Cardiac Telocytes in Heart Disease

Subjects: Cell & Tissue Engineering
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A cell population called telocytes (TCs) described only 16 years ago largely contributed to the research area of cardiovascular regeneration. TCs are cells with small bodies and extremely long cytoplasmic projections called telopodes, described in all layers of the heart wall.

Keywords: cardiac telocytes

1. Telocytes in Heart Diseases

It will be no exaggeration to say that TCs are unmatched in the vastness of their possible roles in the pathogenesis of different diseases, regardless of which animal species or organ we are referring to. In the heart alone, TCs have been studied in myocardial infarction [1], heart failure [2], arrhythmias [3], or atrial amyloidosis [4]. Their numerical alteration was also described in the heart of elderly patients, suggesting one of the many reasons why an aging heart is more disease-prone [5].

1.1. Myocardial Infarction

Multiple studies have demonstrated that the normal function and morphology of cardiac TCs are severely disrupted during myocardial infarction [1][6][7]. At first glance, this finding is not very surprising, given that the myocardial ischemia, with subsequent apoptosis, necrosis, and overall derangement of the cellular microenvironment, alters all the cell populations in the affected site, including TCs. It would suggest that the loss of TCs is merely a consequence of pathological processes occurring in the infarcted myocardium. It is indeed the case, but it has to be stated that previous studies found out that TCs are particularly fragile during hypoxia; hence, they are perhaps among the first cell populations negatively affected by the lack of nutrients and oxygen, leading to further derangement of normal TC-dependent myocardial architecture and function [1]. The most dreaded consequence of myocardial infarction in those patients who survive is the loss of contractile tissue, which is replaced by functionally inferior connective tissue scar, resulting in the loss of inotropic capacity of the heart, eventually progressing to heart failure [8]. The current research shows that TCs may also play a role in the development of these deleterious outcomes, not only in the pathogenesis of the myocardial infarction itself. This is documented by the experimental data, which indicate that TCs can be negatively influenced by dynamical changes in the composition of the extracellular matrix during the reparation process [9]. Moreover, according to a study of TCs and their involvement in the pathogenesis of fibrotic remodeling of the colonic wall in ulcerative colitis, it has been hypothesized that the loss of TCs may lead to deregulation of fibroblast to myofibroblast transition [10]. This transition also promotes cardiac fibrosis since myofibroblasts are excessively active in the synthesis of the extracellular matrix components [11]. The loss of TCs was also described in myocardial fibrotic lesions in patients diagnosed with systemic sclerosis, underscoring the importance of TCs in normal tissue maintenance [12].

1.2. Arrhythmia

Arrhythmias of different etiologies have also been discussed in relation to the possible role of TCs in their development. It is not at all surprising, given that TC discovery is closely linked to ICCs—pacemaker cells of the gut. TCs, formerly known as ICLCs, have been previously described in various organs participating in electrophysiological processes, including mechanoelectrical transduction and pacemaking [13]. DeSimone et al. found out that myocardial TCs of a dog express anoctamin-1. This voltage-gated calcium-activated anion channel is also found in ICCs as a major ion channel responsible for their pacemaker function. These results suggest that electrophysiological regulation and, thus, potential significance in arrhythmogenesis could be linked to myocardial TCs [14]. Not only that, Mitrofanova et al. also described TCs in the human sinoatrial node in close vicinity to pacemaker cells and contractile cardiac muscle cells using immunohistochemistry, confocal laser scanning microscopy, and TEM. The authors hypothesized about the modulating effects of TCs, although conclusive knowledge on their precise role has not been obtained. Future research may elucidate the role of TCs in the regulation of cardiac electrophysiology in the sinoatrial node—the top tier of normal heart rhythm [15].

Back in 2008, when TCs were known only for about 3 years and still referred to as ICLCs, Gherghiceanu et al. demonstrated the presence of TCs in the myocardial sleeves of the human pulmonary veins. According to their immunohistochemical and ultrastructural analysis of TCs in this location, the authors assumed that TCs may act as yet unrecognized agents in the pathogenesis of atrial fibrillation. This assumption was made according to the observation of the TC-derived 3D interstitial network among different components of the myocardial sleeve, including blood vessels, nerves, and cardiomyocytes. Since it is known that the myocardial sleeves can be a source of ectopic beats which can initiate the atrial fibrillation, the authors pondered on the possibility of implicating TCs in this pathological condition [16].

2. Cardiac Telocytes in Cardiovascular Regenerative Medicine—Recent Developments

The potential of cardiac TCs as important players in cardiovascular regeneration is substantiated by the research focused on the integrative, regulative, and nursing functions of TCs in the heart wall. As mentioned earlier, one of the most promising findings is that TCs are located in the epicardial stem-cell niches. Bei et al. comprehensively reviewed the role of TCs in the homeostatic regulation of the whole stem-cell niche, where they are capable of regulating the functional characteristics, dynamics, commitment, and other aspects of stem-cell physiology. In addition to stem cells, the authors provided an excellent overview of the other important heterocellular connections imperative for successful TC-mediated cardiac regeneration. These include connections with cardiomyocytes and different populations of interstitial cells, including fibroblasts, immune cells, pericytes, and endothelial cells, which are also important in the whole orchestration of the regeneration and repair of the heart [17].

