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ON THE ORIGIN OF LUNG CANCER DEVELOPMENT

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In the review on the issues of histogenesis of lung cancer (LC), the significant results of experimental, pathological, immunohistochemical and molecular-biological studies are presented. However, until now, no data has been obtained that would allow scientists to come to an unambiguous decision about the origin and development of this disease. The question remains not yet fully understood, since researchers discuss the origin of LC development in a hypothetical form. This situation poses the task of further in-depth scientific research, which would make it possible to clarify the unambiguous origin of LC development, and, therefore, would allow solving the problem of its early diagnosis and create grounds for screening programs, which is of high scientific and clinical significance.

***Key Words*: lung cancer, alveolar epithelium, stem cells, histogenesis.**

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Lung cancer (LC) is one of the most common malignant diseases in men worldwide with high mortality rate [1–5]. The incidence of LC in women is 7–10 times lower. In Ukraine, the incidence of LC ranged from 77.8 per 100 thousand population in 2001 to 62.3 per 100 thousand population in 2017, while LC-related mortality in the same years ranged from 63.7 and 50.6 per 100 thousand population. The mortality rates recorded within one year from the date of LC diagnosis are rather stable amounting to 63.8–69.6 per 100 thousand population [3, 6]. In all countries LC is diagnosed at stages III–IV in 60–67% of patients, when a fatal clinical course is already observed and any therapeutic measures do not allow achieving positive therapeutic results and prolonging the life of patients. This can be explained by the asymptomatic onset and development of the pathological process until the appearance of clinical symptoms that force the patient to seek medical help [3, 6–9].

The current situation substantiates the need for comprehensive in-depth scientific research to clarify both issues: the origin of LC development and the nature of its spread along the parenchyma of the organ, which may help to approach the issues of early diagnosis and the effective treatment.

In oncology, diagnosis at the early stages of the disease is the only reliable way to combat malignant tumors, including LC [7, 10]. Since the onset and spread of LC are largely interrelated, we paid attention to the study of the literature relating to these two issues.

The key point in oncomorphology is the elucidation of the histogenesis of the tumor, on which the pathogenetic treatment is strongly relied. According to the literature, there are different opinions about the origin of LC development and the nature of its growth [11–15]. In particular, Travis *et al*. [10] state that while the exact origin of squamous cell LC is unknown, it is probably a pluripotent bronchial progenitor cell that can differentiate into any histological type of LC [16]. A similar conclusion was expressed by Brambilla and Travis [17]. They argue that LC develops from pluripotent reserve cells. Central adenocarcinomas, as the authors note, arise from bronchial reserve cells, probably from the alveolar epithelium, and differentiate into different phenotypic histological types.

Colby *et al*. [18] conducted complex studies using light and electron microscopy, and also used immunohistochemical and genetic methods, which showed that in the peripheral adenocarcinoma there are observed type II pneumocytes (alveolar epithelial type II — AE2) and Clara cells. The authors suggested that these cells might be the cells of origin in the development of glandular LC.

The histological studies of poorly differentiated LC forms allowed the authors to conclude that the tumors contain cells of double and triple phenotypic differentiation. This gave grounds to express a maxim about a single origin of LC development. Later, the researchers [11, 19] noted that peripheral LC develops from the epithelium of small bronchi, starting from the distal sections, from the bronchioles and, probably, from the alveoli.

In the study of histological specimens of small cell LC, Erokhin *et al*. [20] also observed in the preparations foci of oat cell, squamous or glandular types of cancer. In some cases, the authors noted glandular-squamous cell carcinoma with "pearls", foci of mucus production characteristic of glandular cancer, and areas of large cell carcinoma. Simultaneously, the heterogeneity of antigenic expression was revealed. A number of researchers have also noted the morphological and genetic heterogeneity of LC at the cellular and tissue levels [21, 22].

