Influence of pulmonary neuroendocrine cells on lung homeostasis

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neuroendocrine cells, airways, allergic inflammation, innate lymphoid cells, stem cells, calcitonin gene-related peptide, γ-aminobutyric acid

Pulmonary neuroendocrine cells (PNECs) – a unique cell population identified at all levels in the epithelium of the respiratory tract, histophysiology of which is still poorly understood. Given its important role as one of the main regulators of the respiratory processes and homeostasis, its studying is one of the urgent tasks of medicine.

According to the International Terms for Human Cytology and Histology published by the Federative International Committee on Anatomical Terminology (FICAT) under the writing of Wolters Kluwer and Lippincott Williams & Wilkins (2008), these cells are called respiratory neuroendocrine cells (in the trachea) or respiratory endocrine cells (in the bronchial tree). However, these cells have documented in modern international scientific literature as pulmonary neuroendocrine cells.

The aim of this work is to analyze the modern scientific literature data on the effect of PNECs on the lung homeostasis in normal and pathological conditions.

PNECs and their clusters – neuroepithelial bodies act as factors that regulate lung growth and maturation in embryogenesis via secretion of serotonin and gastrin-releasing hormone. In postnatal ontogenesis, PNEC secretion products – amines and neuropeptides, are characterized by participation in various physiological and pathological processes in the lung. PNECs normally maintain neurohumoral control over vascular and airway smooth muscle tone, act as peripheral chemoreceptors, and also are responsible for regulation of cell proliferation, differentiation, and mucus production from the respiratory epithelium. In case of respiratory tract damage, PNECs are capable of transdifferentiation by activating the Notch signaling pathway and renewal of other cellular types of respiratory epithelium. PNECs have a neuroimmunomodulating effect by means of neuropeptides and neurotransmitters secretion, which maintain and enhance the airways inflammatory response to an allergen. After the allergen exposition, PNECs activate type 2 innate lymphoid cells (ILC2) which being modulated by the neuropeptide CGRP produce type 2 cytokines IL-5 and IL-13, thereby contributing to an allergic response in the airways. At the same time, secreted by the PNECs neurotransmitter γ-aminobutyric acid (GABA) interacts with IL-13 to activate goblet cell mucus secretion. ILC2 induce eosinophilic inflammation and airways hypersensitivity. Recent studies have shown that ILC2 cells also stimulate Th2-associated immune response. Thus, CGRP and GABA are the key products of PNEC, which stimulate the Th2-associated immune response in the lung.

Conclusions. Pulmonary neuroendocrine cells together with immune cells form a neuroimmunological module for the reception and response to environmental chemotraumnants. The data on the role of pulmonary neuroendocrine cells in the airways allergic inflammation are still controversial in the literature, which necessitates further study of this field.

A – research concept and design; B – collection and/or assembly of data; C – data analysis and interpretation; D – writing the article; E – critical revision of the article; F – final approval of the article

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Я – клітинна популяція, що виявлена на всіх рівнях в епітелії дихальних шляхів (ДШ), гістофізіологія якої дотепер недостатньо вивчена. З огляду на її важливу роль як одного з основних регуляторів процесів дихання та гомеостазу організму, її вивчення є одним з актуальніших завдань медицини.

Відповідно до Міжнародної номенклатури з цитології та гістології людини, яка розроблена Федеративним міжнародним комітетом з анатомічної термінології (FICAT) авторами Wolters Kluwer і Lippincott Williams & Wilkins (2008), ці клітини називаються дихальними нейроендокринними клітинами (у трахеї) або дихальними ендокринними клітинами (у бронхіальному дереві). Однак ці клітини описані в сучасній міжнародній науковій літературі як легеневі нейроендокринні клітини.

Мета роботи – аналіз даних сучасної наукової літератури про вплив дихальних нейроендокринних клітин на гомеостаз легень у нормі та патології.

Вплив дихальних нейроендокриних клітин на гомеостаз легень

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Дихальні нейроендокринні клітини (ДН) – унікальна клітинна популяція, що виявлена на всіх рівнях в епітелії дихальних шляхів (ДШ), гістофізіологія якої дотепер недостатньо вивчена. З огляду на її важливу роль як одного з основних регуляторів процесів дихання та гомеостазу організму, її вивчення є одним з актуальніших завдань медицини.

