UNIVERSITY OF MEDICINE AND PHARMACY OF CRAIOVA

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CONTRIBUTIONS TO THE KNOWLEDGE OF TISSUE INTRRELATIONS IN SALIVARY GLANDS MORPHOGENESIS

PhD Thesis Abstract

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Abstract: The author have made a micro anatomic analysis of the phenotype transformations determined by the epithelial mesenchyme relations at the level of bronchopulmonary and salivary systems in order to evaluate the mechanisms of the architectural genesis of the tube-alveolar and tube-acinar structures during general and forensic ortology and pathology.

Key words: Mesenchyme, Epithelial mesenchyme inductive relations, Tube-alveolar and tube-acinar structures

I. INTRODUCTION

The genesis and 3D evolution of the dichotomic branching structures are of interest for the fundamental as well as for the applicative research. The study of the ‘epithelial type’ branching models that is characteristic to some organs remains a partially explored field [1]. We selected two anatomic and functional systems for the study of the epithelial mesenchyme inductive interactions: the bronchopulmonary and the salivary glands systems. Two phenomena brought our attention during the ontogenesis of those two systems: first of all, the particularities of the morphogenesis and differentiation processes that involved the tube-like structures, and second, the determinant mechanism that leads to functional specialized structures – the blood air barrier inside the pulmonary respiration system and the glandular acinus inside the salivaryglands’ secretion system.

During the morphogenesis processes, an important role is played by the mesenchyme that is responsible for the regional specificity of induction inside competent structures [2, 3]. In the algorithm of the pulmonary respiration system morphogenesis, this specificity is spectacular [4].

Structural heterogeneity of organs containing dichotomized branching elements leads to problems in understanding their architectural mechanisms of ontogenesis on one side, as well as of evaluating the evolution status in normal and pathologic conditions on the other side, such as:

• What are the elements or structures that interact in the algorithm of morphogenetic synergisms?

• What are the rules to ratify the stages of formation for the branched structures?
• What are the consequences of the epithelial mesenchyme inductive relations?
• What are the mechanisms for epithelial mesenchyme inductive relations?
• How is it possible, the growing and dichotomy branching of the epithelial buds inside the tubealveolar and tube-acinary systems?
• What are the means of inductive interactions?

What are the determinant factors of the mesenchyme phenotype transformations during the achievement of functional sectors: blood air barrier inside lungs and secreting acinus inside salivary glands?
• What is the role of the under epithelial basal membrane at the epithelial mesenchyme border?
• What is the practical value for the knowledge of the specific tissue interrelations during the branched structures’ morphogenesis?
• What are the structure patterns for the derived elements from pulmonary and salivary glands mesenchyme?

II. MATERIALS AND METHODS

Our research was conducted on tissue fragments obtained from human embryos of 5 months old (7 cases) and 6 months old (8 cases) as well as on serial sections through four week embryos (3 cases) and 6 weeks embryos (4 cases), from the Pathology Laboratory of the Clinic and City Hospital Filantropia from Craiova during 2000-2010. Biological samples were processed by means of classical histological methods and the imagistic findings have been digitally computed.

III. RESULTS

We evaluated micro anatomic the phenotype changes determined by the inductive epithelial mesenchyme interrelations during the genesis and evolution of the primordial epithelial
buds and of the branched structures derived from those buds inside the respiration pulmonary and salivary glands systems.

A. The microanatomic evaluation of the inductive epiteliomesenchyme inter-relations that determine the genesis and evolution of the primordial epithelial buds

1. In the 4 weeks human embryo pulmonary system, we identified epithelial aggregates formed inside pulmonary mesenchyme. When examining at the x63 objective we noticed those aggregates of epithelial cells with hyper chromatic nuclei that are sometimes mitotic. On the serried sections through lungs fragments from a 16 weeks fetus, we identified terminal bronchi surrounded by hyper cellular mesenchyme. When examining the wall of the terminal bronchi with the x 20 objective, we observed prismatic cells with hyper chromatic nuclei and caliciform cells. At the periphery of the terminal bronchi one can easily identify cells with a fusiform nucleus, located at the border of the adjacent pulmonary mesenchyme. Newly formed blood vessels exist inside the pulmonary mesenchyme surrounding the terminal bronchi.