As suggested by Kitamura *et al*. [23], adenomatosis and hyperplasia of the lung epithelium play a role in the pathogenesis of peripheral glandular LC. Okudela *et al*. [24], when studying the LC histogenesis, came to the conclusion that bronchial metaplasia is involved

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Abbreviations used: AE2 – alveolar epithelial type II; LC – lung cancer; SC – stem cell.

in this process, while Sainz de Aja *et al.* [7] noted squamous cell hyperplasia in the alveolar space. It is pertinent to recall that a number of researchers have established the morphofunctional resistance of cells of the columnar epithelium to any chemical and biological influences [7, 25, 26].

The immunohistochemical studies to identify the E6/E7 oncogenes in bronchial epithelial cells made it possible to classify them as stem cells (SC) [27]. Takahashi [28] reported on multifocal growth of different phenotypic LC types — squamous cell and glandular cancer — in the same patient.

In modern oncopulmonology, the term non-small cell lung cancer is adopted, which includes the two most common histological LC forms — squamous cell and glandular. This generalized name contains many interrelating characteristics that may indicate one shared origin of LC development. Meantime, there is also a similar efficacy in the treatment of these LC types. In addition, in 10% of cases, the areas of squamous cell and glandular LC were observed in one tumor node [16]. The data of Gazdar *et al*. [29] made it possible to state that three most common aberrations are characteristic of the main histological LC types. The data obtained at the tissue, subcellular and genetic levels, can confirm the close biological essence of squamous cell and glandular LC and suggest a single origin of their development.

As noted by Pennycuick and Janes [2], the complexity of the study of lung carcinogenesis is that a heterogeneity of cellular mutations arises even at the early stages of LC development. Histogenetic aspects are reported also by Desai *et al*. [30]. They argue that not only basal, but also non-basal cells can be the origin of development of glandular and squamous cell LC. The authors also report the development of squamous cell carcinoma in the distal parts of the pulmonary tree.

Situ *et al*. [31] studied the synthesis of mucins in AE2 and in cells of the main histological types of LC. They found that in the elements of glandular and squamous cell carcinoma, MUC1 is produced, which make them related by morphological and functional characteristics. The authors associate the presence of MUC1 in squamous cell carcinoma cells with a worse prognosis. Guida *et al*. [32] consider biomarkers highly important for improvement of the LC diagnosis (along with CT exam). However, biomarkers can provide a false negative reaction, which complicates the verification of the pathological process. The study of Quint *et al*. [33] showed the similar metastasis in squamous and glandular LC cases, which reflects the similarity of their clinical course. A single origin of their development could not be excluded.

Multifocal LC growth is reported by Tetsushi *et al*. [34]. The authors stated the triple localization of different histological LC types in one patient — in the upper lobe of the left lung, in the apex of the right lung, and on the left in the 6th segment.

Along with the study of histogenesis, it is important to have a clear idea of the LC spread, since the tactics of treatment largely depends on it [35]. When specifying the biology of LC, Giangreco *et al*. [36], consider important the proximal-distal spread of the disease. An interesting report was made by Kim *et al*. [37], who proposed bronchioalveolar SC as progenitor cells. The authors showed that an increase in the number of bronchioalveolar SCs correlated with tumor progression in mice. However, Rawlins *et al*. [38] do not support this point of view.

Xu *et al*. [39] reported the spread of LC along the submucosal layer or all layers of the bronchial epithelium. An interesting report on the development of glandular LC in the form of a polyp in pulmonary bullae was published by Takahashi *et al*. [40]. This fact can confirm the development of glandular LC from the alveolar epithelium.

Studies by Pingxin *et al*. [41] found that adenocarcinoma is characterized by endobronchial growth. The study using a computed tomography revealed a lesion that looks like centro-lobular nodules as a “tree with buds”, which resembles the growth pattern of bronchioalveolar structures from large bronchi, as in the anatomical atlas of Netter [42]. The same structure of the lung in its central sections, at the root of the lung, as well as on the periphery, is presented earlier in the monograph by Esipova [43].

The presented numerous data suggest a common origin of the development of two histological LC types — squamous cell and glandular.

