of its response to antigenic stimulation [4,9,12,14].

Numerous experimental and clinical studies have shown that not only newborns, but also the fetus is able to synthesize antibodies actively [3,4,10,11]. After birth, as a result of catabolism, the level of class M immunoglobulins begins to decrease, as the reserve possibilities of immunological mechanisms in the first months of a child's life are low, and Class A, immunoglobulins associated antibodies in the newborn's blood, are absent. This information is confirmed by reports of the majority of researchers. The salivary glands participating in the provision of local immunity are incomplete by the time of the child's birth: their differentiation usually ends up in 6 months to 2 years, but morphogenesis continues to 16-20 years [3,5,8].

Currently, the question of salivary gland embryogenesis and perinatal diagnosis is poorly understood and controversial. Elucidation of the topography and formation of salivary glands in the intrauterine period of ontogenesis is important for understanding the structural and functional organization of the oral cavity organs, the interaction of organs and structures of the oral cavity [1,2,3,7].

The ***aim*** of the research – to study the basic morphological processes of embryogenesis of the major human salivary glands, including the formation of rudiments of secretory and non-secretory acinar glands to assess the immune functions of the fetus and newborn.

Materials and methods of the study

The material for the study of the development of human salivary glands in the prenatal period was obtained from the Ternopil Regional Pathological Bureau, which came from the Ternopil Regional Clinical Perinatal Center «Mother and Child». Fetal age was determined based on the results of the patient's history, obstetric and gynecological status, and was confirmed by measuring the parietal-calcaneal and parietal-coccygeal lengths. The study was conducted on 11 fetuses of both sexes, without external signs of anatomical deviations or anomalies and without obvious macroscopic deviations from the normal structure of the skull (in accordance with the order of the Ministry of Health of Ukraine dated 19.02.96 No. 31). The materials of the research were major salivary glands – parotid, submandibular and sublingual glands. The collected samples were fixed in 10% neutral formalin solution. From paraffin and epoxy blocks, we received thin slices. From epoxy blocks – cuts, painted with toluidine blue. On paraffin sections, general histological colorings were performed with hematoxylin-eosin, shik-alcian blue, SHIK-Alzianium blue + Bergan, immunohistochemical studies with grades CX-34, VEGF and electron-microscopic studies.

Bioethical expertise of scientific research on research methods, compliance with international and Ukrainian legal standards was carried out at a meeting of the Bioethics Commission of Ivan Horbachevsky Ternopil National Medical University, 01.11.2023 (protocol No. 75).

Results of the study and discussion

The results of our study show that, despite the different stages of development during embryogenesis, there are stereotypical stages of formation of various salivary glands. The morphological research of different stages of embryogenesis using histochemical and immunohistochemical coloring methods indicates that in the first stage of embryogenesis, the primary oral fossa is covered by a cuticular peripheral epithelium consisting of three types of cells – basal, intermediate and corneous. Basal cells are located on a fuzzy basal membrane and consist of small basophilic cells that have an elongated core form perpendicular to the basement membrane and a small rim of cytoplasm. In basal cells, figures of mitoses are constantly observed, which indicates their high proliferative activity [6].

Intermediate cells with a weakly basophilic, and sometimes vacuolized cytoplasm and eccentrically placed round or oval nucleus, which is sometimes in the state of mitosis, are placed above the basal cells. A third type of cell is placed above the intermediate cells, represented by horny scales, which desquamate, forming layered structures. The submucosal spine subcutane-

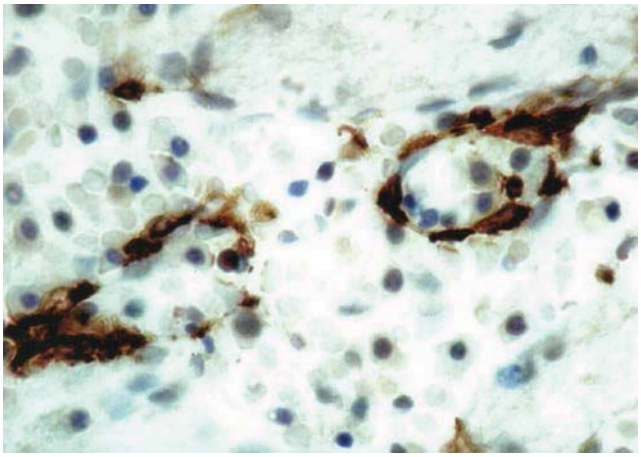

Fig. 1. Cuticular epithelium with two types of cells. Immunohistochemistry, immune response to cytokeratin CX-34. Increase ×100

