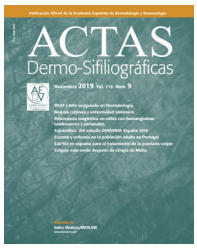
ACTAS Dermo-Sifiliográficas 114 (2023) 229–239

ACADEMIA ESPAÑOLA DE DERMATOLOGÍA Y VENEREOLOGÍA

ACTAS Dermo-Sifiliográficas

Full English text available at www.actasdermo.org



REVIEW

Telocytes in Cutaneous Biology: A Reappraisal

A.M. Ahmed, M.R. Hussein*

Department of Pathology, Faculty of Medicine, Assiut University, Assiut, Egypt

Received 24 May 2022; accepted 30 August 2022

KEYWORDS
Telocytes;
Skin;
Biology;
Cutaneous

Abstract The telocytes (TCs) are novel interstitial cells that have been overlooked for a long time due to their histologic similarity to other stromal cells. TCs can be separated from the stromal cells based on their distinct immunohistochemical, ultrastructural, and molecular features. Functionally, TCs are involved in the tissue renewal, mechanical support, and immune modulation. These cells are also involved in the signal transduction either through their direct interactions with the neighboring cells or through the paracrine signaling via extracellular vesicles. TCs are damaged in several inflammatory and fibrotic conditions such as ulcerative colitis, Crohn's disease, hepatic fibrosis, psoriasis, and systemic sclerosis. The transplantation of TCs in the damaged tissue can promote tissue regeneration. Therefore, enhancing tissue TCs either by their transplantation or by promoting their survival and growth using novel medications represents novel therapeutic strategy in the future. In this review, we addressed several aspects of TCs including their origin, distribution, morphologic features, and functions. We also discussed their involvement of the cutaneous TCs in the development various pathologic conditions.

PALABRAS CLAVE
Telocitos;
Piel;
Biología;
Cutáneo

Los telocitos en la biología cutánea: revaluación

Resumen Los telocitos (TC) son células intersticiales noveles que han sido subvaloradas durante mucho tiempo debido a su similitud histológica con otras células estromales. Los TC pueden separarse de las células estromales debido a sus distintas características inmunohistoquímicas, ultraestructurales y moleculares. A nivel funcional, los TC están implicados en la renovación tisular, el soporte mecánico y la modulación inmune. Dichas células están implicadas también en la transducción de señal, bien mediante sus interacciones directas con las células

Abbreviations: ICCs, interstitial cells of Cajal; TCs, telocytes; TEM, transmission electron microscopy; FIB-SEM, focused ion beam scanning electron microscopy; PDGFR α, platelet-derived growth factor receptor α; α-SMA, α-smooth muscle actin; Sca-1, stem cell antigen-1; ECM, extracellular matrix; VEGF, vascular endothelial growth factor; EGF, epidermal growth factor; IL-6, interleukin 6.

* Corresponding author.
E-mail address: frcpath17@aun.edu.eg (M.R. Hussein).

https://doi.org/10.1016/j.ad.2022.08.023

circundantes, o bien mediante la señalización paracrina, a través de las vesículas extracelulares. Los TC se ven dañados en ciertas situaciones inflamatorias y fibróticas tales como colitis ulcerosa, enfermedad de Crohn, fibrosis hepática, psoriasis y esclerosis sistémica. El trasplante de TC en el tejido dañado puede promover la regeneración tisular. Por tanto, mejorar los TC tisulares mediante trasplante o promoción de su supervivencia y crecimiento, utilizando medicaciones novedosas, representa una estrategia terapéutica innovadora para el futuro. En esta revisión abordamos diversos aspectos de los TC, incluyendo su origen, su distribución, sus características morfológicas y sus funciones. También tratamos la implicación de los TC cutáneos en el desarrollo de diversas situaciones patológicas.

