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From Cell Biology to Tissue Engineering

Review

Telocytes and lung disease

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Summary. Telocytes (TCs) represent a new distinct type of interstitial cells found in many organs, including lungs. TCs are mainly defined by a small cellular body from which arise very long (hundreds of micrometers) extensions named telopodes. During the last years, TCs were characterized in respect with their microRNA profiles, gene features and proteome signatures. Also, the ultrastructural 3D configuration was further elucidated by the aid of the FIB-SEM technology. TCs are able to communicate by homo- and heterocellular contacts with neighboring cells and are also able to transfer genetic information and signaling molecules to influence other cells by means of extracellular vesicle release. However, the exact function of lung TCs remains unclear. Here, we review the potential significance of TCs in the pathogenesis of pulmonary diseases. We will also discuss some future possibilities for targeting TCs as a potential therapeutic strategy.

Keywords: Telocytes, Interstitial lung disease, Pulmonary fibrosis, Chronic obstructive pulmonary disease, Lung cancer

Introduction

Lungs are, together with the heart, the vital organs responsible for the proper oxygenation of the tissues. Impaired lung function is associated with increased morbidity and mortality from chronic lung disease. Moreover, inadequate ventilation represents a risk factor for cardiovascular disease, stroke, and lung cancer (Hole et al., 1996). Regardless of what causes pulmonary damage, the substrate is inflammation and if the cause persists the result is a chronic inflammatory disease sometimes manifested by interstitial fibrosis. In all these phenomena there is definitely a contribution of different cells which accumulate at the place of the injury (Bagnato and Harari, 2015). Among the local connective cells such as fibroblasts, myofibroblasts and different immune cells, TCs involvement must not be overlooked.

Telocytes (TCs) were identified as a new cell type of the stromal space and were firstly described in 2010 by Popescu's group as a case of serendipity (Popescu and Faussone-Pellegrini, 2010). While TCs have been described between 2005 and 2009 by Popescu's group as interstitial Cajal-like cells (ICLC) (Ciontea et al., 2005; Popescu et al., 2005b,c; Cretoiu et al., 2006; Hinescu et al., 2006), in 2010 it became evident that they are completely distinct from 'interstitial cells of Cajal' (ICC) in their ultrastructure, and immunocytochemical phenotype (Popescu and Faussone-Pellegrini, 2010). Further studies have reinforced the belief that indeed TCs are a new individual cell type in terms of their genomic and proteomic profiles (Zheng et al., 2013, 2014a,b; Sun et al., 2014).

The striking ultrastructural hallmark of TCs is their very long and thin prolongations called telopodes (Tps) with dilatations (podoms) and thin segments (podomers) (Zheng et al., 2011; Cretoiu et al., 2012a,b; Cretoiu and Popescu, 2014). The presence of TCs and the detailed conformation their Tps was confirmed by the most advanced microscopic technology available -Focused Ion Beam Scanning Electron Microscopy (FIB-SEM) (Cretoiu et al., 2014, 2015a). TCs were identified in a variety of tissues and organs including trachea and lungs (Popescu, 2011a; Zheng et al., 2012a,c), heart (Rusu et

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al., 2012; Sheng et al., 2014; Yang et al., 2014; Popescu et al., 2015; Tao et al., 2015; Kostin, 2016), female reproductive system (Cretoiu et al., 2013, 2015b; Campeanu et al., 2014; Yang et al., 2015; Cretoiu and Cretoiu, 2016), skin (Ceafalan et al., 2012; Manole et al., 2015), liver (Xiao et al., 2013), urinary tract (Zheng et al., 2012b), prostate (Corradi et al., 2013), skeletal muscle and neuromuscular spindles (Diaz-Flores et al., 2013), eye (Luesma et al., 2013) etc. One of the main problems of differential diagnosis was the differentiation between TCs and fibroblasts. Telocytes are different from fibroblasts not only by their morphology but by their distinctive immunophenotypes (Bei et al., 2015), microRNA profiles (Cismasiu et al., 2011), gene features (Zheng et al., 2014d; Wang et al., 2015; Zhu et al., 2015; Song et al., 2016) and proteome signatures as well (Zheng et al., 2014a).

The goal of this review is to provide a summary of existing data about TCs involvement in lung diseases. We provide an overview of the potential functions of TCs in various lung diseases and present the promising contribution that could be achieved through pre-clinical research development.

Telocytes in the lung

Telocytes - cellular morphology and identification

The golden standard for the identification of TCs is transmission electron microscopy, a technique that allowed their discovery and led to their shortest definition "telocytes are cells with telopodes" (Popescu and Faussone-Pellegrini, 2010; Popescu, 2011b). In general, the cell body of TCs has a nucleus which occupies about 25% of the cell volume, surrounded by a small quantity of cytoplasm containing mitochondria, a small Golgi complex, rare rough and smooth endoplasmic reticulum cisternae and cytoskeletal elements (Popescu et al., 2010, 2011b; Zheng et al., 2011). The shape of TCs cell body varies from piriform to spindle-shaped or triangular, depending on the number of Tps. Telopodes, which normally appear in numbers between 1 to 5 for one cell body, depending on the incidence of the section, are extremely long (tens to hundreds of μm measured by electron microscopy) and thin (below 0.2 μm, under the resolving power of light microscopy), with a moniliform aspect (alternation of thin segments termed podomers and small dilations termed podoms which are accommodating mitochondria, endoplasmic reticulum and caveolae) (Popescu and Faussone-Pellegrini, 2010). Three-dimensional (3D) imaging of human cardiac TCs by FIB-SEM followed by 3D reconstruction indicated a ribbon-like conformation for Tps and podoms were observed to bulge from point to point (Cretoiu et al., 2014). The same morphology is present for TCs in cell cultures when one must also consider the Tps movement (Fig. 1, Supplementary video S1).

In 2011, Popescu's group identified TCs in pleura and in the human and mouse respiratory tree (terminal and respiratory bronchioles, and alveolar ducts) (Hinescu et al., 2011; Popescu et al., 2011a). Always located in the interstitial space, TCs were seen to occupy a strategic position between the cricoid cartilage and smooth muscles within the trachea and in the interstitial space of terminal bronchioles; their Tps were connected with alveolar epithelial cells, stem cell within the niches and other cells in the lung tissues (Popescu et al., 2011a). Simultaneously, Xiangdong Wang's group published an extensive paper describing TCs in mouse trachea and lungs focusing on their aspect in scanning electron microscopy and on their characterization in cell cultures (Zheng et al., 2011). Wang's group showed that although lung TCs were defined by their specific structure of Tps, they can be also identified by some immunocyto-chemical markers such as CD34, PDGFR, vimentin and c-kit. These common markers are shared between TCs and other types of cells, e.g. endothelial cells, which express CD34, fibroblasts, positive to vimentin and stem cells, which express c-kit (Ceafalan et al., 2012; Bei et al., 2015), thus it is important to discriminate between TCs and these cells in tissues and cell cultures and also indicate the potential relationship between them. Therefore, both groups considered the necessity to further characterize the lung TCs with the aid of omics and bioinformatics. Although the genetic make-up of TCs is not yet available, a genetic comparison of mouse lung telocytes with mesenchymal stem cells and fibroblasts was performed (Zheng et al., 2013). Also, a number of papers described the differences in the expression of chromosomes 1, 2, 3, 4, 17, 18 and X genes between lung telocytes and other cells: mesenchymal stem cells, fibroblasts, alveolar type II cells, airway epithelial cells and lymphocytes (Sun et al., 2014; Zheng et al., 2014d; Wang et al., 2015; Zhu et al., 2015; Song et al., 2016). In parallel, the proteome of lung TCs was shown by comparative proteomic analysis with fibroblasts and microvascular endothelial cells using iTRAQ (Zheng, et al., 2014a,b).

