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Behaviour of telocytes during physiopathological activation

Lucio Díaz-Flores [a,*], Ricardo Gutiérrez [a], Lucio Díaz-Flores Jr. [a], Miriam González Gomez [a], Francisco J. Sáez [b], Juan F. Madrid [c]

[a] Department of Basic Medical Science, Faculty of Medicine, University of La Laguna, Tenerife, Spain
[b] Department of Cell Biology and Histology UFI11/44, School of Medicine and Dentistry, University of the Basque Country, UPV/EHU, Leioa, Spain
[c] Department of Cell Biology and Histology, School of Medicine, Regional Campus of International Excellence, "Campus Mare Nostrum", University of Murcia, Espinardo, Spain

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ABSTRACT

We consider CD34+ stromal cells/telocytes (CD34+ SC/TCs) in normal and pathological conditions. These cells are involved in organisation and control of the extracellular matrix, structural support, creation of microenvironments, intercellular communication, neurotransmission, immunomodulation and immunosurveillance, inhibition of apoptosis, and control, regulation and source of other cell types. CD34+ SC/TCs are widely reported in the origin of interstitial cells of Cajal and in regeneration in the heart, skeletal muscle, skin, respiratory tree, liver, urinary system and the eye. In addition, we contribute CD34+ SC/TC hyperplasia associated with several processes, including neurogenous hyperplasia (neuroma of the appendix), hyperplasia of Leydig cells in undescended testes (Cryptorchidism), peripheral areas of inflammatory/repair processes (pericicatricial tissue and transitional zones between diseased segments in Crohn's disease and normal bowel), benign tumours (neurofibromas, Antoni-B zones of neurilemmomas, granular cell tumours, and melanocytic nevi) and in some lesions with myxoid, oedematous and degenerative changes (Reinke's oedema, myxomatous mitral valve degeneration, thyroid-associated ophthalmopathy and basophilic degenerative changes of the collagen in the dermis). We pay particular attention to the role of CD34+ SC/TCs during repair through granulation tissue, including morphologic changes, loss of CD34 expression and gain of αSMA expression with myofibroblast transformation, and interactions with pericytes, endothelial and inflammatory cells. Finally, we consider CD34 or αSMA expression in stromal cells of malignant epithelial tumours, and the role of CD34+ SC/TCs in the origin of carcinoma-associated fibroblasts (CAFs) and myofibroblasts. In conclusion, CD34+ SC/TCs play an important role in the maintenance and modulation of tissue homeostasis and in morphogenesis/renewal/repair.

Contents

* Corresponding author at: Universidad de La Laguna, Facultad de Medicina, Departamento de Ciencias Médicas Básicas, Ofra-La Cuesta, s/n, La Laguna, 38071 Tenerife, Islas Canarias, Spain. Fax: +34 922 319279.
E-mail address: kayto54@gmail.com (L. Díaz-Flores).

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1. Introduction

Telocytes are a subset of stromal cells recently described by Popescu et al. [1,2]. Formerly named interstitial-like (Cajal-like cells), the location, morphology, structure, immunohistochemical and functional properties of these cells have been widely studied (see www.telocytes.com). Based on their different immunohistochemical and ultrastructural characteristics, several telocyte subtypes have been identified. CD34 and PDGFRα are the most useful markers for general identification [3]. In this review, we consider the physiopathological role of the human resident CD34+ telocytes: CD34+ stromal cells/telocytes (CD34+ SC/TCs).

2. Appropriate morphological substrates to study the functions and behaviour of CD34+ SC/TCS

CD34+ SC/TCs are located in multiple anatomical sites (see www.telocytes.com). In order to review and understand the role of these cells, we have selected studies undertaken in several appropriate human locations, based on the following tissue properties: (a) locations in which CD34+ populations of TCs were previously accurately typified and with ideal microstructures for understanding cell arrangement and functions, (b) with abundant CD34+ SC/TC content, (c) with pathologic processes that facilitate the follow-up of CD34+ SC/TC activation *in vivo* during the two principal types of repair (regeneration, including hyperplasia of CD34+ SC/TCs, and repair through granulation tissue), (d) with important literature on tissue-isolated CD34+ SC/TCs *in vitro* (for regenerative medicine) to compare CD34+ SC/TC behaviour during repair *in vivo* and (e) with malignant epithelial tumours to study the role of CD34+ SC/TCs in tumour-associated stroma.

