Telocytes and putative stem cells in the lungs: electron microscopy, electron tomography and laser scanning microscopy

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Abstract This study describes a novel type of interstitial (stromal) cell — telocytes (TCs) — in the human and mouse respiratory tree (terminal and respiratory bronchioles, as well as alveolar ducts). TCs have recently been described in pleura, epicardium, myocardium, endocardium, intestine, uterus, pancreas, mammary gland, etc. (see www.telocytes.com). TCs are cells with specific prolongations called telopodes (Tp), frequently two to three per cell. Tp are very long prolongations (tens up to hundreds of μm) built of alternating thin segments known as podomers (≤200 nm, below the resolving power of light microscope) and dilated segments called podoms, which accommodate mitochondria, rough endoplasmic reticulum and caveolae. Tp ramify dichotomously, making a 3-dimensional network with complex homo- and heterocellular junctions. Confocal microscopy reveals that TCs are c-kit- and CD34-positive. Tp release shed vesicles or exosomes, sending macromolecular signals to neighboring cells and eventually modifying their transcriptional activity. At bronchoalveolar junctions, TCs have been observed in close association with putative stem cells (SCs) in the subepithelial stroma. SCs are recognized by their ultrastructure and Sca-1 positivity. Tp surround SCs, forming complex TC-SC niches (TC-SCNs). Electron tomography allows the identification of bridging nanostructures, which connect Tp with SCs. In conclusion, this study shows the presence of TCs in lungs and identifies a TC-SC tandem in subepithelial niches of the bronchiolar tree. In TC-SCNs, the synergy of TCs and SCs may be based on nanocontacts and shed vesicles.

Keywords Telocytes · Lung · Bronchioles · Stem cell niche · Cellular communication

Introduction

Lung ultrastructure was described in detail approximately 20 years ago (see Schraufnagel 1990) and there are currently standards and recommendations for the quantitative assessment of the lung structure (Matthay et al. 2010). Moreover, a joint task force of experts in lung morphology has been created to guide the research policy of the American Thoracic Society and the European Respiratory Society (Hsia et al. 2010).

Recently, we documented a new type of interstitial (stromal) cell named the telocyte (TC) (Popescu and Faussone-Pellegrini 2010; Popescu 2011a, b). The shortest possible definition of TC is: cells with telopodes (Tp). The name “telopodes” was chosen to highlight that these prolongations are extremely long (from several tens to hundreds of μm) and very thin (50–100 nm), with a caliber usually below the resolving power of light microscope. We have described TCs in pleura (Hinescu et al. 2011) and in various organs (e.g., heart: Popescu et al. 2009, 2010, 2011a; Gherghiceanu and Popescu 2009, 2010, 2011; Gherghiceanu et al. 2010; Mandache et al. 2010; Suciu et al. 2009, 2010a; placenta: Suciu et al. 2010b; pancreas: Nicolescu et al. 2010;...
skeletal muscle: Popescu et al. 2011b). The TC concept was adopted by other laboratories (Faussone-Pellegrini and Bani 2010; Bani et al. 2010; Bojin et al. 2011; Cozzi et al. 2011; Gittenberger-de Groot et al. 2010; Klumpp et al. 2010; Kostin 2010; Polykandriotis et al. 2010; Susman et al. 2010; Zhou et al. 2010; Tommila 2010; Eyden et al. 2011; Cantarero et al. 2011a, b; Gard and Asirvatham 2011; Gevaert et al. 2011; Kostin 2011; Li et al. 2010; Limana et al. 2011; Radenkovic 2011; Rupp et al. 2010; Russell et al. 2011; Rusu et al. 2011a, b; Xia et al. 2011).