Functional implications of telocytes

Multiple electron microscopy techniques, including transmission electron microscopy, electron tomography, SEM and FIB-SEM, have demonstratedthat TCs make up a three-dimensional network and inhabit 'strategic' locations in tissues (Cretoiu and Popescu, 2014). On one hand, TCs can be connected with each other via

Supplementary video S1. Video recording of primary Telocytes (TCs) by the real-time cell monitoring system, using a Cell-IQ cell culturing platform. The adherence, growth, movement, death and the alteration of morphology of a single telocytes cultured *in vitro* were shown.

homocellular junctions through their Tps, or they can be in close vicinity of blood vessels, nerve endings and many other cells (for example in the heart they interconnect with different cells including cardiomyocytes, stem cells, fibroblasts and immunoreactive cells) via heterocellular junctions. All these homo- and heterocellular junctions contribute to the formation of the interstitial 3D network (Faussone-Pellegrini and Gherghiceanu, 2016).

On the other hand, TCs are critically involved in intercellular signaling via paracrine and/or juxtacrine secretion of small molecules, or via shedding of

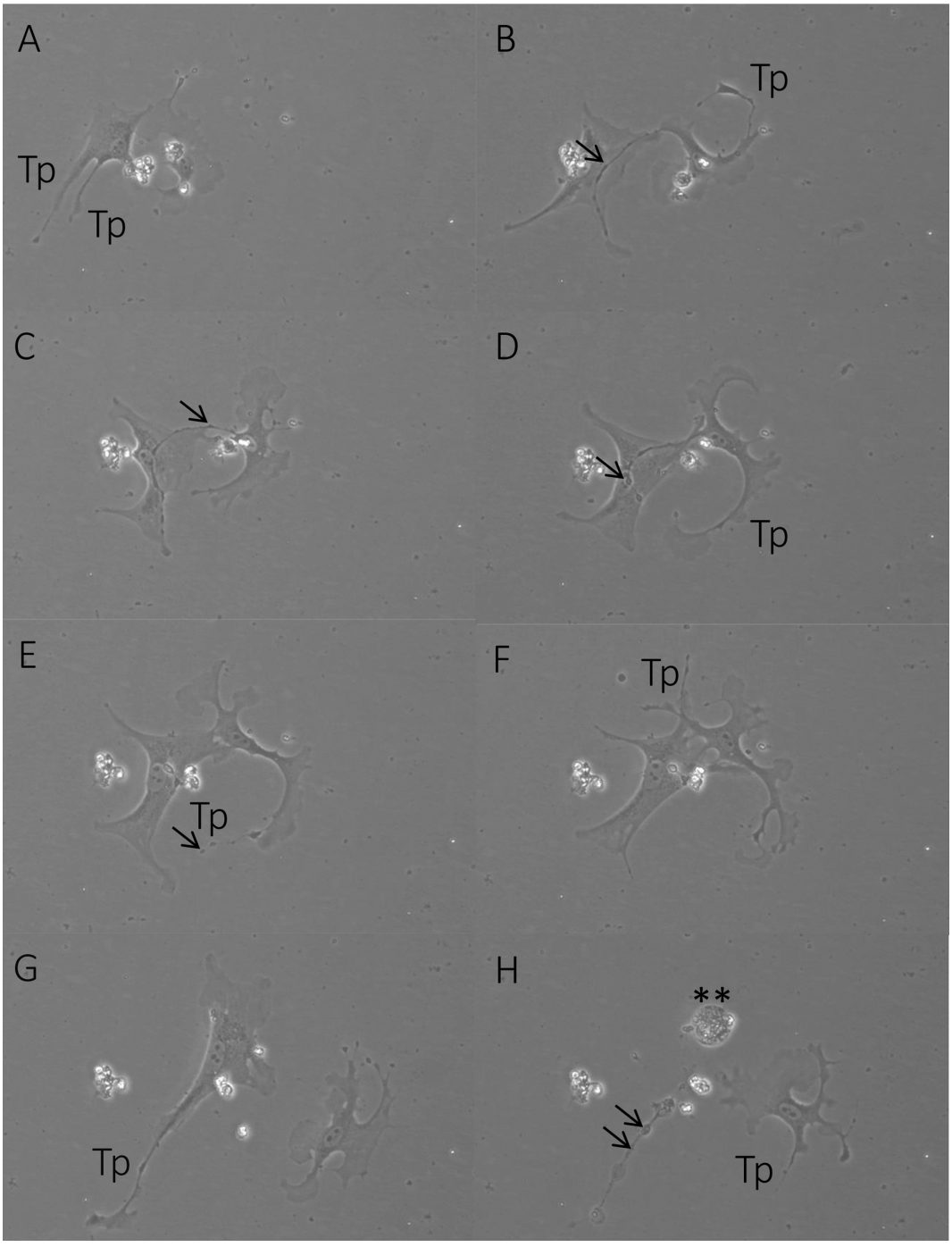

Fig. 1. The bio-behaviors of primary Telocytes (TCs) including total cell number and cell movement were measured by the real-time cell monitoring system, using a Cell-IQ cell culturing platform (Chip-Man Technologies, Tampere, Finland), equipped with a phase-contrast microscope (Nikon CFI Achromat phase contrast objective with 10_x0001_magnification) and a camera. The equipment was controlled by Image software (Chip-Man Technologies). **A-H.** Images of TCs were captured from Day 3 to Day 4 after isolation (200x). TCs is depicted with long and slender telopodes (Tps), which present the alternation of segments—podoms and podomers (black arrows). Dead TCs (**) with autolyzed podom and podomers (double-headed arrows).

extracellular vesicles which act as shuttles for important macromolecules (e.g. RNAs, proteins or microRNAs) between TCs and neighboring cells in normal and diseased states (Fertig et al., 2014; Cismasiu and Popescu, 2015; Penfornis et al., 2016). Extracellular vesicles (EVs) are membrane-covered spheres that share the surface receptors and ligands of the parent cell and transport various biomolecules, such as miRNA, various of proteins and prions (Hunter et al., 2008; Coleman et al., 2012; Rodriguez-Suarez et al., 2014). EVs are classified based on their size, shape and density in electron microscopy images and also by their mechanisms of biogenesis and formation (Kalra et al., 2012; Choi et al., 2013, 2015). Exosomes are formed in the multivesicular endosome and secreted after its fusion with the plasma membrane, whereas ectosomes are formed by direct budding from the plasma membrane (Kalra et al., 2012). EVs were found for the first time associated with TCs by Popescu's group in 2010 in human epicardium (Popescu et al., 2010). Subsequent studies have shown that TCs in the myocardium deliver microRNAs to regulate the surrounding environment including stem cells by means of EVs (Albulescu et al., 2015; Cismasiu and Popescu, 2015). EVs were also observed in lung TCs and moreover we extracted them from mice lung TCs as can be seen in Fig. 2. Although the functions of EVs produced by TCs in the lung were not studied yet, a possible role for the survival, proliferation, differentiation and maturation of the local cell populations cannot be excluded. Also, EVs therapies can be glimpsed in the future in diseases such as the acute lung injury and lung cancer.

Telocytes immunophenotype heterogeneity

Previous studies have confirmed that the most appropriate immunohistochemical markers for TCs identification are CD34, PDGFRα or β and vimentin. However, TCs exhibit expression or (co-) expression of different markers which frequently varies among different organs. For example, some human myometrium TCs are c-kit positive (Salama, 2013) and some are vimentin positive, but c-kit negative (Duquette et al., 2005), while some of themexpress CD34 and PDGFR (Campeanu et al., 2014). In the urinary tract, TCs also have a region-dependent immunohistochemical profile according to their different positivity to caveolin-1, estrogen receptor (ER) and progesterone receptor (PR), which indicates that TCs subsets may exist (Gevaert et al., 2012). In the heart, the immunohistochemical

