The functional morphology and role of cardiac telocytes in myocardium regeneration

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The functional morphology and role of cardiac telocytes in myocardium regeneration

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Abstract

Key morphological discoveries in recent years have included the discovery of new cell populations inside the heart called cardiac telocytes. These newly described cells of the connective tissue have extremely long cytoplasmic processes through which they form functionally connected three-dimensional networks that connect cells of the immune system, nerve fibers, cardiac stem cells, and cardiac muscle cells. Based on their functions, telocytes are also referred to as “connecting cells” or “nurse cells” for cardiac progenitor stem cells. In this critical review, we provide a summary of the latest research on cardiac telocytes localized in all layers of the heart – from the historical background of their discovery, through ultrastructural, immunohistochemical, and functional characterizations, to the application of this knowledge to the fields of cardiology, stem cell research, and regenerative medicine.

Keywords: telocytes, interstitial Cajal-like cells, myocardium, regeneration, functional morphology

Introduction: The path from interstitial cells of Cajal to telocytes

In 1893, the Nobel laureate **Santiago Ramón y Cajal** discovered a new cell type in the muscle layer of the gut, which he named “interstitial neurons”. Cajal used neurohistological methods (silver impregnation method and staining with methylene blue) to visualize this cell population, and made the assumption that they were “primitive neurons” (Popescu and Faussone-Pellegrini 2010). After approximately half a century, electron microscopic examinations of the wall of the digestive tube revealed cells that most likely corresponded to Cajal’s “interstitial, primitive neurons”. Yet, it was immediately clear that these cells were not “real” neurons

(Faussone-Pellegrini et al. 1977; Thuneberg 1982). Thus, they received the new name “**interstitial cells of Cajal (ICCs)**”.

ICCs create a three-dimensional (3D) network within the circular and longitudinal muscle layers of the gut at the level of the autonomic myenteric (Auerbach's) nerve plexus. ICCs have been recognized as important elements in the regulation of gastrointestinal motility. Specifically, they are essential for the generation and propagation of electrical slow waves (“pacemakers of the gut motility”) that regulate the contractile activity of gastrointestinal smooth muscle, and for mediating neurotransmission from enteric neurons to smooth muscle cells (Burns 2007; Ward et al. 2000). ICCs have spindle-shaped cell body morphology with long and dividing cytoplasmic processes that form unique networks. Many of their ultrastructural features, including a discontinuous basal lamina, direct cell-to-cell contacts via gap junctions with other ICCs and smooth muscle cells, and close contacts with nerve fiber endings, suggest that ICCs are specialized smooth muscle cells. However, according to their ultrastructural characteristics, ICCs may also represent a specific type of fibroblast (Ward and Sanders 2001).

In the last decade, the presence of cells morphologically similar to ICCs was not only described inside the gastrointestinal tract but also inside various tissues and organs of the human body. Therefore, they were first named **interstitial Cajal-like cells (ICLCs)**. In some organs, ICLCs have important signaling functions among different cell populations such as nerve cells, muscle cells, immune cells, or stem cells (Edelstein and Smythies 2014). They may function as “pacemaker” cells in organs such as the gall bladder (Matyja et al. 2013), urinary bladder (Rusu et al. 2014), or exocrine part of the pancreas (Nicolescu and Popescu 2012). ICLCs are also part of the cellular microenvironment of some female and male reproductive organs such as

the uterus, uterine tubes, mammary gland, placenta, or prostate. The function of ICLCs in reproductive organs varies and includes sensing sex hormone levels, regulating cellular proliferation and apoptosis in the mammary gland, or monitoring blood flow through chorionic villi of the placenta (Varga et al. 2016). However, in general, details of their functions are lacking. In some organs, ICLCs participate in the processes of tissue regeneration and reparation (e.g., in the liver [Liu et al. 2016], skin [Ceafalan et al. 2012]), or myocardium of the heart [Tao et al. 2016]). Clearly, ICLCs are morphologically and functionally **different** from the “original” ICCs found inside the gut. The term “interstitial Cajal-like cells” is too long and impractical for everyday practice; thus, Popescu and Faussone-Pellegrini (2010) proposed the new term “**telocytes**”.

In this mini-review, we provide a summary of the latest research on **cardiac telocytes**, localized in all layers of the heart, with special emphasis on the potential application of such knowledge to the fields of tissue engineering and regenerative medicine.

