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STATE OF THE ART

Telocytes – a Hope for Cardiac Repair after Myocardial Infarction

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ABSTRACT

Cardiovascular diseases, particularly myocardial infarction, remain the leading cause of morbidity and mortality worldwide, even though pharmacological and interventional therapies improved significantly in the last years. Moreover, despite encouraging results of cell - based therapies in experimental myocardial infarction models, clinical trials showed inconsistent and modest efficiency. Therefore the next step should be the revealing of a new cell type, capable of regenerating the damaged myocardium.

Telocytes (TCs), a relatively new type of interstitial cells, were described few years ago and are credited with important roles in regenerative therapies.

In this paper we review their most important characteristics and functions, showing the evidences of their potential role in cardiac repair and regeneration.

Our research leads to the conclusion that TCs might be a novel target for therapeutic strategies in myocardial infarction.

Keywords: Myocardial infarction, telocytes, regenerative therapies

INTRODUCTION

Cardiovascular diseases remain the leading cause of morbidity and mortality worldwide, being responsible in Europe for 45% of all death, or more than 4 million deaths each year and in United States for 30.8% or 2200 deaths each day (1,2). Even though pharmacological and interventional therapies for myocardial infarction improved significantly in the last years, an important percentage of patients develop severe left ventricular systolic dysfunction, due to adverse remodelling. This is leading to a poor prognosis, a reduced quality of life and an increased risk of death, mainly, due to the fact that none of these therapies treat the loss of the contractile tissue. Therefore cell – based therapies were developed aiming to repair, replace or

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regenerate the damaged myocardium. This opened a new era in medicine, namely regenerative therapy.

Various types of cells have been studied for cardiac repair, stem cell (SC) being the most used one (3). SC is defined as cell with the capacity to self-renew by creating copies of itself through division or to differentiate into at least one other cell type (4). The major types of SC used for cardiac repair are: (1) pluripotent SC, namely embryonic SC and induced pluripotent stem cell (iPSC), and (2) multipotent SC, namely endothelial progenitor cells, cardiac progenitor cells, and mesenchymal SC (3). The precise mechanism for cardiac regeneration of different SC remains unclear, even though there were proposed several mechanisms by which they could improve cardiac function, such as trans-differentiation into cardiomyocytes, paracrine effects, recruitment of progenitor cells, modulation of matrix and apoptosis (5-9). Despite encouraging results of cell - based therapies in experimental myocardial infarction models, clinical trials showed inconsistent and modest efficiency, in terms of both clinical and echocardiographic end-points. Therefore it is mandatory to discover new cell types and methods for cardiac repair.

Telocytes (*TCs*) are a relatively new type of interstitial cells that can play an important role in regenerative therapies (10).

In this paper we review their most important characteristics and functions, which could give them the potential of cardiac repair and regeneration.❑

GENERAL ASPECTS

TCs were formerly known as "interstitial Cajal–like cells" (ICLCs), due to their apparently similar morphological features with "interstitial Cajal cells" (ICCs), described in the gut more than 100 years ago. Since they were shown by electronic microscopy to be clearly two different types of cells, in 2010 Popescu LM *et al.*, inspired by the Greek philosopher Aristotle, considered mandatory to rename ICLCs as "telocytes". The prefix '*Telos*' means an object's or individual greatest potential (11). The main feature of *TCs* is the presence of their peculiar very long and thin cellular prolongations, termed "telopodes". Thus, the shortest definition of *TCs* is "cells with telopodes" (12).

Over the last years the *TCs* were identified in numerous organs, as: heart (in all the three layers), blood vessels, bone marrow, respiratory system, gastrointestinal tract and annexes, urinary system, female reproductive system, prostate, eye, skeletal muscle, skin (13-28). Within heart, *TCs* are not uniformly distributed, their number varying between endocardium, myocardium, and epicardium, respectively, and also between atria and ventricle, being found in a greater proportion at the base of the heart, in the atria (10,14-16,29,30). Moreover the distribution of *TCs* within heart was shown to vary with several normal or pathological states (31-37). A recent study documented the presence of *TCs* in a higher number and with similar ultrastructural features in fragments from the right atrial appendage of children and new-borns compared with adults. This is demonstrating that an ageing human heart is characterized by a decreased number of *TCs*, along with the number of SC and cardiomyocytes (31). Moreover, recently was demonstrated that cardiac *TCs* are increased in exercise-induced cardiac growth, while exercise, was shown previously to stimulate the formation of new cardiomyocyte (32,38). Therefore *TCs* were credited to promote cardiac growth and possible its regeneration. Their higher number in zebrafish and newt hearts, which regenerate after amputation of the apex of the ventricle, supplementary supports this hypothesis (39).

In contrast, a reduced number of *TCs* in the heart was reported in various cardiac pathologies, such as heart failure due to dilated cardiomyopathy of different aetiologies, isolated atrial amyloidosis, which develops after long-standing atrial fibrillation, systemic sclerosis that involves the myocardium, and last but not least, experimental myocardial infarction (33-37). Moreover, in cardiac *TCs* from humans with heart failure were shown important ultrastructural alterations, such as cytoplasmic vacuolization, shrinkage and shortening of telopodes, absence of the labyrinthine components, suggesting that these cells could have an important role in tissue homeostasis (40).