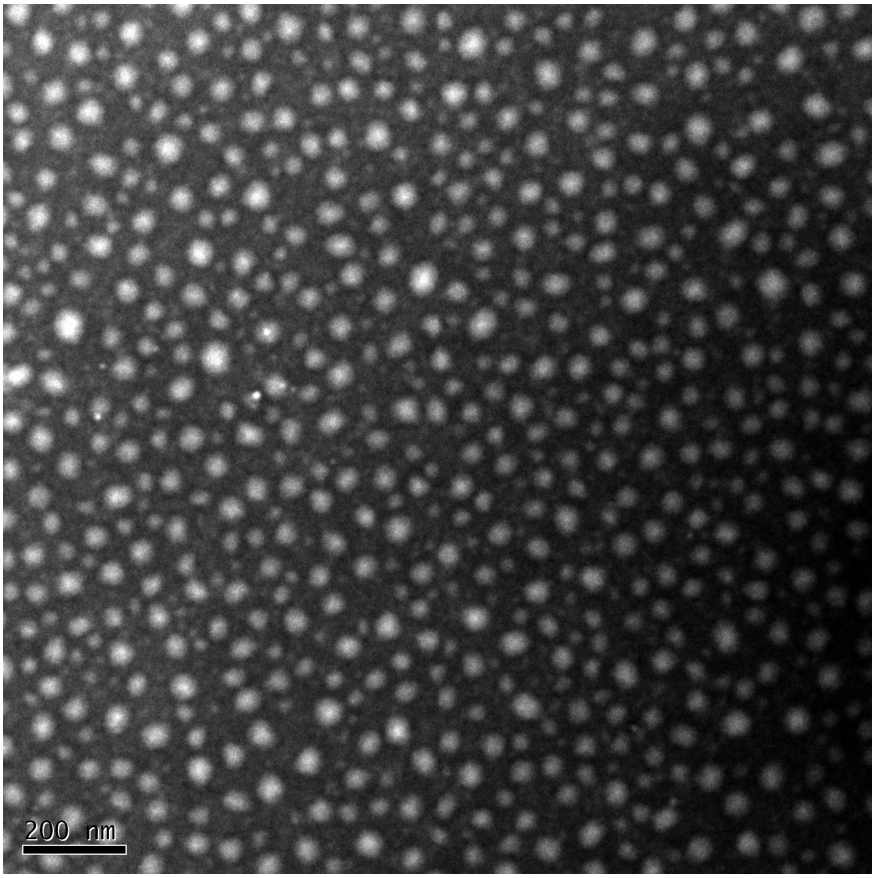

Fig. 2. Gathered exosomes released into the extracellular space as a cargo shielded by plasma membrane from TCs culture medium.

features of TCs are different from fibroblasts: cardiac TCs were positive for CD34 and c-kit, CD34 and vimentin, and CD34 and PDGFR-β, while fibroblasts were negative for CD34 (Chang et al., 2015; Tao et al., 2015; Zhou et al., 2015; Kostin, 2016). Moreover, cardiac TCs in primary culture were CD34 positive and showed a α-SMA weak positivity, while pericytes were CD34 negative but α-SMA positive (Bei et al., 2015). In addition, TCs have been found to be different from pericytes in both ultrastructure and immunophenotypes (Diaz-Flores et al., 2014). Besides, the positivity of TCs to PDGFR-α in the human gastrointestinal tract should not be overlooked (Vannucchi et al., 2013). Therefore, there is not a single specific immunomarker allowing the identification of TCs. Currently, it is considered that the double positive labeling for CD34/PDGFR or CD34/vimentin (for Tps) is appropriate for the identification of TCs (Cretoiu and Cretoiu, 2016; Rusu et al., 2016). Therefore, immunolabeling, especially double-immunolabeling remains a useful tool for discrimination between TCs and other cells, as well as for semi-quantitative data analysis.

Telocytes in lung diseases

Connective tissue diseases and pulmonary fibrosis

Connective tissue diseases (CTDs) are defined as a group of disorders involving the connective tissue and whose specific causes are not known. Usually, CTDsinvolvethe joints, muscles, and skinbut in the majority of thecases are associated with abnormal immune system activity (inflammation in tissues) other organs like heart, kidneys, gastrointestinal tract, and blood vessels are also affected. Lung involvement is common and can lead to significant morbidity and shortened survival (Wallace et al., 2016).

Idiopathic interstitial pneumonias (IIPs) are a heterogeneous group of acute and chronic disorders in which inflammation and fibrosis result from damage to the lung parenchyma. IIPs include idiopathic pulmonary fibrosis (IPF), nonspecific interstitial pneumonia (NSIP), cryptogenic organizing pneumonia (COP), acute interstitial pneumonia (AIP), respiratory bronchiolitis-associated interstitial lung disease, desquamative interstitial pneumonia, and lymphocytic interstitial pneumonia (Hashisako and Fukuoka, 2015). IPF is the most common ofthe IIPs and one of the most prevalent interstitial lung diseases (ILDs). IPFis achronic, progressive, and almost invariably fatal disorder characterized by scarring of the lung and progressive lossof function (Raghu et al., 2011; Spagnolo et al., 2015). This disease with a radiological and/or histopathologic pattern of usual interstitial pneumonia (UIP) is limited to the lungs and occurs primarily in older adults (Raghu et al., 2011). However, UIP can be found in a number of conditions, including connective tissue diseases (CTDs), chronic hypersensitivity pneumonitis (HP), and asbestosis. The incidence of IPF is increasing worldwide, especially in Europe and North America (Hutchinson et al., 2015), and is also likely to account for much of the increased ILD-related mortality (GBD 2013 Mortality and Causes of Death Collaborators, 2015). Although the nature of the stimuli that trigger the fibrotic process in IPF is still unknown, several factors have been associated with an increased risk of developing the disease, including cigarette smoking, environmental/ occupational pollutants, microbial agents, chronic microaspiration secondary to gastroesophageal reflux, and genetic abnormalities (Spagnolo et al., 2014b; Sgalla et al., 2016). The interstitium includes the space between the epithelial and endothelial basement membranes and is the primary site of injury in the IIPs. Moreover, the disorders also affect the airspaces, peripheral airways, and vessels, together with their respective epithelial and endothelial linings (Duquette et al., 2005).

Recent studies have reported that all the above-mentioned pathologies depend, among other factors, onthe local and systemic immune activation (Liu et al., 2016). Moreover, current concepts suggest that on-going microinjury to alveolar epithelial cells induces a fibrotic environment and that growth factors secreted by the injured epithelial cells promote fibrobla strecruitment, proliferation, and differentiation to invasive myofibroblasts (Selman and Pardo, 2014). The excessive collagen production by actively proliferating fibroblasts and myofibroblasts also results in architectural distortion and scarring of the lung (Spagnolo et al., 2014a). Therefore, the multitude of mediators, growth factors, and signaling pathways involved in the fibrotic process are the key points. Telocytes, which were described as novel participants in the homeostasis of the connective tissue, seem to contribute in these pathological processes. Several recent studies refer to the involvementof TCs in various diseases such as inflammatory bowel diseases, including Crohn's disease and ulcerative colitis (Milia et al., 2013), systemic sclerosis (Manetti et al., 2013, 2014), primary Sjögren's syndrome (Alunno et al., 2015) which all share the TCs reductionand network disruption (for details see review (Ibba-Manneschi et al., 2016)). Therefore, TCs involvement in lung CTDs is possible and probably lead to significant morbidity and shortened survival.

Several studies also showed that mitochondrial dysfunction regulates inflammatory responses and cellular senescence involved in the pathogenesis of chronic lung diseases (Agrawal and Mabalirajan, 2016; Yue and Yao, 2016). Thus, since TCs also hold numerous mitochondria in their perinuclear cytoplasm and particularly in the podoms (quasi 5% of the cell), they are expected to be involved in lung diseases associated with mitochondrial alterations (Lazaar and Greenhaff, 2012; Soulitzis et al., 2012). Lung TCs gene analysis showed that they seem to have important functions in the prevention of tissue inflammation and fibrogenesis development in lung inflammatory diseases and they might be capable of acting as modulators of

immune cell response (Sun et al., 2014). Global analyses of Chromosome 17 and 18 genes of lung TCs revealed that Mapk14 and Trem2 genes were up-regulated and indicateda possible biological function of TCs in immune regulation (Wang et al., 2015). The low expression of Ifi203 gene in chromosome 1 suggested that TCs might be involved in the immune response by informative exchange mediated by extracellular vesicles (exo/ectosomes) or by the existence of stromal synapses (Cretoiu and Popescu, 2014).

Bronchial asthma and COPD

Asthma and chronic obstructive pulmonary disease (COPD) are two of the most common chronic lung diseases world wide (Blanc and Toren, 2016). Asthma is characterized by chronic inflammatory disorder of the airways and usually associated with airway hyper-responsiveness and airway inflammation that lead to recurrent episodes of wheeze, shortness of breath, chest tightness and cough, together with variable expiratory airflow limitation (Barnes et al., 2010; Danesh et al., 2016; Hu et al., 2016). Eosinophilic airway inflammation is a key pathological feature of asthma which involve lung interstitial tissueand also mast cells contribute as a key effector cell of asthma pathogenesis (Murdoch and Lloyd, 2010; Szefler et al., 2012).

