Seminars in Cell & Developmental Biology 55 (2016) 62–69

Contents lists available at ScienceDirect

Seminars in Cell & Developmental Biology

journal homepage: www.elsevier.com/locate/semcdb

Review

Telocyte implications in human pathology: An overview

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ARTICLE INFO

Article history:
Received 7 January 2016
Accepted 18 January 2016
Available online 21 January 2016

Keywords:
Telocytes
Stromal cells
Pathology
Chronic inflammation
Organ fibrosis

ABSTRACT

Telocytes are a recently described interstitial cell population widely distributed in the stromal compartment of many organs in vertebrates, including humans. Owing to their close spatial relationship with multiple cell types, telocytes are universally considered as 'connecting cells' mostly committed to intercellular signaling by converting the interstitium into an integrated system that drives organ development and contributes to the maintenance of local tissue homeostasis. Increasing evidence indicates that telocytes may cooperate with tissue-resident stem cells to foster organ repair and regeneration, and that telocyte damage and dysfunction may occur in several disorders. The goal of this review is to provide an overview of the most recent findings concerning the implication of telocytes in a variety of pathologic conditions in humans, including heart disease, chronic inflammation and multiorgan fibrosis. Based on recent promising experimental data, there is realistic hope that by targeting telocytes alone or in tandem with stem cells, we might be able to promote organ regeneration and/or prevent irreversible end-stage organ damage in different pathologies.

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Contents

1. Introduction to telocytes

The stromal (interstitial) compartment not only provides mechanical support and protection to parenchymal cells but also regulates important cell activities, including survival, proliferation, differentiation and metabolism during organ morphogenesis and reparative processes [1,2]. It is therefore not surprising that alterations in the stromal microenvironment may profoundly impair local tissue homeostasis and trigger the development and/or progression of a variety of pathologic conditions.

The stromal compartment is populated by different cells such as fibroblasts which are considered among the most common types. In that regard, stromal cells bearing very long cellular prolongations have been long neglected and simplistically labeled as fibroblasts. However, this view has rapidly changed following the recent identification of a novel stromal cell type in many organs of vertebrates, including humans [3–5]. These cells, named telocytes (TCs), possess a small cell body and extremely long and thin prolongations, termed 'telopodes', making them definitely distinct from the 'classical' fibroblasts [3–7]. 'Cells with telopodes' is the shortest possible definition of TCs (from the Greek affix 'telos', *i.e.*, provided with long-distance cell projections) [5]. Telopodes

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http://dx.doi.org/10.1016/j.semcdb.2016.01.022
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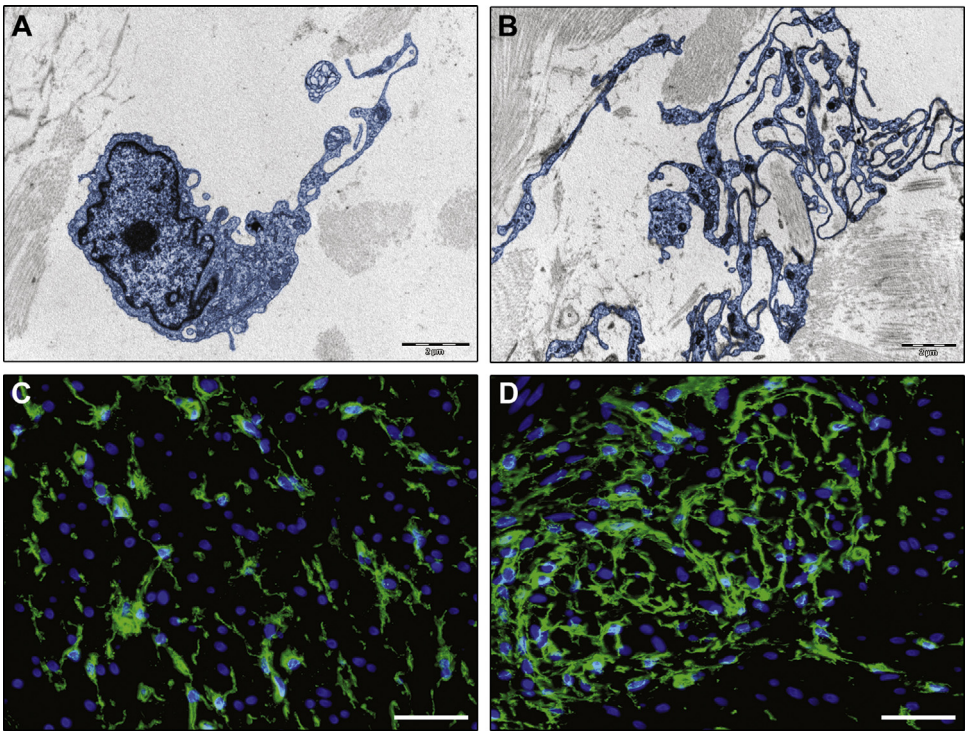