Відповідно до Міжнародної номенклатури з цитології та гістології людини, яка розроблена Федеративним міжнародним комітетом з анатомічної термінології (FICAT) авторами Wolters Kluwer і Lippincott Williams & Wilkins (2008), ці клітини називаються дихальними нейроендокринними клітинами (у трахеї) або дихальними ендокринними клітинами (у бронхіальному дереві). Однак ці клітини описані в сучасній міжнародній науковій літературі як легеневі нейроендокринні клітини.
Влияние дыхательных нейроэндокриноцитов на гомеостаз легких

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Дыхательные нейроэндокриноциты (ДН) – уникальная клеточная популяция, выявленная на всех уровнях в эпителии дыхательных путей (ДП), пистофизиология которой до сих пор плохо изучена. Учитывая ее важную роль как одного из основных регуляторов процессов дыхания и гомеостаза организма, ее изучение является одной из актуальных задач медицины.

Согласно Международной номенклатуре по цитологии и гистологии человека, разработанной Федеративным международным комитетом по анатомической терминологии (FICAT) авторами Wolters Kluwer и Lippincott Williams & Wilkins (2008), эти клетки называются дыхательными нейроэндокринными клетками (в трахее) или дыхательными эндокринными клетками (в бронхиальном дереве). Однако эти клетки описаны в современной международной научной литературе как лёгочные нейроэндокриноциты.

Цель работы – анализ данных современной научной литературы о влиянии дыхательных эндокриноцитов на гомеостаз легких в норме и патологии.

ДН и их клетки – нейропитуиальные тела, действуют как факторы регуляции роста и созревания легких в эмбриогенезе с помощью выделяемых ими серотонина и гастрин-релизинг-гормона. В постнатальном онтогенезе продукты секреции ДН – амины и нейропептиды характеризуются участием в разнообразных физиологических и патологических процессах в легких. ДН в норме осуществляют нейрогуморальный контроль функции бронхиол и эпителиальных клеток, являясь ключевыми структурами организма, которые поддерживают и усиливают воспалительную реакцию в дыхательных путях.

Выводы. ДН вместе с клетками иммунной системы образуют нейроиммунологический модуль для рецепции и реагирования на раздражители окружающей среды. Данные о роли ДН в развитии аллергического воспаления ДП в литературе пока неоднозначны, что обусловливает необходимость дальнейшего изучения данной проблемы.

Ключевые слова: нейроэндокриноциты, дыхательные пути, аллергическое воспаление, врожденные лимфоидные клетки, петиды, связанный с геном кальцитонина, γ-аминомасляная кислота.

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between single PNEC and neuroepithelial body. Further studies are also needed on the role of airway stem cells and PNECs in tissue repair responses, carcinogenesis, induction of inflammatory processes in adults, since these issues are yet to be fully understood.

Among the most important functions of PNECs that are known today, the following can be distinguished. PNEC secretion products act as factors regulating the lung growth and maturation in embryogenesis (serotonin, gastrin-releasing hormone) [4,5]. Both single PNEC and neuroepithelial bodies contain dense core vesicles filled with bioactive neuropeptides or amines. Neuroepithelial bodies are richly innervated by both afferent and efferent nerve endings; serve as intrapulmonary chemoreceptors that are sensitive to hypoxia and environmental factors affecting the respiratory tract [6,7]. These negative factors include a chronic inflammatory process, hypoxia, hyperoxia, tobacco smoking, and nitrosamine. The latter ultimately cause a hyperproliferation and neoplastic transformation of PNECs [8]. PNECs control the tone of the bronchi and vascular smooth muscle cells, thus regulating the volume of inhaled air and the lung blood supply. In addition, PNECs directly mediate immune response, simulating its activity, and are also potential stem cells in the airways [9].

The data of scientific studies have confirmed that after damage to the epithelium of the respiratory tract, PNECs can function as progenitor cells for the renewal of other cellular phenotypes of the respiratory tract, such as bronchiolar exocrinocytes and ciliated airway epithelial cells [10]. These data are coincided with the results presented in the works of other scientists regarding the role of PNECs in the regeneration of the airway epithelium [3–5,11].

But only a small subset of PNECs belongs to potential stem cells – 2–4 cells per one neuroepithelial body. These cells are highly differentiated and function to maintain homeostasis similar to other PNECs. After damage to the respiratory epithelium, they take on the properties of undifferentiated stem cells. A part of them proliferate directly to own neuroepithelial body, renewing their population. Other cells are “scattered” in the surrounding epithelium. The latter are capable of transdifferentiation by activating the Notch signaling pathway and renewal of other cellular types of respiratory epithelium in case of respiratory tract damage [11]. The lung tissue demonstrates remarkable capability to renovate after various kinds of injuries. In this regard, the ability of lung cells to epigenetic modification and transdifferentiation is an important mechanism for reproducing the required number of cells for the regeneration of both epithelial and mesenchymal derivatives.