2. On the serried sections through the salivary glands system of a 6 weeks embryo we pointed paralingual mesenchyme aggregates containing endoderm epithelial buds that will form the submandibular gland parenchyma. One can easily notice the dichotomized branching of the endoderm buds and their progression to the adjacent mesenchyme. On the Hematoxiline eosin stained sections, the endoderm buds appear as epithelial cells with hyper chromatic and sometimes mitotic nucleus. On the Gomori argentic impregnation sections there is a slight differentiation of the basal membrane at the periphery of the epithelial buds.

The gland acini have various shapes depending on the sectioning planes, on the serried sections through a submandibular gland of a 6 months fetus. Some acini form a lobe that is delimited by mesenchyme bands from the neighboring structures. Inside the lobe, the acini are surrounded by highly vascularized mesenchyme.

When examining at the 20x objective, we identified inside the gland acini some cubic cells that have contiguity relations to the myoepithelial cells at the border with the adjacent mesenchyme.

The intermediate and intralobular ducts ensure the continuity of the acini lumen to the extra lobular tube excretory system. The reticulin fibers appears well differentiated at the level
of the basal membrane underneath the intralobular duct epithelium, as seen in the Gomori argentic impregnation sections

B. The micro anatomic analysis of the branching structures differentiation by morphogenesis synergisms

1. On frontal section through the cervical thoracic region of a 6 weeks embryo we identified inside the pulmonary respiration system some components of the tracheo-bronchial tree, such as: tracheae, right and left main bronchi and lobular bronchi. Pulmonary acinus tributary to terminal bronchi can be observed on the serried sections through the lungs of a 5 months fetus. Structures belonging to the pulmonary parenchyma – ductus alveolaris, atrium alveolaris and sacus alveolaris – are visible at the 10x objective, and they appear in the immediate neighborhood of the pulmonary adjacent mesenchyme. After examining the hematoxiline eosin stained sections with the x40 objective, we identified the phenol type transformations of the pulmonary mesenchyme around acinus that contribute to the processes of alveolus genesis, angiogenesis and remodeling of the space adjacent to the sacus alveolaris. On adult lung injected with China ink one can easily see a luxuriant capillary network around alveolus. In the interlobular stroma there are lymph node formations visible in the lungs of 8 month fetus.

2. In the salivary glands system we noted the differentiation of the acinus structures especially of its terminal section and of the vascular network around acinus groups and at the periphery of the intralobular and intermediate ducts; these findings are specifically seen on submandibular gland fragments harvested from a 5 months fetus. The epithelium has a double layer and there is a differentiation of the peripheral myoepithelial cells at the level of the interlobular ducts ‘wall’.

IV. DISCUSSIONS

The micro-anatomic analysis of the genesis and evolution of the human branching structures allows us to evaluate the epithelium mesenchyme interactions, the morphogen synergisms that play a major role in its differentiation and evolution, as well as the effects
of these changes in the ontogenesis of the dichotomized branching systems. The interactions between epithelium and mesenchyme are well known in the genesis of organs containing tubular structures such as kidney, lung, pancreas, salivary and mammal gland; in their genesis is described the processes of reciprocal induction of epithelium by mesenchyme, and of mesenchyme by epithelium [5].