Background

The Discovery and Terminology of Telocytes

It was in 1911 when Santiago Ramón y Cajal identified a new type of cells with long cytoplasmic processes within the muscle layer of the human alimentary canal. Cajal coined these cells as ''interstitial neurons'' due to their characteristic cytoplasmic projections and location among the smooth muscle cells and the nerve endings.[1] In 1977, Faussone-Pellegrini et al. investigated the ultrastructural features of these interstitial neurons using electron microscopy. They indicated that these cells were not true neurons, and therefore they re-named them as 'interstitial cells of Cajal' (ICCs). The authors described the ultrastructural features of ICCs as spindle-shaped cells with long cytoplasmic processes by which these cells can interact with each other and with other cell types.[2] In 1996, Lecoin et al. confirmed the mesenchymal origin of ICCs. They also indicated that ICCs in chick embryos express the gene encoding the cytokine receptor tyrosine kinase ''Kit''.[3]

In 2005, Popescu et al. described cells that closely resemble ICCs in the exocrine pancreas, and they coined those ''interstitial Cajal-like cells (ICLCs).[4] In 2010, Faussone-Pellegrini and Popescu indicated that these cells have unique physical properties, such as the presence of oval nuclei surrounded by scanty cytoplasm and telopodes (Tps). They coined these cells ''telocytes (TCs)''. They indicated that TCs are entirely different from ICCs because they have unique ultrastructural, immunohistochemical, and genetic features, as well as other protein expression profile.[5]

The Distribution of TCs In the Human Tissues

TCs have been detected in the tissue of several vertebrates such as mice, rats, guinea pigs, chickens, and humans. Initially, TCs were thought to be predominantly located in the gut of the human body.[6] However, growing evidence indicates that TCs are present in almost all human organs such as the heart,[7] blood vessels,[8] lungs,[9] meninges,[10] skin,[10,11] salivary glands,[12] liver, gall bladder,[13] pancreas,[4,14,15] bone marrow,[16] breast,[15] fallopian tube,[17] placenta,[18] myometrium,[14] kidney, urinary bladder, and prostate.[19] In these organs, TCs are commonly located in the interstitial tissue, where they can interact with the stromal cells, immune cells, and the surrounding blood vessels. The distribution of the TCs in different human tissues and their cellular interactions is summarized in Table 1.

The Ultrastructural Features of TCs

The two-dimensional (2D) transmission electron microscopy (TEM), focused ion beam-scanning electron microscopy (FIB-SEM) tomography, and the three-dimensional (3D) imaging techniques are used to examine the ultrastructural features of TCs.[20–24] TCs have cell bodies and cytoplasmic processes (Tps) with unique ultrastructural features that distinguish them from other stromal cells (Table 2). Several factors can affect the density and the morphology of TCs, such as pregnancy, aging, and oxidative stress. For instance, during pregnancy, the TCs density of the endometrium significantly increases, whereas the myometrial TCs density significantly decreases as compared to the non-pregnant uteri.[23] Alternatively, oxidative stress and aging affect the morphology of TCs with the formation and migration of Tps of TCs.[17,24–26]

The Immunohistochemical Features of TCs

In the hematoxylin and eosin stained sections, it is hard to distinguish TCs from fibroblast-like stromal cells. The thickness of histological sections hinders capturing the entire 3D structures of the TCs and detecting the distribution of the Tps of these cells.[27] The immunohistochemistry combined with TEM represents a reliable method of identifying TCs. Variable immunohistochemical stains are used to label TCs in the human tissues as C-Kit/CD117, platelet-derived growth factor receptor α (PDGFR α), CD34, α-smooth muscle actin (α-SMA), and vimentin. However, none of these stains is specific by itself for the detection of TCs. Therefore double immunostaining methods such as CD34/vimentin, CD34/PDGFRα, or CD34/c-kit are more reliable for TCs detection.[24,28] A summary of the immunostains used to highlight TCs is presented in Table 3.

Table 1 The Distribution of the Telocytes in the Different Human Tissues and Their Cellular Interactions With Other Cells.