The aim of this study was to establish whether TCs are present in human and rodent lungs, particularly in bronchial tree stroma. We observed TCs using 2-dimensional (2D) transmission electron microscopy and 3-dimensional (3D) electron tomography, as well as laser scanning microscopy. In addition, as in epicardial SCNs (Popescu 2011a, b; Popescu et al. 2009, 2010, 2011a, b; Gherghieanu and Popescu 2010) or in skeletal muscle (Popescu et al. 2011b), we found a close association of TCs with putative stem cells (SCs) within the bronchial SCNs. Different groups of stem cells, at the level of bronchoalveolar junctions, have been described previously (Kim et al. 2005; Kim 2007; Kotton and Fine 2008; Liu and Engelhardt 2008; Warburton et al. 2008; Jiang and Li 2009; Chistiakov 2010). Sca-1 was used to establish cell lineage relationships of lung stem/progenitor cells to differentiated progeny (Raiser and Kim 2009).

Materials and methods

Small rodent lung samples were obtained from four 8-month-old C57BL/6 mice. Human lung samples were obtained from two patients undergoing surgery for neoplastic lung diseases. The Bioethics Committee of the “Vctor Babe” National Institute of Pathology, Bucharest, approved this study in accordance with generally accepted international standards.

Transmission electron microscopy

Transmission electron microscopy (TEM) was performed on small (1 mm³) lung tissue samples, which were processed according to a routine Epon-embedding procedure that we have previously described (Popescu et al. 2009). Thin sections (60 nm) were double-stained with uranyl acetate and lead citrate and examined with a Morgagni 286 transmission electron microscope (FEI Company, Eindhoven, The Netherlands) at 60 kV. Digital electron micrographs were recorded with a MegaView III CCD using iTEM-SIS software (Olympus, Soft Imaging System GmbH, Münster, Germany). TEM images were digitally colored using Adobe © Photoshop CS3 to highlight TC (colored in blue).

Electron microscope tomography

Electron microscope tomography (ET) was performed on 250-nm-thick sections of Epon-embedded tissue using a Tecnai G2 Spirit BioTwin transmission electron microscope with a single-tilt specimen holder (FEI Company) at 100 kV. Electron tomographic data sets were recorded with a MegaView G2 CCD camera (Olympus) in ET mode. Projection images (1024×1024 pixels) were acquired at 1-degree angular increments from −65° to +65° about an axis perpendicular to the optical axis of the microscope, at 36,000× magnification (pixel size 2.65 nm). After data alignment, the data sets were reconstructed into 3D volume (data collection, reconstruction and visualization) using Xplore3D Tomography Suite software (FEI Company). Amira 5.0.1 software (Visage Imaging GmbH, Berlin, Germany) was used for 3D imaging.

Immunofluorescence on frozen sections

Frozen sections (60 μm thick) were fixed in 4% formaldehyde for 30 min, washed for 30 min in PBS (pH 7.4) and blocked with 2% BSA. The samples were then incubated overnight at 4°C in PBS with 0.1% (vol/vol) Triton X-100 and 2% normal goat or donkey serum (all from Sigma Chemical, St. Louis, MO, USA) with rabbit anti-c-kit antibody, rat anti-CD34 antibody, or both, for double immunostaining labeling (both antibodies from Santa Cruz Biotechnology, Santa Cruz, CA, USA). After washing in PBS with 0.1% (vol/vol) Triton X-100, sections were incubated with AlexaFluor-conjugated secondary goat anti-rabbit or donkey anti-rat antibodies (Invitrogen Molecular Probes, Eugene, OR, USA) for another 2 h at room temperature. Following an extensive washing step, the nuclei were stained with 1 μg/ml 4,6-diamidino-2-phenylindole (DAPI) (Sigma Chemical, St. Louis, MO, USA). Negative controls were obtained by omitting the primary antibody, in an otherwise similar protocol.

Three to five immunolabeled sections from each case were examined by laser scanning microscopy, with a Nikon A1 laser on an ECLIPSE Ti-E inverted microscope. The confocal images were collected using a Plan Fluor 60× Oil objective, 1.25-NA water (z-axis step 0.16 μm).