THE ULTRASTRUCTURE AND PHENOTYPE OF CARDIAC TCs

The ultrastructure of *TCs* was established by electron microscopy (14). *TCs* have a small

oval-shaped cellular-body, containing one nucleus surrounded by a rim of scarce cytoplasm (16). The cell membrane frequently presents caveolae (15). The most important ultrastructural attribute is the presence of telopodes, which are particularly very long and thin prolongations, with moniliform aspect, with thin (podomers) and dilated (podoms) segments, branching, with a dichotomous pattern (29,30). A more powerful technique - focused ion beam scanning electron microscopy tomography - demonstrated that telopodes are organized in a 3D network which forms a labyrinthine system (41).

By confocal imaging and immunohistochemistry, cardiac *TCs* were proved to have positive expression for various markers: CD34, CD117/c-kit, vimentin, PDGFR-β, CD34/PDGFR-α, but until now was not found any single specific marker (16,30,42-46).

All these features indicate that *TCs* represent a distinct type of interstitial cells, different from any other cardiac stromal cell.

FUNCTIONS OF TCs IN THE HEART

Some of the described features and functions of *TCs* support their potential roles in cardiac repair and regeneration. The labyrinthine system of telopodes forms a dynamic scaffold and could assure mechanical support for other cells and assist the migration and differentiation of cardiac progenitor cells (41,47). Moreover *TCs* establish connections with each other and with other type of cells, by homocellular and heterocellular contacts, respectively (48). The homocellular contacts are either side to side, probably for exchanging information, or end to end, probably for transmitting the information from one to the other (49). Through heterocellular contacts with cardiomyocytes, putative stem cells, cardiomyocyte progenitors, fibroblasts, mast cells, macrophages, pericytes, endothelial cells and Schwann cells, the *TCs* form an integrated system in order to maintain organ structure and function (48). Furthermore *TCs* have been identified as active members of cardiac SC niches, in epicardium, together with cardiomyocyte progenitors. This is suggesting that they "nurse" and "guide" cardiac progenitor cells in their physiological process of gaining mature working cardiomyocytes attributes, as a part of cardiac regeneration process (10). Consequently the tandem *TCs* - SC could represent a better option for regenerative therapy, rather than SC alone.

Through their secretory capacity of producing cyto- and chemokines : interleukine 6 (IL-6), macrophage inflammatory proteins 1α (MIP-1α), macrophage inflammatory proteins 2 (MIP-2), monocyte chemoattractant protein 1 (MCP-1) and vascular endothelial growth factor (VEGF), *TCs* could have a potential regulatory role on other cell types, including resident SC (50). *TCs* transfer extracellular vesicles loaded with microribonucleic acid (microRNA) to SC therefore could influence the post-transcriptional machinery and contribute to SC self-renewal and transdifferentiation (51).

Consequently, through all these roles, *TCs* could improve the ability of resident SC to repair and regenerate the heart.

TCs IN MYOCARDIAL INFARCTION AND FUTURE PERSPECTIVES

Two independent studies of rat experimental myocardial infarction after occlusion of left coronary artery reported the variation of *TCs* number within the lesion tissue (36,37). The typical lesion of myocardial infarction consists in two distinct zones, the central zone and the border zone, respectively, each with different ultrastructure and cellular activity. The density and distribution of *TCs* varies along the three stages of myocardial infarction: inflammation, scar formation by fibroblast proliferation, and matrix remodelling (37). Accordingly, in the first days, in the border zone, the *TCs* were not so frequently found like in normal myocardium, but their number increased significantly after 30 days (37). By contrast, in the infarction zone they were undetectable by immunofluorescent staining from 4 days to 4 weeks after the occlusion of the coronary artery, although in the non-ischaemic zones the cell density increased after 2 weeks (36). Moreover, using different techniques as immunocytochemistry, electron microscopy and microRNA analysis, was reported that *TCs* are involved in neo-angiogenesis process after myocardial infarction, either direct by physical nano-contacts with capillaries, or indirect by microcrine secretion of pro-angiogenic microRNAs and by paracrine secretion of nitric oxide synthase 2 (NOS2) and vascular endothelial growth factor (VEGF) (37).

Recently, was reported that the intra-myocardial transplant of *TCs* in the border and central zones decreased the infarction size and improved cardiac function, both at 14 days and 14 weeks after the occlusion of the coronary artery (36,52).

Interestingly, the intra-myocardial transplant of iPSC - derived human mesenchymal stem cells or iPSC - derived human cardiac progenitor cells, besides improving ventricular remodelling, was associated with increased number of *TCs* compared to control animals (53,54).

The great number of evidences of the potential role of *TCs* in cardiac repair and regeneration propose them as a novel target for therapeutic strategies in myocardial infarction.❑

Conflict of interests: none declared

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