Methods

The methods of our work were adjusted accordingly to the nature of this review paper and its awareness raising focus. We used the scientific databases PubMed/Medline, SCOPUS, and Web of Knowledge. Within the scope of the topic, we deliberately focused on controversial issues, drew from discussions and responses to articles from other scientists, and tried to cover a maximum set of views governed by a consensus (often chosen by a critical expert dialogue).

General morphology of cardiac telocytes

Telocytes are cells with round or spindle-shaped cell bodies and extremely long cytoplasmic prolongations called “**telopodes**”. The number of telopodes typically varies between 2 and 5, and their length ranges between dozens and hundreds of micrometers, some of which have secondary and tertiary branches that form a 3D network. Telocytes are presumed to be “**connecting cells**,” and the network of their cytoplasmic processes surrounds capillaries and connects neighboring telocytes or other cell types such as immune reactive cells, epithelial cells, dendritic cells, smooth muscle cells, and nerve cells. (Gherghiceanu and Popescu, 2005).

One may ask how such a heterogeneous cell population localized in various organs of the human body was not recognized earlier. A discoverer of telocytes, Professor Laurențiu Popescu (1944–2015) from Romania, explained it by the characteristic structure of these cells. Telocytes have a relatively small body (consisting of a nucleus and small amount of cytoplasm), but extremely long tubular processes of cytoplasm. However, the thickness of their prolongations is only about 0.2 micrometers, which is the resolving power of most light microscopes (Popescu and Faussone-Pellegrini 2010) and the Abbe diffraction limit for photons. Thus, for identification of telocytes, transmission electron microscopy (Cantarero et al. 2016; Kostin 2010) or immunohistochemical and immunofluorescence methods are used. Several different antigens, which are generally characteristic of telocytes, have been identified in recent years by double labeling for CD34 and c-kit (CD117), vimentin, or PDGF receptor- α , or β (Cretoiu and Popescu, 2014; Yang et al. 2014; Urban et al. 2016).

Cardiac telocytes are a special type of interstitial cell present in the heart, with small cell bodies and very long and thin cytoplasmic processes called telopodes. They

are widely distributed in all layers of the heart, and form a network in the endocardium, myocardium, epicardium, and even in stem cell niches (Rusu et al. 2012; Tao et al. 2016). Telocytes have not generally been accepted by the scientific community as a new and distinct cell population. Although entering the term “telocytes” into the Medline/PubMed database resulted in more than 160 articles, there are no references about it in the internationally accepted *Terminologia Histologica* (FICAT 2008), which contains all accepted terms for cellular structures, tissue, and organs at the microscopic level (Allen 2009). Díaz-Flores et al. (2014) termed this heterogeneous cell population “CD34+ stromal fibroblastic cells,” and the term “telocyte” was not used.

Immunohistochemical identification of cardiac telocytes

In some tissues, after routine histological staining methods, it is impossible to distinguish telocytes from fibroblasts of interstitial connective tissue by light microscopy. Thus, immunohistochemistry is typically used to identify telocytes. The c-kit (CD117 antigen), a protein transmembrane protein kinase receptor, is essential for telocyte function and represents the first routinely used marker for its identification. Originally, it was used for identification of ICCs in the gut and for tumors derived from these cells; approximately 95% of gastrointestinal stromal tumors cases are positive for CD117 antigen (Miettinen et al. 2002; Iorio et al. 2014). In most tissues, CD117 is only expressed on the surface of ICCs of the gut, in telocytes of various organs, and in mast cells and some neurons within the trigeminal ganglion (Rusu et al. 2011). Double immunolabeling is very important for the differential diagnosis of telocytes from other interstitial cells, and can be used in both tissues and *in vitro* cell cultures. Immunohistochemically, positivity for CD34/c-kit,

CD34/vimentin, and CD34/PDGFR- β clearly differentiates cardiac telocytes from fibroblasts, whereas fibroblasts are only positive for vimentin and PDGFR- β (Bei et al. 2015a; Chang et al. 2015). Zhou et al. (2015) recommended the use of double staining for CD34/PDGFR- α as a suitable method for identifying cardiac telocytes. During embryonal development, telocytes lack antigens used for routine identification, and are negative for c-kit and CD34 (Faussone-Pellegrini and Bani 2010).