The following lasers and emission filters were used to visualize the labeled structures and collect images: Ar laser at 488 nm (used for the excitation of Alexa Fluor 488), emission filter 500–550 nm, 561.2 nm G-HeNe laser (for Alexa Fluor 546), emission filter 570–620 nm and 405 nm Laser diode and 425–475 nm emission filter (for DAPI).

To improve image quality, some of the original laser scanning microscopy data were subjected to digital deconvolution with the Bitplane Imaris module.
Fig. 1 Transmission electron microscopy: telocytes (TCs) in mouse terminal bronchioles (a, b) and human lung (c). a One telocyte (blue) extends two telopodes (Tp1, Tp2) along the basement membrane of the bronchiolar epithelium. A third telopode (Tp3) is located among smooth muscle cells (SMC). Schwann cells and nerve endings appear in close vicinity to the telocyte. Characteristic dilated podoms (p) alternate with podomers (pm), thin segments along the Tp. b A peri-bronchiolar fibroblast is shown for comparison with TCs: note the numerous dilated cisternae of rough endoplasmic reticulum (rER) and mitochondria (m). The peri-bronchiolar interstitial space also has numerous collagen fibrils (coll) and vascular smooth muscle cells (vSMC). c TC and Tp border the epithelium at the level of the respiratory bronchiole. Pn I, type I pneumocyte; Pn II, type II pneumocyte. Scale bars 5 μm (a, c), 2 μm (b)
Immunofluorescence on paraffin-embedded sections

Adult mouse lungs were tested for vascular endothelial growth factor (VEGF) expression by immunohistochemistry using rabbit polyclonal VEGF (1:300; Abcam, Cambridge, UK) and by immunofluorescence using rat monoclonal Sca-1 (1:50; Abcam, Cambridge, UK). Immunolabeling was performed on 5-μm-thick sections from paraffin-embedded specimens fixed with 4% formalin. The samples were first deparaffinized in xylene, hydrated in alcohol series and washed in distilled water. After blocking endogenous peroxidase with 0.3% H₂O₂, microwave heat-induced epitope-retrieval (in Tris/EDTA buffer, pH 9; DAKO, Carpinteria, CA, USA) was performed. Next, the slides were left to reach room temperature, washed in PBS and incubated with 2% BSA for 20 min. Slides were incubated with primary antibody overnight at 4°C, followed by treatment with a standard labelled streptavidin-antibody biotin (LSAB) kit and development in 3,3’-diaminobenzidine chromogen substrate (DakoCytomation, Glostrup, Denmark) for immunohistochemistry. Slides were stained with donkey anti-rat antibody conjugated with AlexaFluor 488 (1:300, Invitrogen Molecular Probes, Eugene, OR, USA) for immunofluorescence.

For immunohistochemistry, the slides were counterstained with Mayer’s haematoxylin; for immunofluorescence, the nuclei were stained with DAPI (Sigma Chemical, St. Louis, MO, USA). Images were captured on a Nikon Eclipse 600 microscope.

Negative controls were performed by omitting the primary antibody or by substituting the primary antibodies with nonimmune serum in an otherwise similar protocol.

Results

TCs (Figs. 1, 2, 3, 4, 5, 6, 7, 8) were present from the bronchi to the bronchoalveolar junction in both mouse (Fig. 1a) and human specimens (Fig. 1c). Although short segments of interstitial cells or cells with myocytic features (pericytes) have been observed previously by electron microscopy in the interalveolar septa, there was no clear ultrastructural proof for the presence of TCs. Fibroblasts (Fig. 1b), macrophages (Fig. 7), Schwann cells and nerve fibers (Fig. 1a) and mononuclear cells (Figs. 6, 7) were also observed in the lung interstitium.
The shape of TCs was triangular (Fig. 1a), spindle (Fig. 1c), or stellate (Fig. 7), depending on the number of visible telopodes (Tp). The Tp had a narrow emergence from the cellular body (Fig. 1a), were extremely long (30–90 μm) and sinuous (Fig. 6) and had a dichotomous pattern of branching (Fig. 2c). To evaluate the extension potential of the Tp, we assessed their actual length divided by the end-to-end distance in a straight line and defined it as the convolution index (Hinescu et al. 2008, 2011); we calculated a mean convolution index of 3.5. Tp had a moniliform aspect, as well as an uneven caliber (Fig. 1a, c) due to the irregular alternation of podomeres: thin (45–100 nm) segments with podoms (150–300 nm) containing mitochondria, endoplasmic reticulum and caveolae (Fig. 2a). The podomeres were often extremely slender (Fig. 2b); their thickness was comparable with collagen fibrils (Fig. 3d).