For a better understanding of the role of TCs during repair and regeneration, the data from embryonic studies can provide valuable insights. Faussone-Pellegrini and Bani conducted an immunohistochemical and electron microscopic study of a mouse myocardium during the E14 and E17 stages of embryonic development. According to the morphological findings of TCs in close vicinity to immature components of the developing heart, the authors concluded that TCs possibly perform significant tasks during cardiogenesis, including the organization of the cytoarchitecture of the myocardial constituents, mechanical support, and supervision of the correct sequence of stem-cell differentiation [18]. Papers focused on congenital heart defects could also provide additional knowledge. A recent study performed on samples from patients with tetralogy of Fallot revealed that TCs might coordinate the differentiation of stem cells and use paracrine signaling to regulate all the surrounding interstitial compartment [19].

Experimental data also shed light on the prospects of the actual use of TCs in human regenerative medicine. A recent original article by Liao et al. presented a yet unknown mechanism of the regenerative potential of cardiac TCs. The authors found out that cardiac TCs produce exosomes containing miRNA-21-5p, which can inhibit apoptosis in cardiac microvascular endothelial cells. It is essential in the process of angiogenesis, which is necessary for favorable regeneration after myocardial infarction. These paracrine-acting molecules show another fascinating future avenue in the form of cell-free therapy, which would not require the cells themselves since it has been progressively clear that, in many instances, the regeneration happens not via a direct proliferation and differentiation of stem cells but via paracrine signaling through molecules from cell-derived structures (e.g., exosomes) [20]. Cardiac TCs also use other types of extracellular vesicles, namely, ectosomes and multivesicular cargos. Multiple lines of evidence show that these vesicles may epigenetically modulate the physiology of cardiac stem cells, which themselves produce signaling molecule-containing extracellular vesicles, thus reciprocally influencing the cardiac TCs. This not yet entirely understood crosstalk between stem cells and TCs may be the key to fully embracing the regenerative potential of TCs [21][22].

In addition to the paracrine action mediated by extracellular vesicles, TCs make direct cell-to-cell contacts with cardiac stem cells, as observed by Popescu et al., who established a coculture of these two cell populations. They formed classic cell-to-cell junctions but also unusual junctions such as puncta adherentia and stromal synapses. The authors recognized a significant obstacle in the successful implementation of cell therapy in cardiovascular regenerative medicine. The tissue, e.g., after myocardial infarction, has specific characteristics resulting from the damage associated with the pathological process, making it especially challenging for the grafted cells to survive in this inhospitable microenvironment. These include ischemia, inflammation, proapoptotic signaling, and disintegrated extracellular matrix. Therefore, it is vital to thoroughly understand the exact interaction of stem cells and TCs through in vitro reproduction of the processes occurring in the stem-cell niches. Perhaps this is an inevitable step for successfully applying the cell therapy in vivo [23].

In elucidating the role of TCs in cardiac regeneration, a highly valuable course of research is that focused on animals with almost perfect cardiac regenerative capacity. One such experimental paper was published in 2020, describing TCs in the heart of the western clawed frog (*Xenopus tropicalis*). Lv et al. used electron microscopy and immunofluorescence to visualize TCs in this species. Moreover, they surgically removed the apex of the frog's heart to study cardiac TCs on this

injured site. Interestingly, after 8 days, the damaged TCs were among the first cells to regenerate fully. This quick recovery suggests that TC renewal might be the first essential step in any further fruitful regeneration of the tissue architecture ad integrum [24]. As mentioned earlier, the loss of TCs is an important pathogenetic moment in the development of myocardial infarction. In order to study the possible ways to mitigate its progression and/or to alleviate its potential adverse outcomes, Zhao et al. transplanted TCs into the infarction zone, as well as the border zone. They found out that such a procedure provided a significant benefit in terms of the reduction in the infarction size and improved functional aspects of the myocardium [1]. TC transplantation has also been performed in other organs. Zheng et al. found out that transplanted TCs could mitigate the induced renal fibrosis in rats [25]. Focusing on TCs in the respiratory system, Zhang et al. established a rat model of acute lung injury and observed the effect of cotransplantation of TCs with mesenchymal stem cells. The results demonstrated that TCs had a synergic effect on the experimental lung injury's attenuation [26]. TCs were also previously implicated in the pathogenesis of a broad spectrum of chronic inflammatory and fibrotic diseases, including Crohn's disease, liver fibrosis, and psoriasis. TC transplantation, either in a solitary fashion or together with stem cells, was also discussed as a promising future avenue in the state-of-the-art therapeutic management of these conditions [27].

The importance of TCs in cardiac regeneration was also recognized in studies whose research goal was to scrutinize other cell populations with regenerative capabilities. Miao et al. attempted to investigate the effect of the transplantation of induced pluripotent stem cell-derived mesenchymal stem cells in a mouse model of myocardial infarction. Although TCs were not the prime experimental focus in this study, the authors found out that the beneficial effect of the transplanted cells was reinforced by TCs, which contributed to supporting the tissue architecture, mechanotransduction, and elasticity [28]. Similar research was conducted by Ja et al., whose experimental study also involved the induction of pluripotent stem cells, with further differentiation to cardiomyocyte progenitors and cardiomyocytes (induced pluripotent stem cells were differentiated into mesenchymal stem cells in the previous study). They also transplanted the cells into the infarcted myocardium of an animal model. In the group of animals that received the cardiac progenitor cell transplant, the authors observed an improvement in myocardial function. It was correlated with increased angiogenesis and an enhanced network of cardiac TCs in the zone of myocardial infarction [29]. These results suggest that, in the case of TC absence or dysfunction, the cells responsible for cardiac regeneration cannot perform their tasks efficiently. Therefore, TCs should always be considered when researching the cardiac reparative processes.

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