Organ	Localization	Associated cells	References
Heart	Endocardium, myocardium, and epicardium	Capillaries, nerves, lymphocytes, plasma, and satellite cells	7
Heart valves	Apex and base of all heart valves	Stem cells	58
Blood vessels	The surrounding muscle layer	Arterioles, capillaries, and venules	8
Lungs	Subepithelial stroma and bronchoalveolar junctions	Epithelial and stem cells	9
Meninges and choroid plexus	Interstitium	Blood vessels, ependymal, and stem cells	10
Skeletal muscle	Interstitium	capillaries, nerves, and the myocytes	9
Dermis	In the papillary and reticular dermis, around sebaceous and eccrine sweat glands, and perifollicular sheath	Immune and stem cells, blood vessels, and arrector pili muscles	11
Limbus and uvea	Conjuctival lamina propria, sclera, iris stroma, pars palana of ciliary body, and subcorneal epithelium	Epithelial and stromal stem cells, melanocytes, macrophages, and nerve fibers	59
Esophagus	Lamina propria and muscle layer	Lymphocytes, capillaries, and nerves	60
Duodenum	In lamina propria and surrounding the crypts	Immune cells, nerves, and blood vessels	6
Jejunum	Lamina propria and muscularis mucosae	Immune cells, nerve fibers, epithelial, and smooth muscle cells	61
Colon	Lamina propria	Muscle cells, nerve fibers, blood vessels, and epithelial stem cells	6
Parotid gland	Interacinar and subductal stroma	Acini, ducts, and blood vessels	12
Gall bladder	Sub epithelium and between smooth muscle fibers	Capillaries and smooth muscle cells, and nerve bundles	13
Pancreas	Exocrine pancreas	Acinar and ductal cells, and blood vessels	4
Bone marrow	Bone marrow	Capillaries and arterioles	16
Mammary gland	Stroma	Nerve fibers, immune cells, fibroblasts, and capillaries	15
Fallopian tube	Lamina propria and between smooth muscle fibers	Epithelial cells and capillaries	17
Myometrium	Between muscle fibers	Smooth muscle cells, nerves, and capillaries	14
Placenta	Connective tissue core of the villi	Vascular smooth muscle cells and collagen fibers	18
Kidney	Sub-capsular space	Macrophages	19
Urinary bladder	Smooth muscle bundles of muscularis mucosa	Nerve bundles, capillaries, and smooth muscle cells	19
Prostate	Stroma	Blood vessels, immune cells, and nerve bundles	62

The Organ-Specific Immunohistochemical Profiles of the Different Subtypes of TCs

There are also organ-specific subtypes of TCs, which display immunoreactivity for additional immunostains. For instance, TCs in the lung also express stem cell markers such as stem cell antigen-1 (Sca-1),[9,29] suggesting their role in tissue regeneration. TCs in the skeletal muscle express VEGF indicating their role in angiogenesis.[29] TCs from myometrium.[30] Fallopian tubes,[30] lamina propria of the renal pelvis, ureter, bladder, and urethra[31] express estrogen and progesterone steroid receptors indicating that these cells act as sensors for steroid hormones and modulate signal transduction through steroid receptors. In the intestine, TCs express Foxl1 protein that is required for stem cell maintenance.[32] In the spleen, the TCs express Nanog (a transcription factor involved in the self-renewal of undifferentiated embryonic stem cells) and Sca-1.[33] The cardiac TCs express CD34/c-kit, CD34/vimentin, and CD34/PDGFR-β positive.[34,35]

The Genes, Proteins, and MicroRNAs of the TCs

Song et al. examined the gene expression profiles (chromosomes 1, 2, 3, 17, and 18) in TCs of the mouse lung tissue.[36] They reported the upregulation of several genes in TCs such as collagen type IV, connective tissue growth factor, nidogen1, matrix metallopeptidases 3 and10, tissue inhibitor of metalloproteinase-3, and transgelinas as compared to the stromal cells. These genes have regulatory effects on

Table 2 The Ultrastructural Features of the Telocytes.

