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Review

Potential roles of telocytes in lung diseases

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ABSTRACT

Telocytes (TCs) are a unique type of interstitial cells with specific, extremely long prolongations named telopodes (Tps), as shown by immune-positive staining against CD34, c-kit and vimentin. They were found in many organs of mammals, with potential biological functions, including the trachea and lung, even though the exact function remains unclear. Here, we give a historical overview of the TCs research field and summarize the latest findings associated with TCs, with a special focus on the recent progress about TCs specific gene and protein profiles that has been made in understanding that TCs may play a potential, but important, role in the pathogenesis of lung diseases.

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1. Introduction

The lung is a complex organ comprising multiple cell types, cell-associated cytokines, receptors, signaling molecules and others that perform a variety of vital processes, including gas exchange and immune defense. Diseases of the lung, such as chronic obstructive pulmonary disease (COPD), acute lung injury, bronchial asthma, pulmonary fibrosis, lung cancer, and interstitial lung disease, together represent one of the largest causes of patient morbidity and mortality. It should be noted that almost lung diseases are involve in airway obstruction and airway inflammation, finally lead to airway remodeling (Fig. 1). Airway remodeling consists of progressive structural changes in the composition, content and organization of the cellular and molecular constituents of the airway wall [1], to contribute to the pathogenesis of lung diseases.

Lung tissue cells for the treatment of airway remodeling have recently attracted more attention due to the high prevalence and diversity in related diseases. COPD is an inflammatory disease characterized by the progressive deterioration of pulmonary function and increasing airway obstruction [2]. A number of cells, such as neutrophils, mast cells, macrophages, CD8+ T, B lymphocytes, Type II alveolar epithelial cells and inflammatory mediators were found to contribute to the pathogenesis of COPD [3–5]. Acute respiratory distress syndrome is a complex disease process characterized by a range of pathophysiologic processes including lung endothelial injury, alveolar epithelial injury and the accumulation of protein-rich fluid and cellular debris in the alveolar space [6,7]. The pathological mechanism of asthma is based on the inflammatory reflection of mast cells, eosinophils, dendritic cells and T cells [8]. The pathogenesis of pulmonary fibrosis appears to result from a complex interaction between inflammatory cells, fibroblasts and lung parenchymal cells [9]. Lung cancer is the

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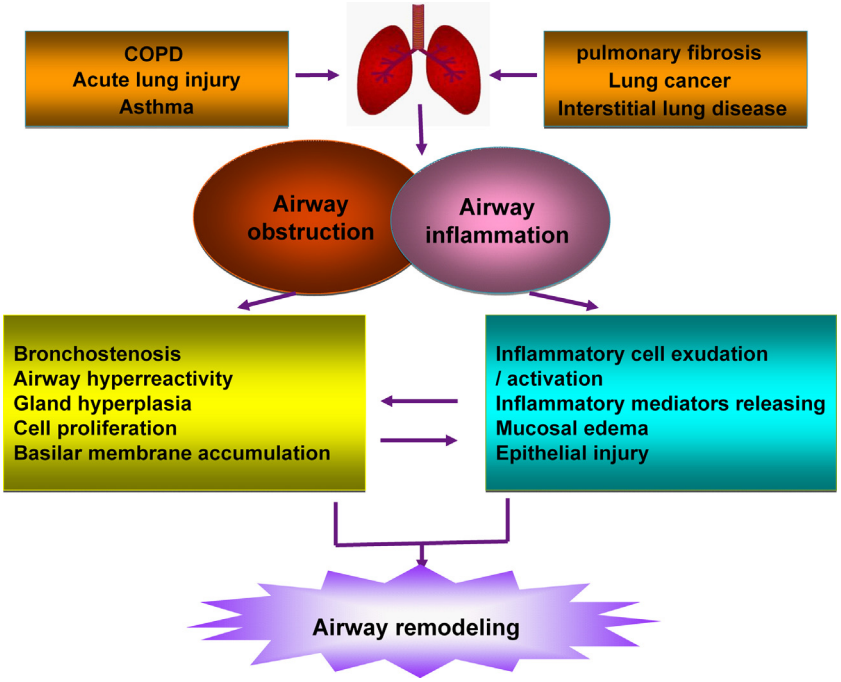