Fig. 1. Ultrastructural morphology and immunophenotype of telocytes. Telocytes display a small cell body and extremely long and thin prolongations (telopodes) with a moniliform aspect characterized by the alternation of thin segments (podomers) and small dilated regions (podoms) accommodating mitochondria, endoplasmic reticulum and caveolae (A). Telopodes typically form a labyrinthine network (B). Telocytes express either CD34 (C) or PDGFRα (D). (A, B): Human skin, transmission electron microscopy. Telocytes have been digitally colored in blue. (C, D): Human intestine, immunofluorescence for CD34 (green, C) or PDGFRα (green, D) with DAPI (blue) counterstain for nuclei. Scale bar: 2 μm (A,B), 50 μm (C,D).

display a moniliform aspect characterized by the alternation of thin segments (called 'podomers') and small dilated regions (called 'podoms') accommodating mitochondria, endoplasmic reticulum and caveolae (Fig. 1A, B) [3–5]. This unique ultrastructural phenotype is regarded as the hallmark for the identification of TCs under transmission electron microscopy [4,5]. Although TCs do not possess a unique antigenic profile, CD34 and platelet-derived growth factor receptor α (PDGFRα) are currently considered the most reliable markers for the immunohistochemical identification of TCs (Fig. 1C, D) [4,5,8–10]. Indeed, co-expression of CD34 and PDGFRα antigens has been widely reported in TCs from different organs [5,9–11]. Moreover, immunoelectron microscopy studies have clearly demonstrated that $CD34^+$ interstitial cells are ultrastructurally identifiable as telopode-bearing TCs [4,12]. It also appears that the TC immunophenotype may vary among different organ systems. In fact, while cardiac TCs express either CD34, PDGFRα or c-kit, in the gastrointestinal tract TCs are $CD34^+/PDGFR\alpha^+$ but do not express c-kit [9,10,13]. Increasing evidence also indicates that TCs possess proteomic profiles and microRNA signatures that are definitely distinct from those of 'classical' fibroblasts [5,14–17].

Owing to their close spatial relationship with different cell types within multiple organs, several roles have been proposed for the TCs some of which support the importance of these cells in tissue differentiation and regenerative processes [4,5]. Indeed, by their extremely long and interconnecting telopodes, TCs form a three-dimensional labyrinthine network (Fig. 1B–D) that may function as a scaffold necessary to define the correct parenchymal organization during morphogenesis or to drive tissue renewal/repair in post-natal life [4,5,18–20]. At variance with fibroblasts which, functionally, are mainly involved in the synthesis of the extracellular matrix (ECM), TCs are universally considered as 'connecting cells' mostly committed to intercellular signaling by converting the interstitium into an integrated system that contributes to the maintenance of local tissue homeostasis [5]. Indeed, telopodes establish either homocellular contacts among TCs or heterocellular junctions with different cell types including fibroblasts, mast cells, macrophages, lymphocytes and plasma cells, as well as non-cellular elements, such as collagen and elastic fibers [5,21,22]. Furthermore, TCs often occupy a strategic position in relation to tissue-resident stem cell niches, blood capillaries and nerve endings [5,9,23–27]. TCs may participate in intercellular signaling not only by cell-to-cell contacts, but also in a paracrine manner *via* the release of at least three different types of extracellular vesicles, namely exosomes, ectosomes and multivesicular cargos [5,23,28–32]. These vesicles might function as intercellular shuttles for the transfer of molecular signals, including microRNAs, to neighboring cells [5]. TCs may also be essential for the survival, proliferation, differentiation, maturation and guidance of stem cells located in the niches of several organs and, eventually, stimulate and sustain tissue regenerative processes [5,15,26,28,33,34]. Moreover, TCs have been proposed to participate in a variety of processes, such as stimulation of angiogenesis, inhibition of oxidative stress and prevention of cellular aging [5,14,29]. TCs might even be considered as active players in immunomodulation and immune surveillance, acting like 'local data suppliers' for the immune response [5,11,21,27]. In some organs, TCs may possess electrophysiologic properties, as recently demonstrated in the myometrium and the heart [5,35–37]. In the enteric neuromuscular compartment, TCs are supposed to participate in the regulation of neurotransmission and intestinal motility, presumably by spreading the slow waves generated by the pacemaker interstitial cells of Cajal (ICC) [4,5,9,12].

Owing to the wide distribution of TCs throughout different organ systems and the many possible roles that have been attributed to these cells, a growing number of studies published over the last few years has addressed their possible involvement in different disorders [5,11,13,38–47]. The goal of this review will be to focus on the

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