TCs formed a labyrinthic system. The overlapping of Tp appears organized in a network alongside the airway tree and vascular system (Figs. 4a, 7a). TCs and Tp were present in the following locations:

- lining the basement membrane of the bronchiolar epithelium (Figs. 1a, 2b);
- in between clusters of airway smooth muscle cells of muscularis (Fig. 1a);
- in the periphery of airway smooth muscle cells (Fig. 1a);
- coating the respiratory epithelium at the bronchoalveolar junction (Fig. 6); and
- surrounding nerves (Fig. 1a), blood vessels (Fig. 6), or clusters of putative stem cells (Figs. 6a, 7a).

Confocal microscopy demonstrated positive reactions for two markers usually expressed by telocytes in other tissues: c-kit and CD34 (Fig. 4). The positive cells were visibly located in the connective tissue of the peri-bronchiolar space, outside the smooth muscle layer. Most positive cells had a TC typical morphology, with long and slender cell projections (Tp) that follow a longitudinal course with respect to the long axis of the airways (Fig. 4a-d). Immunostaining for c-kit and CD34 demonstrated the presence of double positive TCs with long prolongations in the interstitial space surrounding small bronchi and bronchioles (Fig. 4e-g). The primary expression of c-kit was on the cell body and in the proximal part of Tp (Fig. 4c, d, f); however, CD34 expression marked the Tp, making them visible over a long distance (Fig. 4a, b, e). Putative SCs were detected based on Sca-1 expression (Fig. 5) in small clusters located in the peri-bronchiolar space, especially in between bronchioles and the accompanying blood vessels.

Electron microscopy demonstrated that TCs often extended their Tp around groups of mononuclear cells (Figs. 6a, 7a), with few ultrastructural features similar to stem cells (large nuclei, few endoplasmic reticulum cisternae, few mitochondria and ribosomes). The putative SCs were located in the same regions where Sca-1 positive cells have been detected by immunofluorescence. These
Fig. 4 Confocal microscopy of thick sections (60 μm) of lung tissue from an adult mouse, with CD34 immunolabeling visible in the peribronchiolar space. a Volume reconstruction. b Confocal laser scanning microscopy. c c-kit immunolabeling, original volume reconstruction. d The same volume after deconvolution. Double immunofluorescence shows the labeling pattern for CD34 (e, green) and c-kit (f, red); the superimposed images are presented in g. Nuclei were counterstained with DAPI. Confocal images were collected using the 60× 1.2-NA water objective (z-axis step 0.16 μm)
cells (either SCs or precursor cells) were clustered (two to five cells) in the interstitium of the bronchoalveolar junction, near blood vessels (Figs. 5, 6a).

Electron microscopy showed that Tp were coupled to each other by different types of junctions: puncta adhaerentia (Fig. 3a, b) manubria adhaerentia (Fig. 3c) and small electron-dense structures (Fig. 8). Tp also demonstrated close connections or junctions with the basement membrane of epithelial cells (Fig. 2c), basal lamina of airway smooth muscle cells (Fig. 2c), epithelial cells (Fig. 6b-d), macrophages (Fig. 7a, b), or putative stem cells (Fig. 6a, b). Shedding vesicles (100 nm vesicles) and exosomes (250–350 nm) were frequently observed emerging from telopodes (Fig. 3d).

