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Telocyte's contacts

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ABSTRACT

Telocytes (TC) are an interstitial cell type located in the connective tissue of many organs of humans and laboratory mammals. By means of *homocellular contacts*, TC build a scaffold whose meshes integrity and continuity are guaranteed by those contacts having a mechanical function; those contacts acting as sites of intercellular communication allow exchanging information and spreading signals. *Heterocellular contacts* between TC and a great variety of cell types give origin to *mixed networks*. TC, by means of all these types of contacts, their interaction with the extracellular matrix and their vicinity to nerve endings, are part of an *integrated system* playing tissue/organ-specific roles.

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1. The telocytes (TC)

Telocytes, formerly called interstitial Cajal-like cells (ICLC), are an interstitial cell type recently identified in the connective tissue of many organs of humans and laboratory mammals. The term telocyte (TC) was firstly introduced in the scientific literature with the publication of the paper entitled: *TELOCYTES – a case of serendipity: the winding way from Interstitial Cells of Cajal (ICC), via Interstitial Cajal-Like Cells (ICLC) to TELOCYTES* by Popescu and Faussone-Pellegrini [1] to describe connective tissue cells characterized by peculiar features under transmission electron microscope (TEM). Since then an exponential number of papers have been published on this issue and TC have been found in the connective interstitium of almost all the mammalian organs [2,3]. While there is a general consensus on the ultrastructural morphology of TC, i.e. a small oval body and two-three long, convolute, thin and varicose processes (telopodes) with alternating narrow portions (podomeres) and dilated portions (podoms) [1–3] allowing an unequivocal TC identification under TEM, the identification of these cells with certainty by immunohistochemistry is still harder [2]. Indeed, although it has been reported a great variety of TC immunopositivity for numerous markers such as CD34, PDGRFα, αSMA, vimentin, c-kit, caveolin-1, iNOS, VEGF, Oct-4, none of them labels all the TC [2–9]. Briefly, TC display different immunophenotypes but have not yet been found

Abbreviations: TC, telocytes; ICLC, interstitial Cajal-like cells; TEM, transmission electron microscope.

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to express any specific marker. To help those studying TC, it is presently accepted to consider that CD34 is the most reliable TC marker while c-kit has been excluded for some organs [4,6,9].

On the basis of the data obtained on these cells, either by using TEM or immunohistochemistry, it has been raised the possibility that there exist several TC subpopulations, some sharing similar ultrastructural features but displaying different chemical code(s) and others having also specific ultrastructural characteristics [9,and: Vannucchi MG, Faussone-Pellegrini MS. The Telocyte subtypes. In: *Telocytes: connecting cells*. Springer, in press].

After TC discovery, several studies have been performed to clarify the possible role/s played by these cells and the histological and histochemical differences afore-mentioned and the existence of TC subtypes are likely to be considered at the basis of region-specific roles. Two important TC peculiarities support all hypothesized TC role(s): i) to be organized in networks, ii) to have close spatial relationships with themselves, with other cell types and with the connective tissue. The TC capability in releasing signals by means of shed vesicles has to be added to the peculiarities supporting one of their putative roles [10,11].

2. The TC networks

In all the organs examined, the TC, contacting to each other, form networks [2–4,6,9,12–24]. Most of these networks have a 3-D organization but in some organs they might be either 3- or 2-D. As an example, in the gastrointestinal tract, the TC form 3-D networks in the submucosa, muscle coat and at the myenteric plexus level between the longitudinal and circular muscle layers, while at the submucosal border of the *muscularis mucosae* and of the circular muscle layer, around nerve strands, blood vessels, funds of gastric glands and intestinal crypts, these cells form an almost continuous 2-D monolayer [4,6].

In the stroma of the normal adult and developing heart, the TC with their cell bodies and telopodes create a specifically oriented 3-D framework that embeds the columns of the cardiomyocytes [25–27]. Of high interest, this peculiar feature takes place progressively during myocardial histogenesis, suggesting that TC may be involved in molding the 3-D architecture of the developing heart [12,24,27].