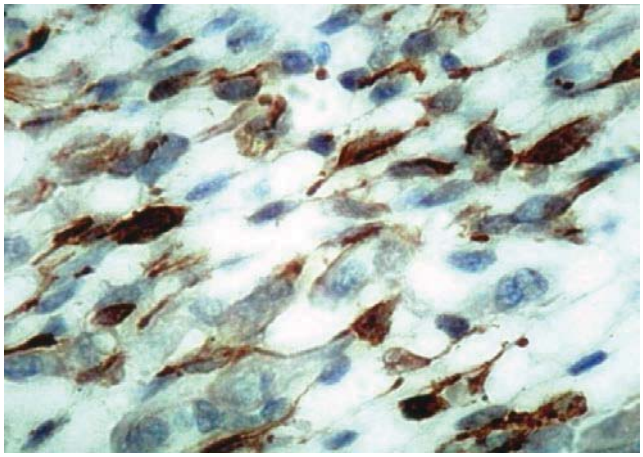

Fig. 2. Small grains of glycogen in the cytoplasm of intermediate cells. Immunohistochemical reaction to the VEGF oncogene. Increase ×100

ous to the cuticular epithelium, is represented by a mycoid tissue in which cells with numerous appendages are located among the homogeneous basic substance. Obviously, due to the presence of mycoid tissue, the formation of its derivatives occurs. Determination of immunohistochemical features of the cuticle epithelium by reaction to cytokeratin CX-34 showed that this type of epithelium contains on the surface two types of epithelial cells (Fig. 1). The first of them expresses cytokeratin moderately or strongly, both directly in the cytoplasm itself, and in their subtle appendages, through which the contacts between individual cells are carried out in syncytic type.

The second variety is represented by cells of larger sizes containing a rounded nucleus with euchromatin and light cytoplasm. Sometimes these cells are in a state of mitosis. Consequently, the cuticular epithelium contains cells that synthesize keratogialin. According to K.V. Holmberg, M.P. Hoffman [9], the cuticular epithelium of the horny scales contains a special type of keratin, rich in lipoproteins – immature keratin. Obviously, due to the presence of this lipoprotein, the amniotic fluid does not penetrate into deep epidermal and dermal layers. As a result of electronic-microscopic research, a certain ultrastructural organization of intermediate cells has been established. Thus, in their cytoplasm, along with well-expressed smooth endoplasmic reticulum, small grains of glycogen are constantly found, which are high-energy material that further provide the morphological processes of salivary gland formation (Fig. 2).

The primordium of the salivary glands is formed as a result of the growth of the cuticular epithelium into the mesenchyme. In this case, the basal cells are clearly identified as an epithelial bud, in the center of which light peridermal epithelial cells are present. There are numerous polymorphic cells around the germ of the salivary gland in the subgenus mesenchyma, which, obviously, are polypotent mesenchymal cells, and from which various connective tissue cellular elements can subsequently be formed.

A further process of differentiation of the salivary gland germ is characterized by the formation of the primordium of the primary excretory ducts. It is characterized by further proliferation of basal cells and the formation of an elongated form of strong components of cells that deeply regenerate into the subjective mesenchyma. The conducted histochemical studies indicate that the primary excretory ducts are covered by two-, three-row, pseudo-large-row shic-positive epithelium with small, rounded nuclei and a narrow rim of the cytoplasm. Homogeneous SHIK-positive secretory masses are constantly observed in the lumen of the tubules. The germ spaces are sometimes wrapped with proliferating cells. Around the primary outflow ducts, a myxoid tissue is placed, represented by a star or oval form of cells around which the alcien-positive substance is present, which contains a large amount of glycosaminoglycans (Fig. 3). Around the epithelium of the duct in the myxoid stroma are elongated or oval mioepithelial cells, which apparently arise from polypotent stem cells by further differentiation.

In order to study the process of vegetation of the cuticular epithelium in the subjective mesenchyma, we conducted an immunohistochemical reaction to VEGF. It has been established that in the epithelial subacute of mesenchyma, an enhanced expression of this marker with the formation of new vascular vessels is observed. In embryogenesis, the germline fac-

tor VEGF stimulates the differentiation of endothelial cells and the formation of the primary vascular wall. Consequently, due to the presence of the germ factor VEGF both in the mesenchymal and epithelial cells, a phenomenon of vegetation occurs – the growth of the epithelium in the subjective mesenchyma with the formation of primary excretory ducts of the salivary glands.