2.1. Anatomic locations with precise typification of stromal cells

The enteric wall (muscularis mucosae, submucosa, muscularis propria and subserosa) and neuromuscular spindles (intrafusal connective tissue and innermost layer of the external capsule) are examples of anatomic regions in which previous studies have confirmed that CD34+ stromal cells are TCs and that they are ideal sites to understand CD34+ SC/TC arrangement and functions [4–10]. Indeed, in the enteric wall (Fig. 1A) and in neuromuscular spindles (Fig. 1B), the characteristics of CD34+ SC/TCs are easily observable, including arrangement (networks connecting CD34+ SC/TCs with each other and with muscle cells, vessels, nerve fibres, and immune cells forming labyrinthine systems), typical morphology (triangular or spindle body, containing small somatic cytoplasm surrounding an ovoid nucleus, and two to five long, slender, moniliform cytoplasmic telopodes, showing podomeres and podoms), ultrastructure (patches of heterochromatin above all in close proximity to nuclear membrane, polysomes, scarce cisternae of rough and smooth endoplasmic reticulum, few mitochondria, a small Golgi apparatus and centrioles in the somatic cytoplasm, microfilaments in podomeres, and mitochondria, endoplasmic reticulum and some caveolae in podoms), and presence of homo and heterocellular interrelations (intercellular junctions and extracellular vesicles).

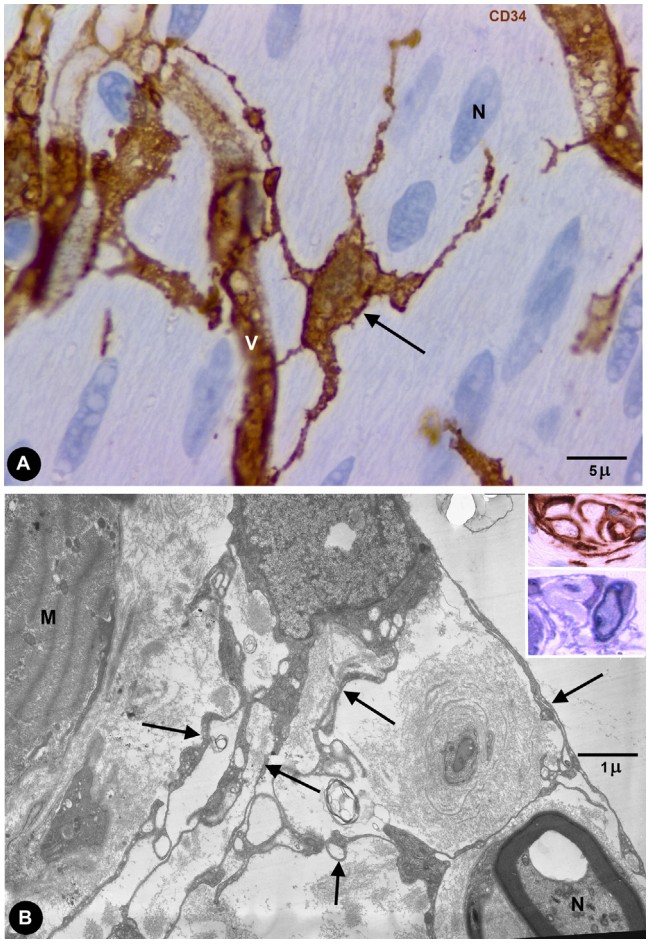

Fig. 1. A: In the enteric wall, a CD34+ SC/TC is shown (arrow), presenting long, slender, moniliform cytoplasmic telopodes (with podomeres and podoms), which connect to a vessel (V) (endothelial cells also express CD34) and intermingle with smooth muscle cells (with haematoxylin-stained nuclei—N) (CD34 immunoperoxidase labelling with haematoxylin counterstain). B: Ultrastructural characteristics of telocytes in a neuromuscular spindle. Note the networks of telopodes (arrows) surrounding a striated muscle cell (M), a nerve (N) and collagen fibres (creating microenvironments). Inserts: Similar images in light microscopy (anti-CD34 stained cells and semi-thin section—Toluidine blue).