Ultrastructure of cardiac telocytes

Transmission electron microscopy is the “gold standard” for the identification of cardiac telocytes. Each telocyte usually has 1–3 dichotomic branching telopodes, with a length of tens of micrometers, usually up to 100 micrometers, but a thickness of only 0.1–0.5 micrometers. Telopodes have thin segments (podomers) and dilated segments (podoms) with mitochondria, membrane-bound vesicles (caveolae), and endoplasmic reticulum (Hinescu and Popescu 2005). Ultrastructurally, they form labyrinth-like structures via convolutions and cytoplasmic overlapping (Kostin 2010). Cardiac telocytes form a 3D network via cell junctions with other telocytes (homocellular junctions), and have characteristics of:

- *Puncta adhaerentia* junctions;
- Ability to be inserted in a tight-fitting manner into deep plasma membrane invaginations (*recessus adhaerentes*), thereby forming a long continuous cuff-like junction (*manubria adhaerentia*); and
- Special tentacle-like cell processes contacting one or several other cells (called *processus adhaerentes*) (Gherghiceanu and Popescu 2012).

These giant adherent cell junction systems are typical (e.g., for human mesenchymal stem cells) (Wuchter et al. 2007). Electron microscopic studies demonstrated that cardiac telocytes can also establish heterocellular junctions with all other cell types within the heart such as cardiac muscle cells, progenitor cells of cardiac muscle cells, fibroblasts, mastocytes, macrophages, pericytes and endothelial cells of blood capillaries, or Schwann cells. Gherghiceanu and Popescu (2012) described these cell junctions as “atypical” (only close contacts or directly connected by a small dense structures, termed “nanocontacts”), with no ultrastructural features of well-described intercellular junctions such as tight junctions, desmosomes, fascia adherens, or gap junctions. However bridging “nanocontacts” among telocytes and other type of cells and narrow intermembrane distance (less than 30 nanometers) suggest a molecular interaction between telocytes and other cells (Gherghiceanu and Popescu 2011).

Telocytes also communicate with other cells by releasing a wide range of extracellular secretory vesicles. This paracrine type of secretion is well described in *in vitro* cell cultures, where telocytes manufacture at least three different types of extracellular vesicles (Fertig et al. 2015):

- Exosomes – numerous intraluminal vesicles;
- Ectosomes – buddings from plasma membrane of telopodes; and
- Multivesicular cargos – clusters of smaller vesicles enclosed by the plasma membrane.

It is believed that these vesicles regulate the activity of neighboring cells (especially cardiac stem cells) by paracrine signaling. Cismasiu et al. (2015) also demonstrated bi-directional signaling between telocytes and cardiac stem cells via extracellular vesicles loaded with microRNAs.

Localization of telocytes inside the heart

Telocytes localized in different layers of the heart have different structures (and probably functions). The general ultrastructural morphology of telocytes from myocardium was described in the aforementioned paragraphs. Telocytes of the epicardium release numerous microvesicles as exosomes into the extracellular matrix (Popescu et al. 2010). Telocytes of endocardium represent the main cell population in the subendothelial layer of the endocardium, and are ultrastructurally similar to telocytes of the myocardium. Subendothelial telocytes often send out telopodes inside the myocardium and are connected with telocytes of the myocardium (Gherghiceanu et al. 2010). In rats, the cardiac telocyte density in the subepicardium is significantly higher than that in the endocardium, and is higher in the atria than in the ventricles (Liu et al. 2011).

Electron microscopy and immunofluorescence showed that telocytes are also present in the human mitral, tricuspid, and aortic valves (Yang et al. 2014). Telocytes and their prolongations inside the heart valves form a 3D network, which probably contributes to the mechanical support and flexibility of the valves, as well as to the intercellular communication and signalization. However, their precise function and the possible application of these data to the treatment of damaged heart valves remain unknown.

Cardiac telocytes during ontogeny of the heart

Faussine-Pellegrini and Bani (2010) demonstrated the irreplaceable function of telocytes in mice during prenatal development of the heart. The growing columns of immature cardiac muscle cells are interconnected and bordered by telocytes. It is

possible that the cytoplasmic processes of telocytes form a 3D architectural scaffold for the developing myocardium. During postnatal life, the number of telocytes significantly decreases in adults. Similarly with telocytes, the number of cardiac stem cells decreases as well, from 0.5% of all interstitial cells in the heart of newborns to 0.1% in adulthood (Popescu et al. 2015).

Telocytes and cardiac stem cells

Recent studies have shown that telocytes are also localized inside or in the close vicinity of stem cell clusters, called “niches” in various organs of the human body. Telocytes participate in the formation of stem cell niches in the bone marrow (Li et al. 2014), lungs (Galiger et al. 2014), corneal limbus of the eye (Luesma et al. 2013), and subepicardial layer of the heart (Gherghiceanu and Popescu 2010; Zhou et al. 2014; Bei et al. 2015b).