We raised ourselves the question whether it is possible to appear changes of the epithelial cells in lungs due to the interaction of the bronchi buds to pulmonary mesenchyme; after this event, some mesenchyme cells organize themselves as epithelium. This phenomenon is quite obvious in kidney development where two tissues derived from mesoderm interact – urethral bud and metaneprogenic mesenchyme. The latter determines the prolonging and branching of the urethral bud. It is well proven that the extremities of the urethral bud induce the mesenchyme cells into producing an epithelial aggregate [6]. On the other hand, the metaneprogenic mesenchyme is capable to respond to the urethral bud induction by forming renal tubes. One has observed that the metaneprogenic mesenchyme induction by other epithelium such as from salivary gland or neural tube will lead to the formation of renal tubes and not other structures [7,8].

Based on that observation, Etheridge [9], hypothesized that induction results after the interaction with the endoderm that is closer on the development scale. During the morphogenesis of all organs, connections are established between the tissues that interact. In the interactions between epithelium and mesenchyme, the mesenchyme influences the epithelium and the modified epithelial tissue secretes factors that can modify the mesenchyme [1]. The identification of those factors that intervene in the inter tissue communication has brought attention to many research laboratories [1]. Many researchers consider that mesenchyme controls the specificity of the epithelial structures branching. Saxen [8] pointed out that inside the kidney there is a single type of mesenchyme that can impose that branching. In salivary glands, the mesenchyme determines the branching pattern while the epithelium differentiation is imposed automatically by the epithelium itself [10,11]. In respiratory and digestive systems the regional mesenchyme determine ramification models and the protein types that intervenes in each region [4, 12-14]. The extra cellular matrix has a major role in the ramification process.
Bernfield et al (1984) [15] and Mizuno and Yasugi (1970) [16] hypothesized that the selective degrading of the underneath epithelial basal membrane is important for the branching mechanism. The ramification of the epithelial buds is dependent on the presence of mesenchyme. The mesenchyme can interact to an epithelial tube to provoke its branching by inducing “fissures” that generate lobules on each side of the fissure. The control of the fissure formation is conditioned by the presence of collagen. It is yet unclear the mechanism by which the collagen intervenes. It has been proven that during the mesenchyme induction that leads to the formation of epithelial branching models, it is TGF-1 protein and activin that intervene. TGF-1 favors protein synthesis inside extra cellular matrix and inhibits metal-proteinases that are capable to digest the extra cellular matrix [18,19].

The activine elaborated by the salivary glands disturbs the normal ramification model [5,20]. In lungs, the mesenchyme is inductive to the endoderm bud growing [21]. The initiation of pulmonary growth is determined by the synthesis of the FGF-10 by the mesenchyme cells that soon acts upon III B isoform of the FGF R2 receptor present on the endoderm cells surface. The antepartum development of lungs is particular to other organs. Although the lungs are not necessary as respiratory organs before birth, it must be developed in order to be functional at the time of parturition. There have been described four stages in the genesis and evolution of the lung structural and functional elements. During each stage, elements of the bronchial tree and pulmonary parenchyma are formed.

The mesenchyme exerts three major functions in the tube alveolar pulmonary system: it inducts the growing and differentiation of the endoderm branched canals system up to the terminal bronchi; it generates the vascular networks, bio dynamic structures (smooth muscles) and cartilage structures; and finally it is implicated in the genesis of the respiratory changes sector that includes alveolar ducts, sacus alveolaris and pulmonary alveolae. In our opinion, the structural characteristics of the pulmonary parenchyma during its ontogenesis dynamics and the immaturity of the gas exchange structures at the time of parturition, raise the problem of pulmonary mesenchyme competence for the genesis and differentiation of the pulmonary alveoli under the inductive action of endoderm derivates.
V. CONCLUSIONS

The bronchial tree with a competent aerial transport function is formed after a complex tube genesis process from the endoderm material in the anterior intestine under the inductor action of the pulmonary mesenchyme. The pulmonary parenchyma specialized for aerial exchange derives from the pulmonary mesenchyme that undergoes mesenchyme and epithelial phenotype changes, remaniation of the newly formed structures, vasculogenesis and time and space remodeling.

VI. REFERENCES


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