The third stage in the embryogenesis of the salivary glands is characterized by the appearance of the insertion sections on the background of neoanogeogenesis, as well as the transverse strain ducts, which, when stained with shik-alcian blue, are formed predominantly by the dichotomous section of the primary excretory ducts. The origin of the inserted duct has a narrow lumen, which is surrounded by proliferating epithelial cells that form a multi-row structure. The last is characterized by the presence of interphase and mitotic cells. The first ones have an oval nucleus and a SHIK-positive cytoplasm that contacts a weakly expressed basal membrane and an apical surface that reaches the narrow lumen of the insertion duct (Fig. 4).

Mitotically divided cells do not have contact with the basal membrane; their nucleus is in the prometaphase, sometimes the body phase. The migration of mitotic cells from the basement membrane to the narrow lumen of the insertion duct is observed. Due to the different placement of nuclei of the interphase and mitotic cells that form a pseudo-binary epithelium, common to all embryonic rudiments of organs [10].

In the formation of insert glands, their stroma is represented by fluffy SHIK-positive structures, among which homogeneous trabeculae are detected, and sometimes small light enlightenment resembles vascular enlargement (Fig. 5). In order to confirm the position on the formation of new vessels – neoangiogeogenesis in the stroma of the embryonic rudiments of the inserted glands, we carried out an immunohistochemical study on the marker VEGF.

It is established that among the myxoid stroma of the rudiments, newly formed lacunar vessels are found, some of which have a small space, separated by elongated cells of dark brown color. The cells that form the kidney have pronounced VEGF-positive expression (Fig. 6).

The transverse strain of the duct of the salivary glands with a combined coloring of the SHIK-alcian blue + under Bergman is characterized by the presence of a larger lumen, which extends over two parts of the epithelium. The first section resembles

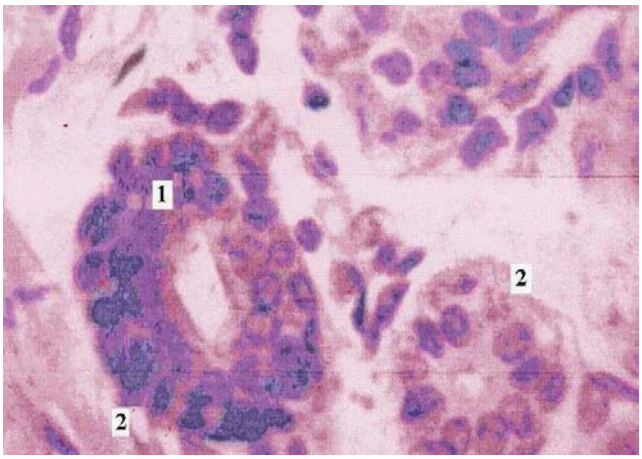

Fig. 3. The germ of the primary excretory ducts of the salivary glands: 1 – epithelial cells; 2 – basement membrane. Colouring SHIK + by Bergman. Enlarg. ×10, rpm ×100

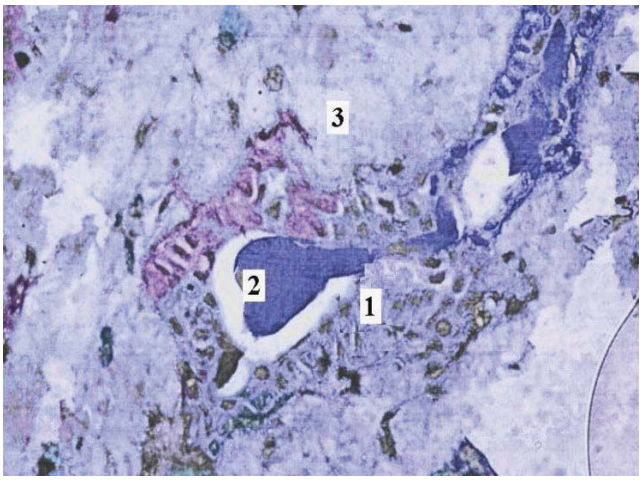

Fig. 4. Pseudocordial epithelium of primary excretory ducts among myxoid mesenchyma: 1 – duct epithelium; 2 – homogeneous secret; 3 – alcian-positive mesenchyma. Colouring by SHIK-alcian blue. Enlarg. ×10, rpm ×40