COPD is a progressive condition that usually leads to a steady decline in lung function, increased symptoms, and recurrent and worsening exacerbations (Agusti, 2005). Parenchymal destruction leads to further decreased gas transfer and increased air trapping which induce coughing, and variable sputum production that greatly impact a patient's quality of life (Stallberg et al., 2014). The progressive airflow limitation that characterizes COPD is a consequence of chronic airway inflammation in response to the inhalation of noxious stimuli, resulting in parenchymal destruction (Vestbo et al., 2013). The parenchymal damage in respiratory bronchioles, alveolar ducts, and alveoli result from loss of lung elastic recoil, fibrosis, narrowing of small airways and a reduction of vascularity within the alveolar septa (Brusasco and Martinez, 2014). TCs were found to occupy a strategic position in lung structures, between the smooth muscle layer and cricoid cartilage of bronchi and bronchiole (Zheng et al., 2011) and moreover, they have the ability to interact with different immune cells by stromal synapses (Popescu et al., 2005a; Cretoiu et al., 2012a). It was showed that TCs are morelikely to have a role in the maintenance and modulation of tissue homeostasis and morphogenesis, and also in immunomodulation and immunosurveillance (Roatesi et al., 2015). Therefore, the disruption of TCs during the process of COPD might also be involved in the remodeling of lung structure. The specific up-regulated genes identified in chromosome 1 of lung TCs, like the overexpression of Capn2, Fhl2 and Qsox1, strengthened the association of TCs with morphogenesis and local tissue homeostasis (Sun et al., 2014). Moreover, down-expression of Pde5 in chromosome 3 might be associated with the development of pulmonary fibrosis and other interstitial lung diseases (Zheng et al., 2014d).

Lung cancer

Lung cancers are the leading cause of cancer-related deaths worldwide and are thus a major therapeutic burden. While the incidence of lung cancer has reached a plateau in the developed world, it continues to increase in the developing world. Predominantly caused by smoking, lung cancers have a poor prognosis with a combined five-year survival rate of less than 20% (Torre et al., 2015). Lung cancer mainly includes small-cell lung cancer (SCLC) and non-small-cell lung cancer (NSCLC). NSCLCs account for over 80% of all lung cancers and include adenocarcinomas, squamous cell carcinomas, bronchioalveolar and large cell carcinomas. The remaining 15% - 20% of lung cancers show features of neuroendocrine differentiation and are classified as SCLC. Bronchioalveolar stem cells are postulated to play a role in NSCLC tumorigenesis, while a rare population of neuroendocrine cells or less differentiated cells are thought to be the progenitor cells forSCLC (Semenova et al., 2015). Microenvironment, including stromal cell types, play a key role in cancer development, progression and metastasis (Horch et al., 2013). Bidirectional signaling mechanisms between cells and their microenvironment is important for the control of cell morphology, adhesion, migration and invasion (Quail and Joyce, 2013) and TCs might be participants in these events (Smythies, 2015). Recent studies showed that TCs communicate with stem cells by junctions and by extracellular vesicles (Fertig et al., 2014; Popescu et al., 2016). Moreover, there is a shuttle mechanism of vesicle transfer between TCs and stem cells and the secretome of myocardial TCs modulates the activity of cardiac stem cells in cell culture (Albulescu et al., 2015). Telocytes involvement in cancer was showed by Mou et al. which demonstrated their participation in self-assembly of EMT-6/stromal cells reconstituted breast cancer tissue (Mou et al., 2013). Also, it was showed that the overexpression of Sh3glb1, Tm4sf1 or Csf1 in chromosome 3 of TCs are mainly associated the development of lung cancer (Zheng et al., 2014d). Moreover, acid ceramidase, (an enzyme encoded by the ASAH1 gene) was found to be up-regulated in TCs suggesting that they might inhibit the oxidative stress and cellular aging and may have pro-proliferative effects through the inhibition of apoptosis (Zheng et al., 2014b).

Acute lung injury

The Acute Respiratory Distress Syndrome (ARDS) was first recognized in the 1960s as a clinical syndrome of severe acute respiratory failure (Cherniack, 1970). Although definitions have been recently revised, the consistent hallmarks are the acuity of presentation, and

the presence of severe hypoxemia and bilateral pulmonary infiltrates (Papazian et al., 2016). Despite improvements in intensive care during the last fifteen years, ARDS is still a frequent, morbid, and life-threatening condition, with a mortality rate around 30%. Those who do recover experience a significant decrease in quality of life with long term physical, physiological, and emotional dysfunction (Chiumello et al., 2016). ARDS is an acute-onset hypoxic condition characterized by two phases that may sometimes overlap temporally and spatially: exudative and proliferative phases. An alveolar-capillary barrier dysfunction resulting in altered permeability of epithelial and endothelial alveolar cells characterizes the early exudative phase (Dong et al., 2013). Other proinflammatory mechanisms are also involved and consist of a significant release of proinflammatory cytokines by lungs cells, inflammatory cells, and fibroblasts (Butt et al., 2016). Therefore, one could suspect that lung TCs might be involved in the early stage of ARDS, since there are studies showing close contacts between them and immune cells, e.g. macrophages, eosinophils, plasma cells, mast cells (Zheng et al., 2012a). Human lung TCs have been reported to promote the proliferation and angiogenesis of human pulmonary microvascular endothelial cells in vitro (Zheng et al., 2014c) and therefore TCs might be also involved in the late stage of ARDS.

Targeting TCs as a potential therapeutic strategy

Since TCs were identified and characterized in lung interstitial tissue it became clear that they are also involved in a lot of biological processes such as mechanical support sometimes acting as stretch sensors, organization and guidance of the surrounding cells and extracellular matrix components, maintenance of the local homeostasis and creation of an appropriate environment for stem cells in their niches. Although their involvement in the pathogenesis of lung diseases is not very well studied.

TCs were found in close vicinity with airway or alveolar epithelial cells fact which might be suggestive of their involvement in the maintenance of the integrity these epithelial barriers. TCs have large amounts of mitochondria, both in their cell body, but also in their podoms. Moreover, *in vitro*, Tps are dynamic structures

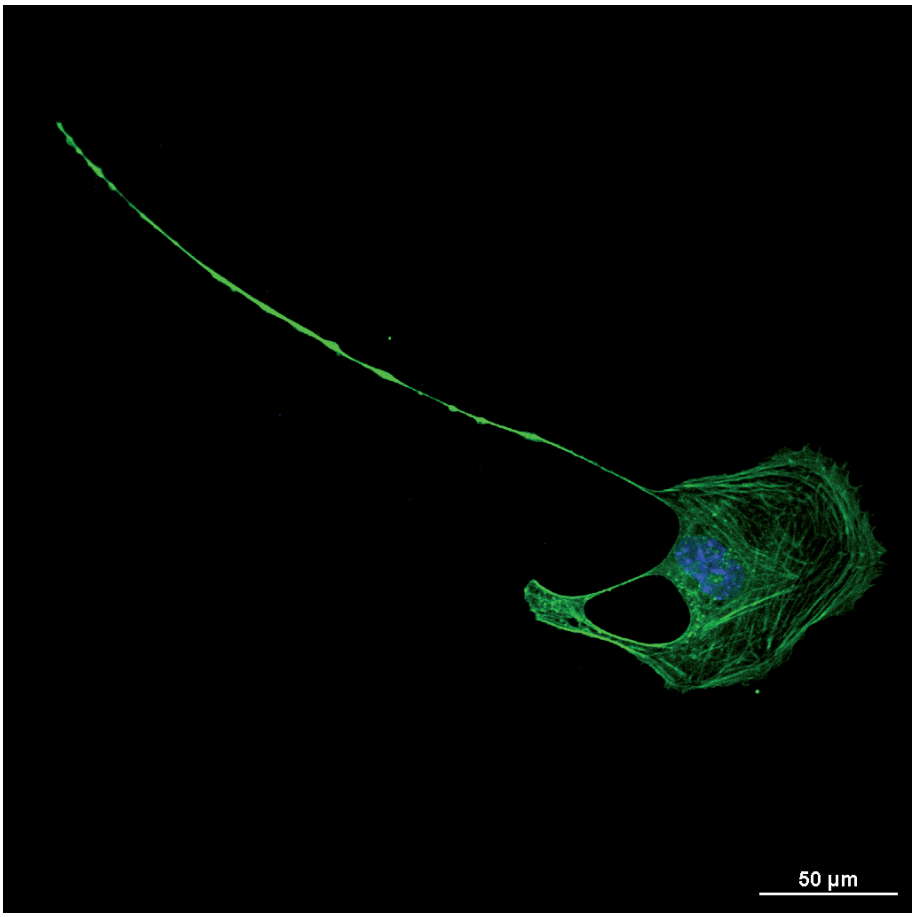

Fig. 3. Actin-Tracker Green staining. A molecular probe with high affinity for actin, Actin-Tracker Green shows amount of actin in most TCs and Tps which further demonstrate the movement ability of TCs and podoms.