Multifocal growth of LC in the lung parenchyma may indicate tumor growth originating from the alveolar epithelium. There are known some observations of small focal changes in the lung parenchyma, which were exposed to radiation therapy, the foci were reduced and further progression was not observed [34]. If there is no possibility of morphological verification, detection of small forms of LC at the periphery of the organ allows one to take a number of therapeutic measures and thus improve the prognosis of the disease.

Have-Opbroek *et al*. [15] showed that the most common LC types (squamous and glandular) develop from a multipotent cell of AE2 type; however, they did not exclude the possible development of LC from basal cells. The data that AE2 are multipotent, giving rise to LC, are confirmed in experimental studies [44, 45]. In addition, the study of SCs made it possible to state that both in normal state and under the development of pathological conditions in the lung, AE2 cells react most rapidly and constantly. To clarify the morphofunctional features of the epithelial cells of the lung, it is necessary to refer to the special literature on the structure of the lung in normal conditions and during the development of pathological processes.

Thus, fundamental morphological publications present a wide aspect of morphological studies of one of the most important vital systems of the human body — the respiratory system. The authors used a complex of morphological methods to study the versatile characteristics of lung epithelial cells [20, 43, 46].

Recall that the lung parenchyma consists of 20 thousand respiratory bronchioles. Each respiratory bronchiole is subdivided into alveolar passages, and each of them ends in two alveolar sacs. On the walls of the respiratory bronchioles, there are separate alveoli that open into the lumen of the bronchioles. There are 300–400 million alveoli in the human body. The total area of the alveoli is 90–120 m^2, and in some cases increases up to 194 m^2. When you exhale, it decreases 2–2.5 times [46].

Esipova [43] has supplemented the known structural data on the bronchial tree. She presented the schematic organization of the pulmonary structures under the pleura and at the gate of the lung, which have in principle similar signs. Later, these data were colorfully demonstrated in the atlas authored by Netter [42], who submitted diagrams of the structure of the lung, which clearly show bronchiolo-alveolar structures growing from bronchi of various orders. This fact emphasizes the presence of bronchiolo-alveolar structures not only in the parechima of the lung, but also at its root. In addition, data are presented concerning the structural and functional characteristics of the cells of the alveolar epithelium, which accounts for the entire effect of the inhaled air [20, 46]. Air, most often polluted and containing cigarette smoke, causes reactive changes in AE2 of varying degrees. It is AE2, which, according to a number of authors, belong to SC, begin to show the potential for proliferation and active excessive growth, which can lead to the LC development [30, 47, 48]. The research by Have-Opbroek *et al*. [15] made it possible to assert that AE2 cells are ones of the pluripotent origin of LC development.

AE2 cells are called secretory because of their ability to secrete lipoprotein substances (surfactants) that form a film on the surface of the alveolar epithelium [20, 43]. The authors disclose 4 characteristic types of functional activity of AE2: secretory, reutilization of degraded surfactant molecules, absorption of fluid from the alveoli and, which is most interesting for pathologists in terms of proliferative activity, reproductive. Significant levels of secretion, a large total area of the apical surface of AE2 facing the lumen of the alveoli explaining their role as an origin of surfactants and protein, led to the conclusion that the respiratory part of the human breathing lungs is an "actively synthesizing gland" [20, 49]. The fact that the lung is a complex alveolar-tubular gland, has been reported by the famous anatomist Ivanov [50].

AE2 cells are also characterized by high proliferation aimed not only at replenishing their own population, but also at transformation into type 1 alveolocytes when they are damaged. The kinetics of this process has been studied and documented by ultrastructural methods in combination with autoradiography, and gives grounds to refer them to the SC of the respiratory part of the lung [48]. The increased proliferative activity leads to the fact that in the alveoli one can find large areas lined with many rows of AE2 cells. Among them, the so-called "light" cells predominate, which are young, immature forms of AE2 cells, which gives reason to call them "stem" cells of the pulmonary epithelial lining [20, 48]. Consequently, AE2 is one of the most intensively proliferating epithelial cell populations of the lungs, which plays an important role in the regeneration of the alveolar lining [20, 46, 49].