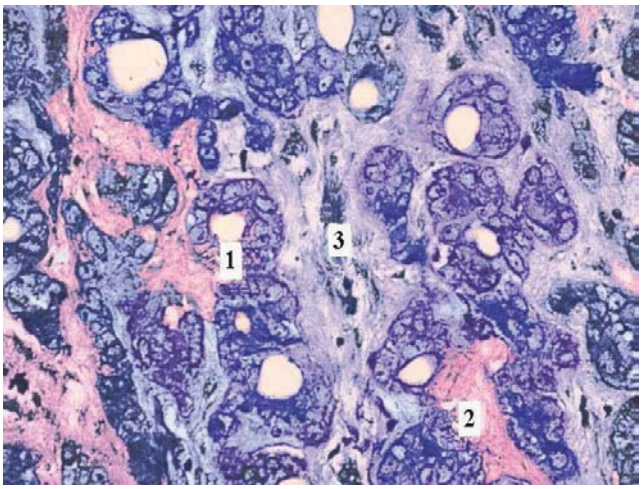

Fig. 5. The rudiments of the inserted gland divisions: 1 – homogeneous shik-positive cell clusters; 2 – myoepithelial cells; 3 – shik-positive trabeculae. Colouring by SHIK + thionic blue. Enlarg. ×10, rpm ×40

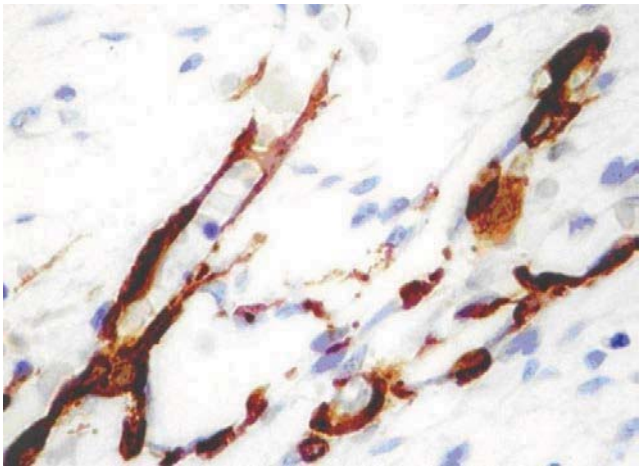

Fig. 6. Expression of VEGF in the newly formed vessels of the germ stroma of the excretory ducts. Immunohistochemical reaction to the VEGF oncogene. Enlarg. ×10, rpm ×100

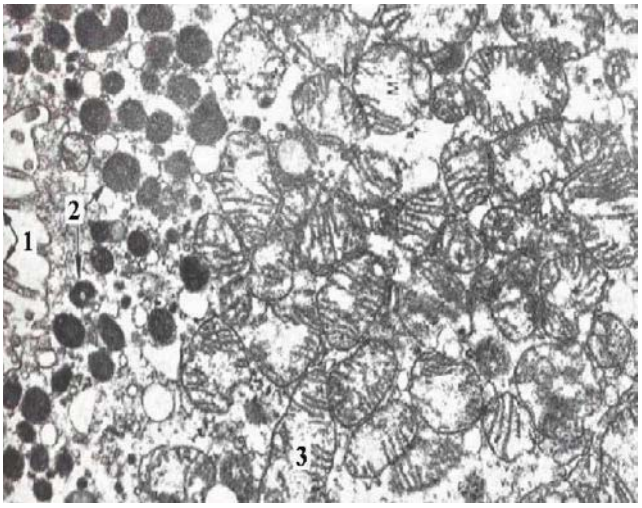

Fig. 7. Ultrastructure of the oncocyte (B-cells): 1 – microvilli; 2 – neurosecretory granules; 3 – mitochondria. Electron microscopy; ×1000