which extend and retract leaving behind traces of signaling molecules leading to the division of cells which they previously contacted. The telopodal movement is possible due to the richness of actin filaments which are also present in TCs and Tps as can be seen by molecular probes of Actin-Tracker Green (Fig. 3). These findings imply that the maintenance of TCs biological functions requires a large amount of energy, while the energy necessary to the extension and retraction of the Tps is assured by the mitochondria present in the podoms. Therefore, we could presume that pathological mitochondrial changes could lead to a TCs dysfunctionality.

Telocytes have been found to be decreased in experimental myocardial infarction (MI), especially in fibrotic areas (Zhao et al., 2013). Intramyocardial transplantation of cardiac TCs could decrease MI and improve post-infarcted cardiac function via increasing cardiac angiogenesis, the reconstruction of the TCs network and by decreasing cardiac fibrosis (Zhao et al., 2014). Also lung TCs have been reported to promote the proliferation and angiogenesis of human pulmonary microvascular endothelial cells and several reports have indicated that TCs were decreased in fibrotic remodeling, such as systemic sclerosis, liver fibrosis, and ulcerative colitis, one can consider as priority to determine if TCs could prevent the activation of fibroblasts and attenuate the altered organization of extracellular matrix during fibrotic processes (Manetti et al., 2014, 2015). Given that endometriosis-affected rat oviduct displayed damaged TCs which might be related to impaired stem cell-mediated tissue repair, we might target the use of TCs alone or in tandem with stem cells to promote regeneration and prevent the evolution to irreversible tissue damage (Popescu, 2011a). It has been shown that TCs could produceVEGF and this might suggestive for a TCs role in the signaling pathway by which VEGF promotes the proliferation of endothelial cells and augment lung tissue repair after injury (Gavard and Gutkind, 2006). Low-level laser stimulation (LLLS) has been reported to accelerate the growth of telopodal lateral extensions in pregnant myometrium primary cultures (Campeanu et al., 2014) and exploring other pharmacological or non-pharmacological methods to enhance the growth of TCs could be regarded as novel therapeutic strategies besides exogenous transplantation.

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References

Agrawal A. and Mabalirajan U. (2016). Rejuvenating cellular respiration for optimizing respiratory function: Targeting mitochondria. Am. J. Physiol. Lung Cell Mol. Physiol. 310, L103-113.

Agusti A.G. (2005). COPD, a multicomponent disease: Implications for management. Respir. Med. 99, 670-682.

Albulescu R., Tanase C., Codrici E., Popescu D.I., Cretoiu S.M. and Popescu L.M. (2015). The secretome of myocardial telocytes modulates the activity of cardiac stem cells. J. Cell Mol. Med. 19, 1783-1794.

Alunno A., Ibba-Manneschi L., Bistoni O., Rosa I., Caterbi S., Gerli R. and Manetti M. (2015). Telocytes in minor salivary glands of primary sjogren's syndrome: Association with the extent of inflammation and ectopic lymphoid neogenesis. J. Cell Mol. Med. 19, 1689-1696.

Bagnato G. and Harari S. (2015). Cellular interactions in the pathogenesis of interstitial lung diseases. Eur. Respir. Rev. 24, 102-114.

Barnes P.J., Dweik R.A., Gelb A.F., Gibson P.G., George S.C., Grasemann H., Pavord I.D., Ratjen F., Silkoff P.E., Taylor D.R. and Zamel N. (2010). Exhaled nitric oxide in pulmonary diseases: A comprehensive review. Chest 138, 682-692.

Bei Y., Zhou Q., Fu S., Lv D., Chen P., Chen Y., Wang F. and Xiao J. (2015). Cardiac telocytes and fibroblasts in primary culture: Different morphologies and immunophenotypes. PLoS One 10, e0115991.

Blanc P.D. and Toren K. (2016). COPD and occupation: Resetting the agenda. Occup. Environ. Med. 73, 357-358.

Brusasco V. and Martinez F. (2014). Chronic obstructive pulmonary disease. Compr. Physiol. 4, 1-31.

Butt Y., Kurdowska A. and Allen T.C. (2016). Acute lung injury: A clinical and molecular review. Arch. Pathol. Lab. Med. 140, 345-350.

Campeanu R.A., Radu B.M., Cretoiu S.M., Banciu D.D., Banciu A., Cretoiu D. and Popescu L.M. (2014). Near-infrared low-level laser stimulation of telocytes from human myometrium. Lasers Med. Sci. 29, 1867-1874.

Ceafalan L., Gherghiceanu M., Popescu L.M. and Simionescu O. (2012). Telocytes in human skin--are they involved in skin regeneration? J. Cell Mol. Med. 16, 1405-1420.

Chang Y., Li C., Lu Z., Li H. and Guo Z. (2015). Multiple immunophenotypes of cardiac telocytes. Exp. Cell Res. 338, 239-244.

Cherniack R.M. (1970). The management of acute respiratory failure. Chest 58 (Suppl 2), 427-436.

Chiumello D., Coppola S., Froio S. and Gotti M. (2016). What's next after ARDS: Long-term outcomes. Respir. Care 61, 689-699.

Choi D.S., Kim D.K., Kim Y.K. and Gho Y.S. (2013). Proteomics, transcriptomics and lipidomics of exosomes and ectosomes. Proteomics 13, 1554-1571.

Choi D.S., Kim D.K., Kim Y.K. and Gho Y.S. (2015). Proteomics of extracellular vesicles: Exosomes and ectosomes. Mass. Spectrom. Rev. 34, 474-490.

Ciontea S.M., Radu E., Regalia T., Ceafalan L., Cretoiu D., Gherghiceanu M., Braga R.I., Malincenco M., Zagrean L., Hinescu M.E. and Popescu L.M. (2005). C-kit immunopositive interstitial cells (cajal-type) in human myometrium. J. Cell Mol. Med. 9, 407-420.

Cismasiu V.B. and Popescu L.M. (2015). Telocytes transfer extracellular vesicles loaded with microRNAs to stem cells. J. Cell Mol. Med. 19,

351-358.

Cismasiu V.B., Radu E. and Popescu L.M. (2011). Mir-193 expression differentiates telocytes from other stromal cells. J. Cell Mol. Med. 15, 1071-1074.

Coleman B.M., Hanssen E., Lawson V.A. and Hill A.F. (2012). Prion-infected cells regulate the release of exosomes with distinct ultrastructural features. FASEB J. 26, 4160-4173.

Corradi L.S., Jesus M.M., Fochi R.A., Vilamaior P.S., Justulin L.A. Jr., Goes R.M., Felisbino S.L. and Taboga S.R. (2013). Structural and ultrastructural evidence for telocytes in prostate stroma. J. Cell Mol. Med. 17, 398-406.

Cretoiu D. and Cretoiu S.M. (2016). Telocytes in the reproductive organs: Current understanding and future challenges. Semin. Cell Dev. Biol. 55, 40-49.

Cretoiu S.M. and Popescu L.M. (2014). Telocytes revisited. Biomol. Concepts. 5, 353-369.