We also investigated the expression of molecules potentially involved in intercellular communication. Immunohistochemistry showed VEGF-positive TCs in the peri-bronchiolar space (Fig. 9). VEGF was expressed concomitantly at the level of the cell body and cell prolongations.

We also performed ET to detail heterocellular and homocellular communication. Tp were usually connected by puncta adhaerentia (Fig. 7c-f); however, there were also 10-nm, faintly electron-dense structures (Fig. 8). These small structures were generally clustered, indicating the presence of molecular junctions (Fig. 8c) between Tp and they were frequently seen connecting Tp and putative stem cells (Fig. 7d-g). ET also revealed that some segments of Tp (podomeres) are extremely narrow (approximately 100 nm diameter) and sometimes their thickness is comparable with collagen fibrils (Fig. 8c). Caveolae were observed in these narrow segments and had contacts with cellular membrane on the entire circumference of Tp (Fig. 8c, d).

Discussion

Traditionally, the recognition and characterization of cell types have been based on morphological characteristics that are visible using light and electron microscopy (Bell and Mooers 1997; Valentine 2002, 2003); however, topographical and functional criteria are also important. Five years ago, Vickaryous and Hall (2006) proposed an updated list of cell types for the adult Homo sapiens, with 411 cell types, including 145 types of neurons. However, most textbooks group different cells into a limited number of types. The modern, generalized scheme of tissue classification consists in four group subdivisions: epithelial, muscular, nervous and connective (interstitial) tissues. Additionally, a very small number of cell types could include epitheliocytes, mechanocytes (typical ex: fibroblasts), amoebocytes (wandering cells) and nerve cells (Willmer 1970).

During the last 5 years, we have collected and reported on numerous data showing the existence of a novel cell type that we have named telocytes (TCs); for reviews see (Popescu and Faussone-Pellegrini 2010; Popescu 2011b; Faussone-Pellegrini and Popescu 2011). This name was
chosen to underscore the primary characteristic of TC cytoanatomy: telopodes, very long and extremely thin prolongations of the cell body. Formally, TCs belong to the connective tissue cell group, or may be considered mechanocytes. In any case, TCs are not epitheliocytes, muscle cells, or nerve cells, being located in the interstitial spaces. In brief, TCs are interstitial or stromal cells of mesenchymal origin.

We have described TCs in many human and rodent organs:

a) cavitary: heart (Hinescu and Popescu 2005; Popescu et al. 2006a, 2009; Hinescu et al. 2006; Gherghiceanu and Popescu 2010, 2011; Kostin and Popescu 2009); pulmonary veins (Gherghiceanu et al. 2008); intestine (Popescu 2011a); gall bladder (Hinescu et al. 2007); and uterus and fallopian tube (Ciontea et al. 2005; Cretoiu et al. 2009; Popescu et al. 2005a, 2006b, 2007);

b) non-cavitary: pleura (Hinescu et al. 2011); skeletal muscle (Popescu et al. 2011b); mesentery (Hinescu et al. 2008); pancreas (Popescu et al. 2005b; Nicolescu et al. 2010); mammary gland (Gherghiceanu and Popescu 2005; Radu et al. 2005); and placenta (Suciu et al. 2007, 2010b).

Preliminary data about the presence of TC in trachea were recently reported (Zheng et al. 2011). Therefore, it seems reasonable to hypothesize that TCs exist in almost all organs. While no two TCs are identical in appearance, a generalized ultrastructural pattern or some guidelines can be established to identify TCs using electron microscopy. With regard to the immunophenotypes of TCs from various organs, TCs share some features rather than having overall similarity (Popescu and Faussone-Pellegrini 2010).

The data presented here may support the hypothesis of an integrative role for telocytes in lung physiology based on their involvement in mechanical support, intercellular signaling, immune surveillance and stem-cell guidance.