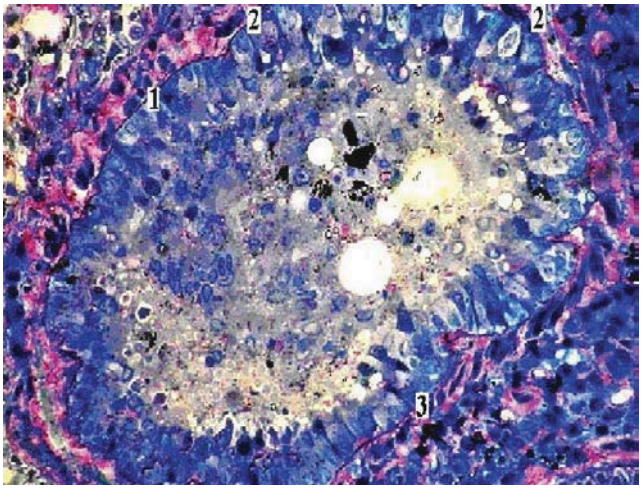

Fig. 8. The structure of salivary acinus germ: 1 – cambial cells; 2 – myoepithelial cells; 3 – basal membrane. Coloring by SHIK-thionic blue. Enlarg. ×200

the structure of a multi-row epithelium with a multi-level arrangement of nuclei – a pseudo-large artery epithelium, characteristic of the insertion duct, and the second is represented by cylindrical cells located on the basement membrane. Cells found in the cytoplasm contain Bergman-positive grains, which sometimes connect with each other, forming light brown masses around the nucleus.

Due to histochemical chromophilic properties of grains, it can be argued that they are part of the neurosecretory cells that make up the APUD system (Amine Precursor Uptake and Decarboxylation) and synthesize biogenic amines and polypeptide hormones. Due to this, the cellular elements of the APUD system are neurohumoral transducers that cause the development of the organs' germs in a certain sequence. This is confirmed by the data of electronic microscopy, which show that cylindrical cells that line up the lumen of the strained ducts of the salivary glands belong to the APUD system and consist of oncocytes that are internationally classified as B-cells (Fig. 7).

Typical ultrastructural features of oncocytes are the presence of a significant number of mitochondria that almost completely fill the cytoplasm, leaving little space for other organelles and neurosecretory granules. The last are first placed around the nucleus near the Golgi apparatus, and then go out to the periphery of the cytoplasm in the form of polymorphs with different osmiophilic densities of granules, which provide an increase in important endocrine factors of the salivary gland. Neurosecretory cells are formed by the formation of organ rudiments by their migration from the neural crest along the vessels in the epithelium, which perform a certain homeostatic function. The fourth stage of the embryogenesis of the salivary glands is characterized by the formation of the actinus rudiments, which, when stained with SHIK-thionine blue, are represented by branched different sizes and shaped by light tubules (Fig. 8). Epithelial cells that line up the acinus rudiments are predominantly cubic in shape with a SHIK-positive cytoplasm and a rounded nucleus, which contains clearly expressed nucleoli, indicating a high synthetic activity of the cells [3]. Between epithelial cells and the basal membrane are located myoepithelial cells that have a spindle-shaped nucleus and processes that are stained with thionine in blue.

The beginnings of acini of the salivary glands are formed due to the concentric placement of epithelial and myoepithelial cells. Unlike the mature acinus,

there is no secretion in the rudiments, although their cytoplasm has a homogeneous SHIK-positive color, indicating the onset of synthetic processes in it. The morphological research carried out by us during embryogenesis showed that despite the different timing of the laying of large salivary glands, they observed stereotypical stages of morphogenesis: formation of a cuticle-peridermal epithelium in the primary oral fossa; the ingestion of it in an underlying mesenchyme by vegetation; formation of insert and transverse strains; formation of rudiments of secretive and non-secreting acinus glands.

Conclusion

A study of the laying, development and formation peculiarities of major salivary glands topography in the prenatal period of human ontogenesis has shown that during embryogenesis, there are stereotypical stages of formation; however, until the birth of the child, salivary glands are incompletely formed. The period of embryogenesis ends with the formation of acini rudiments of the salivary glands, the cytoplasm of which, though it has a homogeneous SHIK-positive color, indicates the onset of synthetic processes in it, but unlike the mature acinus, secretion is absent. Consequently, at the moment of birth, in the neonatal and thoracic periods, there is a reduced excretory function of the salivary glands. The research on immune response formation in ontogenesis, the study of immune function features of salivary glands of fetus and the newborn baby in norm and under the influence of pathological factors has important practical value, based on the knowledge of immunopathogenesis, which will promote optimization of therapy, full rehabilitation and reduce the incidence in early childhood.

Prospects for future research. Study of secretion of major salivary glands in children with secondary immunodeficiency.

The authors declare no conflict of interest.

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