Cretoiu D., Ciontea S.M., Popescu L.M., Ceafalan L. and Ardeleanu C. (2006). Interstitial cajal-like cells (ICLC) as steroid hormone sensors in human myometrium: Immunocytochemical approach. J. Cell Mol. Med. 10, 789-795.

Cretoiu D., Cretoiu S.M., Simionescu A.A. and Popescu L.M. (2012a). Telocytes, a distinct type of cell among the stromal cells present in the lamina propria of jejunum. Histol. Histopathol. 27, 1067-1078.

Cretoiu S.M., Cretoiu D. and Popescu L.M. (2012b). Human myometrium - the ultrastructural 3D network of telocytes. J. Cell Mol. Med. 16, 2844-2849.

Cretoiu S.M., Cretoiu D., Marin A., Radu B.M. and Popescu L.M. (2013). Telocytes: Ultrastructural, immunohistochemical and electrophysiological characteristics in human myometrium. Reproduction 145, 357-370.

Cretoiu D., Hummel E., Zimmermann H., Gherghiceanu M. and Popescu L.M. (2014). Human cardiac telocytes: 3D imaging by FIB-SEM tomography. J. Cell Mol. Med. 18, 2157-2164.

Cretoiu D., Gherghiceanu M., Hummel E., Zimmermann H., Simionescu O. and Popescu L.M. (2015a). FIB-SEM tomography of human skin telocytes and their extracellular vesicles. J. Cell Mol. Med. 19, 714-722.

Cretoiu S.M., Radu B.M., Banciu A., Banciu D.D., Cretoiu D., Ceafalan L.C. and Popescu L.M. (2015b). Isolated human uterine telocytes: Immunocytochemistry and electrophysiology of t-type calcium channels. Histochem. Cell Biol. 143, 83-94.

Danesh M.J., Saylor D.K., Leard L.E., North J.P. and Fox L.P. (2016). Acquired acanthosis nigricans with tripe palms in a patient with interstitial lung disease. JAAD Case Rep. 2, 59-62.

Diaz-Flores L., Gutierrez R., Saez F.J., Diaz-Flores L. Jr. and Madrid J.F. (2013). Telocytes in neuromuscular spindles. J. Cell Mol. Med. 17, 457-465.

Diaz-Flores L., Gutierrez R., Garcia M.P., Saez F.J., Diaz-Flores L. Jr., Valladares F. and Madrid J.F. (2014). Cd34+ stromal cells/fibroblasts/fibrocytes/telocytes as a tissue reserve and a principal source of mesenchymal cells. Location, morphology, function and role in pathology. Histol. Histopathol. 29, 831-870.

Dong H., Li J., Lv Y., Zhou Y., Wang G., Hu S., He X., Yang P., Zhou Z., Xiang X. and Wang C.Y. (2013). Comparative analysis of the alveolar macrophage proteome in ali/ards patients between the exudative phase and recovery phase. BMC Immunol. 14, 25.

Duquette R.A., Shmygol A., Vaillant C., Mobasheri A., Pope M., Burdyga T. and Wray S. (2005). Vimentin-positive, c-kit-negative interstitial cells in human and rat uterus: A role in pacemaking? Biol. Reprod. 72, 276-283.

Faussone-Pellegrini M.S. and Gherghiceanu M. (2016). Telocyte's contacts. Semin. Cell Dev. Biol. 55, 3-8.

Fertig E.T., Gherghiceanu M. and Popescu L.M. (2014). Extracellular vesicles release by cardiac telocytes: Electron microscopy and electron tomography. J. Cell Mol. Med. 18, 1938-1943.

Gavard J. and Gutkind J.S. (2006). VEGF controls endothelial-cell permeability by promoting the beta-arrestin-dependent endocytosis of ve-cadherin. Nat. Cell Biol. 8, 1223-1234.

GBD 2013 Mortality and Causes of Death Collaborators (2015). Global, regional, and national age-sex specific all-cause and cause-specific mortality for 240 causes of death, 1990-2013: A systematic analysis for the global burden of disease study 2013. Lancet 385, 117-171.

Gevaert T., De Vos R., Van Der Aa F., Joniau S., van den Oord J., Roskams T. and De Ridder D. (2012). Identification of telocytes in the upper lamina propria of the human urinary tract. J. Cell Mol. Med. 16, 2085-2093.

Hashisako M. and Fukuoka J. (2015). Pathology of idiopathic interstitial pneumonias. Clin. Med. Insights Circ. Respir. Pulm. Med. 9, 123-133.

Hinescu M.E., Gherghiceanu M., Mandache E., Ciontea S.M. and Popescu L.M. (2006). Interstitial cajal-like cells (ICLC) in atrial myocardium: Ultrastructural and immunohistochemical characterization. J. Cell Mol. Med. 10, 243-257.

Hinescu M.E., Gherghiceanu M., Suciu L. and Popescu L.M. (2011). Telocytes in pleura: Two- and three-dimensional imaging by transmission electron microscopy. Cell Tissue Res. 343, 389-397.

Hole D.J., Watt G.C., Davey-Smith G., Hart C.L., Gillis C.R. and Hawthorne V.M. (1996). Impaired lung function and mortality risk in men and women: Findings from the renfrew and paisley prospective population study. BMJ 313, 711-715; discussion 715-716.

Horch R.E., Boos A.M., Quan Y., Bleiziffer O., Detsch R., Boccaccini A.R., Alexiou C., Sun J., Beier J.P. and Arkudas A. (2013). Cancer research by means of tissue engineering - is there a rationale? J. Cell Mol. Med. 17, 1197-1206.

Hu Y., Wang L.S., Wei Y.R., Du S.S., Du Y.K., He X., Li N., Zhou Y., Li Q.H., Su Y.L., Zhang F., Shen L., Weng D., Brown K.K. and Li H.P. (2016). Clinical characteristics of connective tissue disease-associated interstitial lung disease in 1,044 chinese patients. Chest 149, 201-208.

Hunter M.P., Ismail N., Zhang X., Aguda B.D., Lee E.J., Yu L., Xiao T., Schafer J., Lee M.L., Schmittgen T.D., Nana-Sinkam S.P., Jarjoura D. and Marsh C.B. (2008). Detection of microrna expression in human peripheral blood microvesicles. PLoS One 3, e3694.

Hutchinson J., Fogarty A., Hubbard R. and McKeever T. (2015). Global incidence and mortality of idiopathic pulmonary fibrosis: A systematic review. Eur. Respir. J. 46, 795-806.

Ibba-Manneschi L., Rosa I. and Manetti M. (2016). Telocyte implications in human pathology: An overview. Semin. Cell Dev. Biol. 55, 62-69.

Kalra H., Simpson R.J., Ji H., Aikawa E., Altevogt P., Askenase P., Bond V.C., Borras F.E., Breakefield X., Budnik V., Buzas E., Camussi G., Clayton A., Cocucci E., Falcon-Perez J.M., Gabrielsson S., Gho Y.S., Gupta D., Harsha H.C., Hendrix A., Hill A.F., Inal J.M., Jenster G., Kramer-Albers E.M., Lim S.K., Llorente A., Lotvall J., Marcilla A., Mincheva-Nilsson L., Nazarenko I., Nieuwland R., Nolte-

't Hoen E.N., Pandey A., Patel T., Piper M.G., Pluchino S., Prasad T.S., Rajendran L., Raposo G., Record M., Reid G.E., Sanchez-Madrid F., Schiffelers R.M., Siljander P., Stensballe A., Stoorvogel W., Taylor D., Thery C., Valadi H., van Balkom B.W., Vazquez J., Vidal M., Wauben M.H., Yanez-Mo M., Zoeller M. and Mathivanan S. (2012). Vesiclepedia: A compendium for extracellular vesicles with continuous community annotation. PLoS Biol. 10, e1001450.

Kostin S. (2016). Cardiac telocytes in normal and diseased hearts. Semin Cell Dev Biol. 55, 22-30.

Lazaar A.L. and Greenhaff P.L. (2012). Impaired muscle mitochondrial density and/or function: A COPD-specific mitochondropathy or simply deconditioning? Eur. Respir. J. 40, 1070-1071.

Liu M., Zeng X., Wang J., Fu Z., Wang J., Liu M., Ren D., Yu B., Zheng L., Hu X., Shi W. and Xu J. (2016). Immunomodulation by mesenchymal stem cells in treating human autoimmune disease-associated lung fibrosis. Stem Cell Res. Ther. 7, 63.