Mechanical support and mechanotransduction

We have previously suggested a mechanical supporting role for the 3D TC network existing in the mesentery (Hinescu et al. 2008). This paper describes a similar 3D network in the walls of the intralobular tree, which lacks cartilage. Therefore, we may hypothesize that the 3D network, at the...
same time deformable and resistant, may contribute to keeping open the lumen of intralobular bronchioles and avoiding blood vessel closure during respiratory movements. TCs are frequently found in the vicinity of small blood vessels. Moreover, the convoluted conformation of Tp (convolution index 3.3) may be particularly important in tensional integration of the tissue (Ingberg 2006). Due to their distribution, TCs could be a key factor in lung tissue response to the mechanical stretch induced by the airflow and blood flow.

**Intercellular communication**

The results of this study demonstrate that TCs are interconnected through the 3D network of TCs. TCs seem to be involved in intercellular communication and long-distance signaling through:

- homocellular junctions between TCs (*puncta adhaerentia* and *manubria adhaerentia*) and
- heterocellular junctions (*puncta adherentia*, *puncta adhaerentia minima*): TC junctions with tissue-specific cells (e.g., epithelial cells), immunocompetent cells (e.g., macrophages) and putative SCs or progenitor cells.

*Puncta adhaerentia* and *manubria adhaerentia* have been described between mesenchymal cells and they seem to be involved in long-distance cellular communication (Wuchter et al. 2007; Franke 2009; Franke et al. 2009; Barth et al. 2009).
A different type of communication seems to occur via a sequence of 10 nm small foot-like nanostructures, suggesting molecular interactions (Fig. 8). This type of molecular connection has been observed previously between TCs and putative SCs or precursor cells (Fig. 7). Foot-like nanostructures have been described previously connecting intracellular organelles with important roles in calcium homeostasis (Popescu et al. 2006c; Gherghieanu and Popescu 2007; Franzini-Armstrong 2007). The presence of caveolae as nodal signaling platforms (Bastiani and Parton 2010) in the segments connected by these ‘molecular’ junctions (Fig. 8) boosts the hypothesis that TCs are involved in local cellular homeostasis (Popescu and Faussone-Pellegrini 2010).

TCs regularly generate exosomes and shed vesicles in the interstitial space (Figs. 3d, 8). These extracellular organelles seem to be involved in complex intercellular communication (Cocucci et al. 2009; Mathivanan et al. 2010) and exosomes are likely carriers of small RNAs, including regulatory microRNAs (Zomer et al. 2010; Cismasiu et al. 2011).

Immune surveillance

We have repeatedly reported the so-called ‘stromal synapse’ between TCs and immunoreactive cells (Popescu et al. 2005c; Suciu et al. 2010b; Hinescu et al. 2011). An immune surveillance role has been suggested for the fibroblast-like
cells located in the human fallopian tubes, which have been termed a ‘CD34-positive reticular network’ (Yamazaki and Eyden 1996). Such direct contacts are also frequently formed in the lamina propria of the epithelium along the intralobular bronchiolar tree.

The tandem telocytes-putative stem cells

The respiratory tract seems to contain several sources of endogenous adult SCs (Murphy et al. 2008; Weiss et al. 2008; Stripp 2008; Bucchieri et al. 2009; Chistiakov 2010; Roomans 2010), which contribute to the repair of the airway wall. SCNs (Reynolds et al. 2000) and specialized neuroepithelial bodies serving as reservoirs of progenitors (Engelhardt 2001) have been described; although these SCs are dispensable for lung homeostasis, they are required for lung injury repair (Giangreco et al. 2009). SCs require a niche — a basic unit of tissue physiology, integrating signals that mediate the balanced response of SCs to the needs of the tissue (Scadden 2006; Walker et al. 2009). Cells in developing tissues are also influenced by multiple signals through direct cell-to-cell contacts (Doljanski 2004; Roy et al. 2011).

This study reveals a direct connection between TCs and putative SCs, suggesting that TCs are stromal support cells within the lung SCN. The identification of a TC–SC tandem (due to specific intercellular junctions) provides a new perspective linking a potential cell source located in subepithelial niches of the bronchiolar tree with the hypothetical cell-guiding capacity of TCs (Popescu et al. 2011a).

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