Features	Description	References
Location	-Non-epithelial spaces	17,20,22–26
Cellular contacts	-Epithelial cells, nerve fibers, capillaries, and smooth muscle cells	
Cell body	-Small cell body that measures about 9–15 μm. -The shape of the cellular body differs according to the number of Tps present, so the shape may be pyriform or spindle or triangular with 1 or 2 or 3 Tps respectively. If ≥3 Tps, the body may be stellate	
Nucleus	-Single, oval-shaped nucleus with condensed chromatin (40–45% euchromatin, and 55–60% heterochromatin) -No obvious nucleolus	
Cytoplasm	-Scanty cytoplasm that contains few organelles such as mitochondria, small Golgi apparatus, endoplasmic reticulum, microtubules, intermediate, and thin filaments -Several caveolae are detected on the cell membrane	
Cytoplasmic processes (Tps)	-Number: 1–5, average of 2–3 in the two-dimensional sections -Length: 10–1000 μm -Thickness: 0.05–0.2 μm -Branching: dichotomous branching pattern -Shape: alternating long thin segments called ''podomers'' (75–80 nm) and dilated segments called ''podoms'' (250–300 nm) creating a bead on a string pattern -Podoms contain the functional units needed for Ca^{2+} uptake/release, including mitochondria, endoplasmic reticulum, and caveolae -Podomers are anchored by homocellular and heterocellular junctions (allow interactions with the nerve bundles, blood capillaries, smooth muscle fibers, stem cells, and the extracellular matrix such as collagen and elastin fibers)	

Table 3 The Immunohistochemical Features of the TCs in the Different Human Tissues.

Organs	Immune profile of the telocytes	References
Heart	CD34, c-kit, and S100	7
Heart valves	CD34, c-kit, vimentin, and PDGFR-β	58
Lungs and trachea	CD34, c-kit, vimentin, PDGFR- β, Sca-1, and VEGF	9,29
Meninges and choroid plexus	C-Kit	10
Gastrointestinal tract(lamina propria)	CD34, c-kit, vimentin, PDGFRα, FOXL1, GLI1, SOX6, and CD90	32,63,64
Gall bladder	CD34, c-kit, and vimentin	13
Salivary glands	c-kit, vimentin, and α-SMA	12,65
Pancreas	CD34, c-kit, vimentin, occasional α-SMA, and S100	65
Myometrium	CD34 and c-kit	66
Placenta	CD34, c-kit, and vimentin	18
Fallopian tube	CD34, c-kit, S100, and occasionally vimentin	17
Ureter and urinary bladder	Double positivity for CD34/calreticulin, and PDGFRα/calreticulin	67
Kidney	CD34, c-kit, and vimentin	68
Skin	CD34, c-kit, and vimentin	11
Striated muscle	c-kit, PDGFR- β, vimentin, caveolin-1, and VEGF	29

cell signaling, division, migration, adhesion, embryogenesis, and tissue repair. They also have essential roles in tissue homeostasis, immune modulation, and maintenance of the oxidative microenvironment. Accordingly, they can prevent tumorigenesis and anti-inflammatory responses.[36] The TCs also express many pro-angiogenic microRNAs (miR126, miR-21, miR130a, miR-143, miR-503, miR-27b, miR-199a, and miR-100).[37,38]

The Functions of the TCs in Human biology

TCs have several functions, as summarized in Table 4, including (i) cell-to-cell communication and signaling, (ii) mechanical support and organ structure, (iii) tissue repair, angiogenesis, regeneration, and homeostasis, (iv) immune modulation and surveillance, and (v) hormone sensors in the female reproductive tract.

Table 4 Functions of Telocytes in Human Biology.