Luesma M.J., Gherghiceanu M. and Popescu L.M. (2013). Telocytes and stem cells in limbus and uvea of mouse eye. J. Cell Mol. Med. 17, 1016-1024.

Manetti M., Rosa I., Messerini L., Guiducci S., Matucci-Cerinic M. and Ibba-Manneschi L. (2014). A loss of telocytes accompanies fibrosis of multiple organs in systemic sclerosis. J. Cell Mol. Med. 18, 253-262.

Manetti M., Guiducci S., Ruffo M., Rosa I., Faussone-Pellegrini M.S., Matucci-Cerinic M. and Ibba-Manneschi L. (2013). Evidence for progressive reduction and loss of telocytes in the dermal cellular network of systemic sclerosis. J. Cell Mol. Med. 17, 482-496.

Manetti M., Rosa I., Messerini L. and Ibba-Manneschi L. (2015). Telocytes are reduced during fibrotic remodelling of the colonic wall in ulcerative colitis. J. Cell Mol. Med. 19, 62-73.

Manole C.G., Gherghiceanu M. and Simionescu O. (2015). Telocyte dynamics in psoriasis. J. Cell Mol. Med. 19, 1504-1519.

Milia A.F., Ruffo M., Manetti M., Rosa I., Conte D., Fazi M., Messerini L. and Ibba-Manneschi L. (2013). Telocytes in crohn's disease. J. Cell Mol. Med. 17, 1525-1536.

Mou Y., Wang Y., Li J., Lu S., Duan C., Du Z., Yang G., Chen W., Zhao S., Zhou J. and Wang C. (2013). Immunohistochemical characterization and functional identification of mammary gland telocytes in the self-assembly of reconstituted breast cancer tissue in vitro. J. Cell Mol. Med. 17, 65-75.

Murdoch J.R. and Lloyd C.M. (2010). Chronic inflammation and asthma. Mutat. Res. 690, 24-39.

Papazian L., Calfee C.S., Chiumello D., Luyt C.E., Meyer N.J., Sekiguchi H., Matthay M.A. and Meduri G.U. (2016). Diagnostic workup for ards patients. Intensive Care Med. 42, 674-685.

Penfornis P., Vallabhaneni K.C., Whitt J. and Pochampally R. (2016). Extracellular vesicles as carriers of microrna, proteins and lipids in tumor microenvironment. Int. J. Cancer 138, 14-21.

Popescu L.M. (2011a). Telocytes and stem cells: A tandem in cardiac regenerative medicine. Curr. Med. Chem. 18, 94.

Popescu L.M. (2011b). The tandem: Telocytes-stem cells. Int. J. Biol. Biomed. Eng. 5, 83-92.

Popescu L.M. and Faussone-Pellegrini M.S. (2010). Telocytes - a case of serendipity: The winding way from interstitial cells of cajal (ICC), via interstitial cajal-like cells (ICLC) to telocytes. J. Cell Mol. Med. 14, 729-740.

Popescu L.M., Gherghiceanu M., Cretoiu D. and Radu E. (2005a). The connective connection: Interstitial cells of cajal (ICC) and ICC-like cells establish synapses with immunoreactive cells. Electron microscope study in situ. J. Cell Mol. Med. 9, 714-730.

Popescu L.M., Hinescu M.E., Ionescu N., Ciontea S.M., Cretoiu D. and Ardelean C. (2005b). Interstitial cells of cajal in pancreas. J. Cell Mol. Med. 9, 169-190.

Popescu L.M., Ciontea S.M., Cretoiu D., Hinescu M.E., Radu E., Ionescu N., Ceausu M., Gherghiceanu M., Braga R.I., Vasilescu F., Zagrean L. and Ardeleanu C. (2005c). Novel type of interstitial cell (cajal-like) in human fallopian tube. J. Cell Mol. Med. 9, 479-523.

Popescu L.M., Manole C.G., Gherghiceanu M., Ardelean A., Nicolescu M.I., Hinescu M.E. and Kostin S. (2010). Telocytes in human epicardium. J. Cell Mol. Med. 14, 2085-2093.

Popescu L.M., Gherghiceanu M., Suciu L.C., Manole C.G. and Hinescu M.E. (2011a). Telocytes and putative stem cells in the lungs: Electron microscopy, electron tomography and laser scanning microscopy. Cell Tissue Res. 345, 391-403.

Popescu L.M., Manole E., Serboiu C.S., Manole C.G., Suciu L.C., Gherghiceanu M. and Popescu B.O. (2011b). Identification of telocytes in skeletal muscle interstitium: Implication for muscle regeneration. J. Cell Mol. Med. 15, 1379-1392.

Popescu L.M., Curici A., Wang E., Zhang H., Hu S. and Gherghiceanu M. (2015). Telocytes and putative stem cells in ageing human heart. J. Cell Mol. Med. 19, 31-45.

Popescu L.M., Fertig E.T. and Gherghiceanu M. (2016). Reaching out: Junctions between cardiac telocytes and cardiac stem cells in culture. J. Cell Mol. Med. 20, 370-380.

Quail D.F. and Joyce J.A. (2013). Microenvironmental regulation of tumor progression and metastasis. Nat. Med. 19, 1423-1437.

Raghu G., Collard H.R., Egan J.J., Martinez F.J., Behr J., Brown K.K., Colby T.V., Cordier J.F., Flaherty K.R., Lasky J.A., Lynch D.A., Ryu J.H., Swigris J.J., Wells A.U., Ancochea J., Bouros D., Carvalho C., Costabel U., Ebina M., Hansell D.M., Johkoh T., Kim D.S., King T.E. Jr., Kondoh Y., Myers J., Muller N.L., Nicholson A.G., Richeldi L., Selman M., Dudden R.F., Griss B.S., Protzko S.L., Schunemann H.J. and ATS/ERS/JRS/ALAT Committee on Idiopathic Pulmonary Fibrosis (2011). An official ats/ers/jrs/alat statement: Idiopathic pulmonary fibrosis: Evidence-based guidelines for diagnosis and management. Am J. Respir. Crit. Care Med. 183, 788-824.

Roatesi I., Radu B.M., Cretoiu D. and Cretoiu S.M. (2015). Uterine telocytes: A review of current knowledge. Biol. Reprod. 93, 10.

Rodriguez-Suarez E., Gonzalez E., Hughes C., Conde-Vancells J., Rudella A., Royo F., Palomo L., Elortza F., Lu S.C., Mato J.M., Vissers J.P. and Falcon-Perez J.M. (2014). Quantitative proteomic analysis of hepatocyte-secreted extracellular vesicles reveals candidate markers for liver toxicity. J. Proteomics 103, 227-240.

Rusu M.C., Pop F., Hostiuc S., Curca G.C., Jianu A.M. and Paduraru D. (2012). Telocytes form networks in normal cardiac tissues. Histol. Histopathol. 27, 807-816.

Rusu M.C., Cretoiu D., Vrapciu A.D., Hostiuc S., Dermengiu D., Manoiu V.S., Cretoiu S.M. and Mirancea N. (2016). Telocytes of the human adult trigeminal ganglion. Cell. Biol. Toxicol. 32, 199-207.

Salama N.M. (2013). Immunohistochemical characterization of telocytes in rat uterus in different reproductive states. Egypt. J. Histol. 36, 185-194.

Selman M. and Pardo A. (2014). Revealing the pathogenic and aging-related mechanisms of the enigmatic idiopathic pulmonary fibrosis. An integral model. Am. J. Respir. Crit. Care Med. 189, 1161-1172.

Semenova E.A., Nagel R. and Berns A. (2015). Origins, genetic

landscape, and emerging therapies of small cell lung cancer. Genes Dev. 29, 1447-1462.

Sgalla G., Biffi A. and Richeldi L. (2016). Idiopathic pulmonary fibrosis: Diagnosis, epidemiology and natural history. Respirology 21, 427-437.

Sheng J., Shim W., Lu J., Lim S.Y., Ong B.H., Lim T.S., Liew R., Chua Y.L. and Wong P. (2014). Electrophysiology of human cardiac atrial and ventricular telocytes. J. Cell Mol. Med. 18, 355-362.