Cardiac stem cell niches containing cardiac muscle cells progenitors are found in the subepicardium, surrounding the coronary arteries (Bursac 2012). Each niche is not only from cardiac progenitors in different stages of development, but also from surrounding loose connective tissue with numerous cells (adipocytes, fibroblasts, mast cells, macrophages, telocytes), nerve fibers, and a rich capillary bed (Gherghiceanu and Popescu 2010). It is well known that fixed cells of connective tissue (e.g., fibroblasts, adipocytes, endothelial cells, pericytes, telocytes) and their extracellular matrices have an essential function in the regulation of regeneration processes. These cells create a proper 3D scaffold composed of their cell bodies and cytoplasmic processes, and stimulate the growth and differentiation of precursor cells (Bani and Nistri 2014). Recent *in vitro* experiments support the evidence that, telocytes in particular, form networks (scaffolds) with their long telopodes and are probably

essential for the architectural organization of regenerated myocardium (Zhou et al. 2014). Telocytes also transmit information to cardiac stem cells and cardiac muscle cells through direct membrane contacts and vesicle release (both described above). Telocytes are often termed “nurse cells” for cardiac stem cells, which help them differentiate and integrate into the heart’s architecture (Bei et al. 2015b).

Cardiac telocytes during different pathological conditions

In recent literature, only a few studies have investigated changes in the distribution and function of telocytes (especially their decrease in the number) during different cardiac diseases. However, this is not the case in other organs. For example, loss of telocytes in the uterine tubes (due to inflammatory diseases or endometriosis) causes tubal infertility (Dixon et al. 2010; Yang et al. 2015), and the loss of telocytes within the wall of the gallbladder causes hypomotility of the muscle layer and consecutive gallstone disease (Matyja et al. 2013).

Richter and Kostin (2015) demonstrated the decreased number of cardiac telocytes in the end-stage failing heart of patients who underwent heart transplantation. Ultrastructurally, these cells are characterized by degenerative processes including cytoplasmic vacuolization, shrinkage, and shortening of the cytoplasmic prolongations (telopodes). The reduced number of cardiac telocytes was also described during experimental myocardial infarction in rats (Zhao et al. 2013). Another important finding was that in subsequent weeks, the cardiac telocytes failed to migrate into the infarction zone from neighboring healthy myocardium, which may result in poor regeneration of the affected myocardium.

Telocytes are probably involved in neoangiogenesis after myocardial infarction (Manole et al. 2011). Experimentally, cardiac telocytes transplanted into the

site of myocardial infarction in rats, caused reduction in the size of damaged tissue and improved myocardial function. Cardiac telocyte transplantation could significantly increase vessel density (an increase in cardiac neoangiogenesis) and decrease myocardial fibrosis at the heart infarct site (Zhao et al. 2014).

In different tissues, the quiescent form of telocytes represents “nurse cells” for stem cells, and after activation, they are probably a source of fibroblasts and myofibroblasts in the repair process through granulation tissue or fibrosis (Díaz-Flores et al. 2016).

Conclusions

So the question remains whether telocytes represent a distinct and new cell population or are just a specific type of fibroblast with cell surface markers similar to embryonal mesenchymal cells. In both cases, their role in the human body is remarkable as they are a reservoir of tissue mesenchymal cells, regulate the functions of immune cells, and regulate the growth, maturation, and differentiation of parenchymal cells. They are also important during the induction of angiogenesis and scaffolding support of other cells during tissue regeneration (Díaz-Flores et al. 2014). Smythies and Edelstein (2013) suggested that telocytes could function as an extensive intercellular information transmission system that utilizes small molecules, exosomes, and possibly electrical events in the cytoskeleton. Their role is modulation of homeostasis and stem cell activity in many organs. This network might be well regarded as forming a very primitive nervous system at the cellular level. Professor Popescu strongly believed that telocytes might have huge therapeutic potential for the design of some future cell-based cardiac repair strategies (Popescu et al. 2010). In the future, exploring pharmacological or non-pharmacological methods to enhance the growth of

telocytes would be a novel therapeutic strategy, in addition to exogenous transplantation for many diseases including chronic and acute heart diseases (Bei et al. 2015b).

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Conflict of interest

We declare that we have no conflict of interest.

Ethical approval

This article does not contain any studies with human participants or animals performed by any of the authors.

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