Until now, the possibilities and limitations of these mechanisms of cell differentiation and proliferation have not been fully studied, both in normal and in any lung damaging factor influence. Both during the lung embryogenesis and for reparative regeneration, the same signaling cascade pathways, such as the Wnt-signaling pathway and Notch, are involved.

Indeed, in the study of Y. Ouadah, (2019), Notch-active PNECs demonstrated the suppression of neuroendocrine phenotype and simultaneous activation of specific markers of other cell types, such as bronchiolar exocrinocytes, ciliated airway epithelial cells, type 2 alveolar cells, and even pulmonary stromal cells [12]. Thus, a subpopulation of PNECs isolated from their neuroepithelial body, expresses the Notch2 receptor and demonstrates active Notch-signaling initiates deprogramming of the neuroendocrine line and reprogramming to various other cellular types of respiratory epithelium.

At the same time, the gene transcription factor GFI1 plays an essential role in the transdifferentiation of PNECs into other cellular phenotypes. In its absence or mutation, the proliferation of PNECs is impaired, which leads to the development of a tumor blasttransformation reaction [13].

Recent studies of L. Meder et al. (2016), D. Laakas et al. (2015) have proved the hypothesis that activation of the Notch pathway is a key factor in the induction of transdifferentiation of PNECs into other cellular phenotypes following lung damage. In this case, PNECs lose the expression of neuroendocrine differentiation markers. In addition, the studied mechanism of the PNEC transdifferentiation consists in the epigenetic modification of the cells. In other words, there is a change in gene expression and cell phenotype caused by mechanisms that do not affect the DNA sequence of the genes. Along with this, polycomb repressive complex 2 (PRC2), a complex of proteins with histone methyl transferase activity, plays an important role. These proteins are necessary for long-term “rest” of chromat and responsible for the differentiation of stem cells being the basis of cell memory after differentiation [13,14].

Notch-signaling is one of the mostly used intercellular communication pathways [15]. Key components of the Notch signaling pathway are studied by scientists as drug targets for therapeutic modalities. The Notch receptor family includes a group of transmembrane proteins, extra-cellular and intracellular domains of which are involved in ligand binding and signaling to the cell nucleus controlling the expression of Notch target genes.

An increase in the number of PNECs was recorded in a wide range of chronic lung diseases, including bronchial asthma, bronchopulmonary dysplasia, cystic fibrosis, chronic obstructive pulmonary disease, congenital diaphragmatic hernia, infant death syndrome and pulmonary hypertension [16]. They also are target cells for tumor blasttransformation reactions for small-cell lung cancer which is common nowadays [17].

PNECs express gene of the Robo receptor (Roundabout receptor) [16]. Signal transmission through this transmembrane protein plays a crucial role in neurogenesis, angiogenesis, tumorgenesis, and even organogenesis of a large number of internal organs, including the airways. When the Robo receptor is inactivated in experimental mice, disorganization of PNECs occurs, as well as an impossibility to form the neuroepithelial bodies, and most importantly, an increase in the secretion of neuropeptides after air – lung interaction. In turn, excess neuropeptides lead to an increase in immune infiltration in the lung, irreversible disorganization processes and a change in the alveolar structure – lung remodeling.

PNECs are airway sensors which activate immune responses mediated by their neuropeptides action [18]. PNECs have a neuroimmunomodulating effect owing to secretion of neuropeptides and neurotransmitters, which support and enhance the inflammatory response in the respiratory tract triggered by allergen challenge [19].
Innate immunity, which is a non-specific mechanism of protection against numerous pathogenic factors, provides immediate recognition and response to pathogens. Relatively little was known about the role of innate immunity in the pathology of allergic airway inflammation until the recent discovery of innate lymphoid cells (ILCs) that produce a large amount of type 2 cytokines after stimulation by cytokines of the respiratory epithelial cells (IL-25, IL-33, TSLP – thymic stromal lymphopoietin) [20, 21].