The most significant indicators for determining the severity of proliferation of epithelial cells are they mitotic activity and the time of renewal. Researchers have established the highest mitotic activity in AE2 cells in comparison with all other lung epithelial cells [20, 46]. In the epithelium of the trachea, mitotic activity is 3.4 per thousand cells, in the bronchi of medium caliber — 1–1.5, in the small bronchi — 0.5–1.5 and in the cells of the interalveolar septa, where mostly AE2 cells are found, it is 5–6 times higher and reaches 8.25 [20, 46]. Exactly these cells play an important role in the recovery processes in acute and chronic inflammatory processes, which are accompanied by an increase in their number and signs of hyperplasia. The second important argument for the proliferative activity of AE2 cells is the comparative time for the renewal of lung epithelial cells. In the cells of the epithelial lining of the trachea, the renewal time is 47.6 days, large bronchi — 18.1, medium bronchi — 7–10, small bronchi — 167–200, and in the cells of interalveolar septa, where AE2 cells are located, it is the fastest, 3–7 days [20, 46].

Currently, the issues of lung SC in normal and pathological processes are widely studied, which, as already noted, are characterized by rapid renewal and the most pronounced potential growth [37, 48, 49]. The structural and morphological complex of epithelial cells of the lung, the so-called "niche", is also being studied. "Niches" are of special attention in the study of tumor processes in the lung, primarily because there is a model according to which certain disorders of cellular niches result in overexpression of factors that stimulate proliferation and unrestrained growth of SCs, which is characteristic of precancerous processes and LC [27, 51, 52].

A number of authors studied in detail the morphological features of SC in one niche and their influence on neighboring ones [36, 53, 54]. Researchers point to the possibility of transformed SCs to activate not only cells of their own niche, but also those of neighboring niches, which leads to the onset and spread of proliferation, and then to the development of specific pathological processes. The results of the experimental work made it possible to clarify the fact of the beginning of the development of the pathological process in the lungs from the epithelial cells of the so-called niche. These cells are AE2 [36, 53–55]. A number of authors note the presence of SC in all structures of the lung [56], which is important for clarifying the origin of LC and nature of its spread.

It is known that the degree of tissue blood supply is a predetermining condition for the growth and reproduction of cellular structures. Thus, the alveoli of the lung are maximally supplied with blood vessels

in the form of a narrow-looped capillary network, which tightly entwines each alveoli, which is demonstrated in many human anatomical atlases, including the edition authored by Netter [42].

According to the data of Weibel [46], pulmonary (alveolar) blood capillaries form a dense network, which can be represented as a thin continuous vascular "web". The established abundant blood supply ensures growth and the possibility of reactive proliferation; with chronic exposure to biological or chemical reagents, an uncontrolled proliferation of cells and violation of their differentiation can occur, leading to malignant growth.

The results of studies of the morphological and physiological characteristics of lung cells allowed scientists to come to a consensus that the terminal bronchiole is the morphological and functional unit of the lung, which responds integrally under various pathological conditions. This definition was approved by the international nomenclature, as mentioned by Esipova [57]. Somewhat later, this position was confirmed by Erokhin *et al*. [20]. The authors also came to the conclusion that the simplest and most logical definition of the disease — "pneumonia", may be "an inflammatory process that develops in the respiratory part of the lung" [20]. Consequently, the term "pneumonia" can designate a pathological process accompanied by the appearance of obvious signs of alteration, exudation and proliferation in the alveoli and terminal bronchioles associated with the influence of an etiological factor, most often of a biological nature. The reliable results of the fundamental research carried out by the mentioned authors are confirmed by medical practice. Thus, Maksimovich [58], based on the study of pathoanatomical samples in viral pneumonia, showed the possibility of the primary ingress of air containing the influenza virus directly into the lumen of the alveoli with primary damage of AE2 cells.

Kogan *et al*. [59] studied the morphological formation of sarcoid granulomas and noted that they were localized in the zone of the bronchiolo-alveolar junction, which, according to the literature, is a niche of pulmonary epithelial SC, the presence of which is mentioned by Giangreco [36].