In some organs the TC have been seen to form 3-D networks intermingled with other cell types, such as the interstitial cells of Cajal (ICC) in the gut [4] and the myofibroblasts in the urinary bladder [9], thus forming *mixed networks*.

3. The TC contacts

3.1. The cell-to-cell contacts

Several attachments areas occur between neighboring cells that are thought to aid in holding adjacent cell membranes close together, likely serving as anchoring sites for their cytoskeleton, and in favoring exchange information. We can distinguish two main types of contacts: those between cells of the same type, ***homocellular contacts***, and those between cells of different type, ***heterocellular contacts***. Moreover, areas of contacts between the plasma membrane of one cell and its surrounding connective tissue have been described (see later). The TC possess all these types of contacts whose morphology and number often characterize the TC subtypes and, likely, are at the basis of their organ-specific role.

4. The TC homocellular contacts

The homocellular contacts are fundamental for the formation of a cellular network. They are of several types and received a lot of different names. Fundamentally, these contacts are made by either simple appositions of the plasma membranes of the two contiguous cells or by complex junctional areas, some of which have a mechanical function and others accomplish to functional intercellular exchanges.

By means of simple ***apposition of the two contiguous plasma membranes*** with an interposed space of about 200 nm (Fig. 1), the telopodes of the TC run parallel to each other and often give origin to further convolute and interweaving telopodes [1–4,11,13,17,20,21]. All the TC subtypes have many of these contacts whose extension, however, is variable according to the organ where these cells are located. Likely, such apposition areas, maintaining the cell-to-cell adhesion, should guarantee the network integrity and the continuity of its meshes when the tissue/organ undergoes to distension/elongation.

4.1. Junctional complexes with a mechanical function

These junctions received many names [28]. These junctional areas can be found in all the TC [3,7,9,10,29–35] but have been studied and described in particularly exhaustive details in the heart, where, by TEM and FIB-SEM tomography, a lot of peculiar types of these contacts have been found and characterized [32,33]. Most of these contacts, that, since resembling various types of the *junctions adherentes,* have been named: *puncta adhaerentia minima* (Fig. 2A) and *processus adhaerens* (fig. 2A), usually connecting the overlapping telopodes, and *recessus adhaerens* or *manubria adhaerentia* having a cuff-like appearance (fig. 2B). Similar junctional areas have been seen also in the trachea and lung [35] choroid plexus [36], eye [37], etc. Likely, the role of all these types of contacts is more than to maintain firmly attached to each other the TC when the tissue/organ is stretched. Recent research shows that catenin is the core mechanosensor that allows cells to locally sense, transduce and adapt to environmental mechanical constrains and mechanotransduction pathways affect cell shape, migration, survival as well as differentiation [38–41].

4.2. Junctional complexes favoring intercellular exchanges and signaling

In the TC the most represented are the *Nexuses (gap junctions)* (fig. 2C, inset) [2,4,7,17,32,36,37,42–45]. These junctions are known to allow the exchanges of metabolites and signals. Indeed, at the nexus level there is a gap 2 nm wide and the two contiguous plasma membranes are bridged by particles 8 nm in diameter (connexons), made by connexins, each of them having a hydrophilic channel that permits the intercellular passage of small molecules. Consequently, although from a mechanical point of view this type of junction also forms a relatively firm point of attachment between adjacent cells, nexus is particularly important acting as site of communication between cells.

5. The TC heterocellular contacts

Heterocellular contacts between TC and a great variety of cell types (Fig. 3) occur more frequently than what occurs among any other cell type. These contacts consist in minute junctions (*point contacts*, *nanocontacts* and *planar contacts*) whose mean inter-membrane distance is 10–30 nm, but more often by variably extended *simple apposition* of the contiguous plasma membranes.

TC and cardiomyocytes. The contacts between these two types of cells are of fundamental importance in the heart where have been widely studied. In the so-called 'cardiogenic niches', located in the epicardium close to coronary artery branching, TC establish several types of junctional areas with the resident cardiac stem cells [3,11,26,27,29,32,33,46–48] some of which (nanocontacts, Fig. 3A)