For the first time, these cells were discovered by scientists in 2010. A classification of ILCs was proposed in 2013. It is based on the phenotypic and functional characteristics of ILCs. So, ILCs were divided into three groups: group 1 (IFN-γ-producing cells), group 2 (IL-5- and IL-13-producing) and group 3 (IL-17- and/or IL-22-producing). ILC2s depend on the transcription factors GATA3 and RORα, necessary for their maturation and functioning. Recent studies have shown that ILC2s in mice are the main source of IL-5 and IL-13 in airways, so ILC2s can play a major role in the induction of allergic airway inflammation.

ILC2-derived cytokine IL-5 activates eosinophils. It serves to increase their number and secretion of leukotriene C4 and platelet-activating factor [22]. The latter, in its turn, increases secretion of mucin by goblet cells and stimulates contraction of the bronchial smooth muscle component [23, 24]. ILC2-derived IL-13 stimulates goblet cell hyperplasia and mucin secretion.

An important fact is that PNECs are localized in close proximity to ILC2s at the sites of bifurcation of the trachea and bronchi of different diameter. PNECs interact with ILC2s through calcitonin gene-related peptide (CGRP) and elicit downstream immune responses. Furthermore, PNECs act through neurotransmitter γ-aminobutyric acid (GABA) resulting in goblet cell hyperplasia. ILC2s have been found to be direct target cells for the implementation of signals from PNECs (Fig. 1).

This fact is proved by the results of studies of J. Barrios, et al. (2017, 2019), showing that ILC2s express CGRP co-receptors Calcrl and Ramp1 and GABA receptor Gabrr1 [25, 26]. These findings are coincided with the results presented in the works of other scientists regarding the role of ILC2s in the regulation of the local airway immune responses to allergens [20, 21].

In vivo model of the PNECs study has shown that CGRP increases IL-5 production by ILC2s in culture conditions in response to IL-25 and/or IL-33 [27]. IL-33 is a new member of the IL-1 cytokine superfamily, which is expressed by epithelial cells and endothelialcytes after pro-inflammatory stimulation. IL-33 can function both as a traditional cytokine and as a nuclear factor regulating gene transcription. It is believed that it acts as an “alarm” signal in case of cell damage in order to inform the immune system. IL-33 mediates its biological effects through interaction with ST2 receptors (IL-1RL1) and auxiliary protein of the IL-1 receptor (IL-1RAcP). The latter is expressed by ILC2s and Th2. IL-33 activates the production of Th2 cytokines by these cells and may contribute to the pathogenesis of Th2-related diseases such as bronchial asthma, atopic dermatitis and anaphylaxis. However, IL-33 demonstrated various protective effects in cardiovascular diseases such as atherosclerosis, obesity, type 2 diabetes mellitus, and heart remodeling. Thus, the effects of IL-33 are either pro-inflammatory or anti-inflammatory, depending on the disease and the model [28].

An interesting fact is that CGRP has not stimulated secretion of IL-5 from ILC2s providing that IL-33 was absent. In addition, it has been shown that CGRP activates only cytokine secretion, but not ILC2s proliferation [29]. Th2 adaptive immunity cells did not respond to CGRP and GABA signals from PNECs at all. GABA also had no significant effect on ILC2s. Based on these data, we can assume a completely different way of the Th2 adaptive immune response activation in airway allergic process development.

Once again, the indisputable participation of PNECs in the initiation of the Th2 immune response during ovalbumin (OVA) allergization proves the study result showing that the introduction of a CGRP and GABA mixture into the respiratory tract of Ascl1 – mutant mice (lacking PNECs) reconstructs the immune response in experimentally induced allergic inflammation [19, 30].

Recently, the study results of Y. Vázquez, et al. (2019) have shown that the neuroimmunological modules of PNEC-ILC2 function towards airway bifurcation, enhancing the reactions of allergic inflammation [31]. In turn, ILC2s provoke eosinophilic inflammation, accompanied by hypersensitivity of the respiratory tract. Moreover, recent studies in mice have shown that ILC2s also stimulate acquired immunity towards differentiation of Th0 into Th2, inducing a Th2 immune response [32]. Thus, CGRP and GABA are key biologically active PNEC products that stimulate the Th2 immune response in the airways.