Smythies J. (2015). Intercellular signaling in cancer-the smt and toft hypotheses, exosomes, telocytes and metastases: Is the messenger in the message? J. Cancer 6, 604-609.

Song D., Cretoiu D., Zheng M., Qian M., Zhang M., Cretoiu S.M., Chen L., Fang H., Popescu L.M. and Wang X. (2016). Comparison of chromosome 4 gene expression profile between lung telocytes and other local cell types. J. Cell Mol. Med. 20, 71-80.

Soulitzis N., Neofytou E., Psarrou M., Anagnostis A., Tavernarakis N., Siafakas N. and Tzortzaki E.G. (2012). Downregulation of lung mitochondrial prohibitin in copd. Respir. Med. 106, 954-961.

Spagnolo P., Rossi G. and Cavazza A. (2014a). Pathogenesis of idiopathic pulmonary fibrosis and its clinical implications. Expert Rev. Clin. Immunol. 10, 1005-1017.

Spagnolo P., Grunewald J. and du Bois R.M. (2014b). Genetic determinants of pulmonary fibrosis: Evolving concepts. Lancet Respir. Med. 2, 416-428.

Spagnolo P., Sverzellati N., Rossi G., Cavazza A., Tzouvelekis A., Crestani B. and Vancheri C. (2015). Idiopathic pulmonary fibrosis: An update. Ann. Med. 47, 15-27.

Stallberg B., Janson C., Johansson G., Larsson K., Stratelis G., Telg G. and Lisspers K.H. (2014). Management, morbidity and mortality of COPD during an 11-year period: An observational retrospective epidemiological register study in sweden (pathos). Prim. Care Respir. J. 23, 38-45.

Sun X., Zheng M., Zhang M., Qian M., Zheng Y., Li M., Cretoiu D., Chen C., Chen L., Popescu L.M. and Wang X. (2014). Differences in the expression of chromosome 1 genes between lung telocytes and other cells: Mesenchymal stem cells, fibroblasts, alveolar type ii cells, airway epithelial cells and lymphocytes. J. Cell Mol. Med. 18, 801-810.

Szefler S.J., Wenzel S., Brown R., Erzurum S.C., Fahy J.V., Hamilton R.G., Hunt J.F., Kita H., Liu A.H., Panettieri R.A. Jr., Schleimer R.P. and Minnicozzi M. (2012). Asthma outcomes: Biomarkers. J. Allergy Clin. Immunol. 129, S9-23.

Tao L., Wang H., Wang X., Kong X. and Li X. (2015). Cardiac telocytes. Curr. Stem Cell Res. Ther. 11, 404-409.

Torre L.A., Bray F., Siegel R.L., Ferlay J., Lortet-Tieulent J. and Jemal A. (2015). Global cancer statistics, 2012. CA Cancer J. Clin. 65, 87-108.

Vannucchi M.G., Traini C., Manetti M., Ibba-Manneschi L. and Faussone-Pellegrini M.S. (2013). Telocytes express pdgfralpha in the human gastrointestinal tract. J. Cell Mol. Med. 17, 1099-1108.

Vestbo J., Hurd S.S., Agusti A.G., Jones P.W., Vogelmeier C., Anzueto A., Barnes P.J., Fabbri L.M., Martinez F.J., Nishimura M., Stockley R.A., Sin D.D. and Rodriguez-Roisin R. (2013). Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: Gold executive summary. Am. J. Respir. Crit. Care Med. 187, 347-365.

Wallace B., Vummidi D. and Khanna D. (2016). Management of connective tissue diseases associated interstitial lung disease: A review of the published literature. Curr. Opin. Rheumatol. 28, 236-245.

Wang J., Ye L., Jin M. and Wang X. (2015). Global analyses of chromosome 17 and 18 genes of lung telocytes compared with mesenchymal stem cells, fibroblasts, alveolar type II cells, airway epithelial cells, and lymphocytes. Biol. Direct. 10, 9.

Xiao J., Wang F., Liu Z. and Yang C. (2013). Telocytes in liver: Electron microscopic and immunofluorescent evidence. J. Cell Mol. Med. 17, 1537-1542.

Yang Y., Sun W., Wu S.M., Xiao J. and Kong X. (2014). Telocytes in human heart valves. J. Cell Mol. Med. 18, 759-765.

Yang X.J., Yang J., Liu Z., Yang G. and Shen Z.J. (2015). Telocytes damage in endometriosis-affected rat oviduct and potential impact on fertility. J. Cell Mol. Med. 19, 452-462.

Yue L. and Yao H. (2016). Mitochondrial dysfunction in inflammatory responses and cellular senescence: Pathogenesis and pharmacological targets for chronic lung diseases. Br. J. Pharmacol. 173, 2305-2318.

Zhao B., Chen S., Liu J., Yuan Z., Qi X., Qin J., Zheng X., Shen X., Yu Y., Qnin T.J., Chan J.Y. and Cai D. (2013). Cardiac telocytes were decreased during myocardial infarction and their therapeutic effects for ischaemic heart in rat. J. Cell Mol. Med. 17, 123-133.

Zhao B., Liao Z., Chen S., Yuan Z., Yilin C., Lee K.K., Qi X., Shen X., Zheng X., Quinn T. and Cai D. (2014). Intramyocardial transplantation of cardiac telocytes decreases myocardial infarction and improves post-infarcted cardiac function in rats. J. Cell Mol. Med. 18, 780-789.

Zheng Y., Li H., Manole C.G., Sun A., Ge J. and Wang X. (2011). Telocytes in trachea and lungs. J. Cell Mol. Med. 15, 2262-2268.

Zheng Y., Bai C. and Wang X. (2012a). Telocyte morphologies and potential roles in diseases. J. Cell Physiol. 227, 2311-2317.

Zheng Y., Zhu T., Lin M., Wu D. and Wang X. (2012b). Telocytes in the urinary system. J. Transl. Med. 10, 188.

Zheng Y.H., Li H., Ge J.B., Gao H.J. and Wang X.D. (2012c). Location of telocytes in mouse bronchial and pulmonary tissues. Zhonghua Bing Li Xue Za Zhi 41, 172-175 (in chinese).

Zheng Y., Zhang M., Qian M., Wang L., Cismasiu V.B., Bai C., Popescu L.M. and Wang X. (2013). Genetic comparison of mouse lung telocytes with mesenchymal stem cells and fibroblasts. J. Cell Mol. Med. 17, 567-577.

Zheng M., Sun X., Zhang M., Qian M., Zheng Y., Li M., Cretoiu S.M., Chen C., Chen L., Cretoiu D., Popescu L.M., Fang H. and Wang X. (2014a). Variations of chromosomes 2 and 3 gene expression profiles among pulmonary telocytes, pneumocytes, airway cells, mesenchymal stem cells and lymphocytes. J. Cell Mol. Med. 18, 2044-2060.

Zheng Y., Cretoiu D., Yan G., Cretoiu S.M., Popescu L.M. and Wang X. (2014b). Comparative proteomic analysis of human lung telocytes with fibroblasts. J. Cell Mol. Med. 18, 568-589.

Zheng Y., Cretoiu D., Yan G., Cretoiu S.M., Popescu L.M., Fang H. and Wang X. (2014c). Protein profiling of human lung telocytes and microvascular endothelial cells using itraq quantitative proteomics. J. Cell Mol. Med. 18, 1035-1059.

Zheng Y., Chen X., Qian M., Zhang M., Zhang D., Bai C., Wang Q. and Wang X. (2014d). Human lung telocytes could promote the proliferation and angiogenesis of human pulmonary microvascular

endothelial cells in vitro. Mol. Cell Ther. 2, 3.

Zhou Q., Wei L., Zhong C., Fu S., Bei Y., Huica R.I., Wang F. and Xiao J. (2015). Cardiac telocytes are double positive for CD34/PDGFR-alpha. J. Cell Mol. Med. 19, 2036-2042.

Zhu Y., Zheng M., Song D., Ye L. and Wang X. (2015). Global comparison of chromosome X genes of pulmonary telocytes with mesenchymal stem cells, fibroblasts, alveolar type II cells, airway epithelial cells, and lymphocytes. J. Transl. Med. 13, 318.

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