The presented data on the development of pneumonia, formation of sarcoid granulomas in the respiratory part of the lung, as well as data on the pluripotent AE2 cell during the development of LC [15] etc. indicate the general biological pattern of the development of pathological processes of tumor and non-tumor genesis in the lung parenchyma. The revealed regularity confirms the position accepted in the international nomenclature that pathological processes in the lung begin from the terminal bronchiole.

An interesting research was carried out by Kathiriya *et al*. [60]. The authors transplanted cells of unchanged cylindrical epithelium into the damaged lung and observed what was happening. It was found that the transplanted cells of the cylindrical epithelium acquired the features of the cells of the alveolar epithelium (AE2), and then the morphological and functional features of the cylindrical epithelium were restored. The established fact testifies to the potential biological and functional primacy of AE2 cells, from which cells of the cylindrical epithelium develop in succession. As noted in [7, 25, 26], the cells of the cylindrical epithelium belong to the mature cells of the lung tissue and are the most resistant to various adverse effects.

Thus, the presented data concerning the onset of tumor and non-tumor processes and their development confirm their occurrence in the parenchyma, in the alveoli of the lung tissue.

The presence and distribution of immunocompetent lymphoid cells in various parts of the lung was studied. It was found that the lung has signs of an immune organ [20, 49]. The degree of development of lymphoid tissue is shown depending on the structural parts of the lung. Thus, it was revealed that the number of lymphoid cells progressively decreases from the proximal airways towards the distal parts of the pulmonary parenchyma. A regularity was revealed, according to which the respiratory section contains significantly lower content of immunocompetent lymphoid cells in comparison with the airways, and is more vulnerable to the development of a pathological process.

The data of literature indicate two origins of LC development — reserve cells of bronchial epithelium and AE2. Similar data are presented by Have-Obroek *et al*. [15]. But, despite this, until now in the literature, when it comes to the origin of the LC development, researchers express their opinion only in a hypothetical form. Apparently, not everything sounds so convincing and is in accordance with the morphological and clinical manifestations of the onset and development of LC. Therefore, in this communication, an attempt has been made to compare the available data on the versatile morphofunctional characteristics of the epithelial tissue of the lung, on the study of the SC of the organ in normal and pathological conditions, clarification of the so-called niches, the onset and growth of tumors in experimental carcinogenesis, as well as the pathological study of LC.

Shutherland *et al.* [61] state that the cellular origin of LC has not yet been established. Kathiriya *et al.* [60] conclude the same and state that the main origin of LC, other than basal cells, has not been identified yet. The authors express the need to have small, reliable subpopulations of specialized SCs for the study of evidence-based regeneration.

Summing up the literature data concerning the results of various studies regarding the origin of LC, the nature of its growth and many other clarifying questions, scientists have not yet come to an unambiguous decision that would be consistent with the general biological laws and clinical manifestations of this disease. In the relevant publications, researchers express their point of view on the histogenesis of LC in a hypothetical form. This fact indicates the need to continue scientific research that could clarify LC histogenesis and,

ultimately, contribute to solving the problem of early diagnosis of this disease, validation and development of screening programs, which are crucial in providing timely and effective care to the patients.

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ПРО ДЖЕРЕЛО РОЗВИТКУ РАКУ ЛЕГЕНІ

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У цьому огляді літератури, присвяченому питанням гістогенезу раку легені (РЛ), подано значущі результати експериментальних, патологоанатомічних, імуногістохімічних та молекулярно-біологічних досліджень. Разом з тим до цього часу не отримано дані, які б дозволили вченим прийти до однозначного рішення про джерело і розвиток цього захворювання. Питання залишається не до кінця вивченим, і тому дослідники в своїх публікаціях щодо джерела розвитку РЛ висловлюються переважно в імовірній формі. Тому потрібні подальші дослідження, які б дозволили уточнити однозначно джерело розвитку РЛ, що дозволило б вирішити проблему ранньої діагностики цього захворювання та обґрунтувати скринінгові програми, що має надзвичайно важливе наукове і клінічне значення.

Ключові слова: рак легені, альвеолярний епітелій, стовбурові клітини, гістогенез.