Ascl1 mutant mice were studied by P. Sui et al. (2018) in the early stages of lung development [19]. They blocked Ascl1, a transcription factor that plays a key role in the di-
Differentiation of neurons and neuroendocrine cells. Subsequently, CGRP- and Sympathin- cells were not found in the lung of such mice. Interestingly, Ascl1- mutant mice were viable at birth, which is counter to the role of PNECs in transition from intra-uterine environment to air breathing. Moreover, mutant lungs showed normal morphogenesis without defects of the bronchiolar exocrinocytes (Clara cells), ciliated airway epithelial cells as well as type 1 and 2 alveolocytes. This fact indicates that although PNECs are the first differentiated cellular phenotype in the fetal lung maturation, they do not significantly affect the other cell types development.

Other authors suggest that the differentiation and functioning of PNECs and the neuroendocrine system of the respiratory tract as early as the stage of prenatal ontogenesis indicates their involvement in the processes of histogenesis and organogenesis of the respiratory system [2–4]. This issue is currently debatable and should be studied further.

A completely different situation arises with respect to OVA-induced pneumonia [19]. In the control group, sensitization and subsequent allergization of OVA caused persistent goblet cell hyperplasia. At the same time, there was a significant decrease in the expression of Muc5ac, a goblet cell marker in Ascl1- mutant mice. Changes in other cell populations (Clara cells, ciliated airway epithelial cells) were not observed. Thus, PNECs stimulate hyperplasia of the goblet cells and abnormal patterns of mucin secretion [30,31].

PNECs enhanced the development of eosinophilic infiltration and Th2 immune response in the airways of mice exposed to OVA, since Ascl1- mutant mice lacking PNECs had significantly less eosinophils, ILC2s, Th2 lymphocytes, as well as less expression of IL-5 and IL-13 after allergization induced by OVA [33].

OVA-induced allergy resulted in an increased expression of various neuropeptides from PNECs such as Calca (encoding CGRP), chromogranin A (Chga), neuropeptide Y (Npy) and the GABA neurotransmitter [19]. The role of GABA in the airways, as IL-13, is to enhance goblet cell hyperplasia and mucus overproduction [25,26]. In mice with reduced PNECs combined with OVA-induced allergy, the GABA level was significantly lower than that in the control group. There is no doubt that bronchial asthma patients have an increased number of PNECs in the airways [33].

However, studies have shown [34] that mast cell tryptase stimulates the release of CGRP from afferent nerves in inflammation. CGRP receptors are expressed in multiple cell types of the immune system, including macrophages (TLR4). Activation of CGRP receptors in macrophages caused an increase in the cellular level of cAMP and activation of protein kinase A, followed by an increased secretion of IL-10. Thus, scientists have found that CGRP promotes the development of a regulatory phenotype in activated macrophages that has an anti-inflammatory effect in immune responses. CGRP is a mediator in neuroimmune interaction in the development of inflammation [35].

Therefore, the role of PNECs in the amplifying an allergic inflammatory response in the airways is currently debatable. On the one hand, PNEC-derived secretion of neuropeptides such as CGRP and GABA stimulates the ILC2s to produce type 2 cytokines IL-5 and IL-13 [20–22,31–34]. On the other hand, scientists postulated that CGRP activates TLR4 in M2 macrophages, providing an anti-inflammatory effect [35]. Though concerning the latter claim, scientific data and research results published in the modern scientific literature cover studies on other systems and organs, rather than lungs [35,36]. Probably, the effect of CGRP and its implementation differ in organs and tissues, based on scientific papers available [29,36].

Thus, PNECs transmit signals directly to ILC2s, and together they form a neuroimmunological module for reception and response to environmental stimuli that enter the airway [36]. A specific localization of these modules, namely, in places of airway bifurcations, is of great moment, which was established as early as in the embryonic period. Branch points of the airways are the prime sites to sample various chemoattractants. It is worth noting that PNECs are essential for protection against pathogens and lung damage [37].

Conclusions

1. PNEC together with the cells of the immune system form a neuroimmunological module for responding to chemoattractants. The data on the role of pulmonary neuroendocrine cells in the airways allergic inflammation are still controversial in the literature, which necessitates further study of this issue.

2. The extreme importance of studying the histophysiology of PNECs in health and pathology is clear since it will help to understand how their functions or the functions of neuropeptides and neurotransmitters secreted from them can be blocked for the effective and safe treatment of allergic airway diseases, including bronchial asthma.

3. A better understanding of the specific PNEC responses to various effects on lung functions in normal conditions and in the pathogenesis of pulmonary diseases is a determining factor in the development of targeted therapeutic agents for pulmonary neuroendocrine system disorders.

Conflicts of interest: authors have no conflict of interest to declare.

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