Fig. 1. The process of airway remodeling. Different kinds of lung diseases could induce airway obstruction and airway inflammation by different mechanisms, including Bronchostenosis, airway hyperreactivity, gland hyperplasia, cell proliferation, basilar membrane accumulation, inflammatory cell exudation/activation, inflammatory mediators releasing, mucosal edema, epithelial injury, and so on, finally lead to airway remodeling.

most commonly diagnosed cancer, and the primary and leading cause of cancer- associated mortalities and modalities, mainly includes small-cell lung cancer (SCLC) and non-small-cell lung cancer (NSCLC) [10]. Cancer-associated inflammatory cells include innate immune cells (e.g., macrophages, neutrophils, mast cells, myeloid-derived suppressor cells, dendritic cells, or natural killer cells), adaptive immune cells (e.g., T and B lymphocytes), and cancer tissue cells per se (e.g., fibroblasts, endothelial cells, pericytes, or mesenchymal cells) involving in the development of lung cancer [11]. Interstitial lung disease also known as diffuse parenchymal lung disease refers to alveolar epithelium, capillary endothelium, basement membrane, and/or perivascular and perilymphatic tissues [12].

It is important to select the appropriate cell type and identify suitable conditions for cell growth and proliferation as well as subsequent implantation into the body, to repair and regenerate damaged tissues. TCs have been considered to be a new type of interstitial cell since 2005 and concerned to distinguish from other interstitial cell types [13], associated with different kind of cells (Fig. 2). It was identified in the interstitial space of many organs of mammals with biological functions [14–24], even though the exact function remains unclear. Our group initially identified and isolated TCs from the trachea and lung and confirmed the existence of TCs in lung tissues [20]. TCs were found to be allocated between the smooth muscle layer and cartilage of bronchi and bronchiole, where they form a 3D network that are deformable and resistant, and play a role during the process of regeneration and reparation for the alveolar and bronchial epithelial cells, airway smooth muscle, or pulmonary microvascular endothelial cells. This was also noticed by evidence that TCs could support the tissue reorganization in development of adult heart [25].

2. TCs: A burgeoning field

Santiago Ramony Cajal who won the Nobel Prize in Physiology or Medicine in 1906 (shared with Camillo Golgi), discovered a particular type of cells in the gut and named “interstitial neurons” in 1899 [26]. Until the early 1970s, electron microscopy/electron microscope (EM) studies showed that indeed a special interstitial cell type corresponding to the cells discovered by Cajal is localized in the gut muscle coat, but it became obvious that they were not neurons. Consequently, they were renamed “interstitial cells of Cajal” (ICC) and considered to be pace-makers for gut motility [27]. For the past 10 years, many groups were interested in whether or not ICC are present outside the gastrointestinal tract, and indeed, peculiar interstitial cells were found in a number of tissues and organs, e.g. upper and lower urinary tracts, blood vessels, pancreas, reproductive tracts, mammary gland, placenta, and heart as well as in the gut. Those cells are mainly located in the interstitial space of organs, with extensively long and thin prolongations, visible only by EM [28], networking within themselves and with local cell populations. Such interstitial cells were then named as Interstitial Cajal-Like Cells (ICLC) [28,29], morphologically similar to ICC. In fact, EM and cell cultures revealed very particular features of ICLC, which unequivocally distinguishes them from ICC and all other interstitial cells: a small oval-shaped body, from which are emerging very long (up to 10–100 μm) and very thin (mostly below 0.5 μm) prolongations – the telopodes (from podos, meaning foot). Given the unique dimensions of these prolongations (very long and very thin) and to avoid further confusion with other interstitial cell types (fibroblast, fibrocyte, fibroblast-like cells, mesenchymal cells), a new name was coined as TCs to replace ICLC, according to the morphological characteristics through EM [13]. The term comes from the greek affix “telos” meaning scope, objective, fulfillment and from the root “cytes” meaning cells.

In the same fashion that “interstitial neurons” became now known as “Interstitial Cells of Cajal”, formerly known “Interstitial Cajal-Like Cells” are now being called “Telocytes”. The historical perspective of TCs is shown in Fig. 3. TCs have been identified in the interstitial space of many organs, including trachea and lung [20,21], oesophagus [30,31], intestine [32], liver [33,34], kidney [35], heart [36,37], skin [38,39], eyes [40], urinary tract [41,42],