Function	Mechanism and effect	References
Cell-to-cell communication and signaling with homo- or heterogenous neighboring cells	The signaling is established by the gap junctions which facilitate direct contact among the cells and allow the passage of ions and molecules (e.g., proteins or microRNA) among them	24
Mechanical support of the different tissues	The distinct 3D structure of TCs and their ability to connect the surrounding cells provide structural support throughout the different tissues. For example, TCs can establish mechanical support to protect against bladder wall deformation during distension and relaxation	67
Tissue repair, angiogenesis, regeneration, and homeostasis	These roles are mediated by two mechanisms:	
	-First: following tissue damage, the TCs act as CD34-positive progenitor cells that become activated with their subsequent proliferation, alterations in their morphology, distribution, and the differentiation into other cell types.	69,70
	-Second: the TCs act as interstitial cells within stem cell niches (microenvironment for stem cells) where they are integrated with stem cells and other components of the niche such as extracellular matrix and blood vessels. The TCs in the niches carry out several functions including the homeostatic control, support, nurse, signal induction, and regulation	71,72
Immune modulation and surveillance	-The TCs can activate several immune cells (lymphocytes, mast cells, macrophages and eosinophils) by secretion of several cytokines such as IL-10, IL1-R1, TNFα, and IL-6, and therefore, they play some roles in immune regulation	73
	-The TCs constitute a functional component of the main immunologic barriers in the human tissues as the blood-testis barrier and blood-myocardium barrier	74
Hormone sensors in the female reproductive tract	TCs can express estrogen and progesterone receptors and they might regulate myometrial contractions and fallopian tube motility by gap junctions or juxtacrine and/or paracrine signaling	30

The TCs Associated Pathological Conditions ''Telocytopathies''

Alterations of the TCs occur in several diseases and are collectively known as ''telocytopathies''. A summary of these conditions is presented in Table 5. There is significant functional disturbance and loss of TCs in several chronic inflammatory and fibrotic diseases. These include scleroderma, primary Sjögren's syndrome, ulcerative colitis, Crohn's disease, and liver fibrosis. It is unclear whether this deranged function and quantitative loss are the primary cause of disease development or occur as a result of other unknown factors that disrupt the cellular microenvironment with subsequent TCs loss.[39] Some tumors arise from TCs (telocytomas), such as gastrointestinal stromal tumors (GISTs), inflammatory fibroid polyps of the gastrointestinal tract, and extra-gastrointestinal stromal tumors.[40] These neoplasms bear PDGFRα mutation, one of the specific antigens of TCs in the gastrointestinal tract.[41] Some extra-gastrointestinal stromal tumors (eGISTs) in the prostate,[42] uterus,[43] and vagina[44] arise from the TCs because these tumors and TCs share the expression of c-kit (CD117) protein.[6] In 2018, Ricci et al. suggested the term ''telocytoma'' for tumors with possible telocytic origin.[40] In lobular breast carcinoma, there is a proliferative effect of TCs by secreting extracellular vesicles suggesting that TCs have been activated at the wrong time and place.[45]

The Cutaneous TCs

The human skin is the body's largest organ, and an insight into the biology of the dermal TCs will improve our understanding of the basic mechanisms of cutaneous homeostasis.

The Distribution of TCs in the Normal Human skin

Histologically, TCs are finely distributed throughout the dermis of normal skin. They appear as spindle-shaped cells. They are located mainly in the reticular dermis surrounding the blood vessels. The TCs form 2–3 incomplete concentric sheaths around the dermal structures, including the sebaceous glands, eccrine sweat glands, arrector pili muscles, and within the perifollicular sheath. In the papillary dermis, the density of the TCs is gradually reduced toward the dermo-epidermal junction. The epidermis is devoid of the TCs.[11]

Table 5 The Pathological Conditions (Telopathies) Associated With the Dystrophy (Altered Functions) and Decreased Density of the Telocytes.

Organs	Diseases (telocytopathies)	References
Skin	Squamous cell carcinoma, basal cell carcinoma, psoriasis, and systemic sclerosis	51,52 47,49,50
Intestine	Inflammatory bowel diseases (ulcerative colitis, and Crohn's disease)	75,76
Salivary glands	Sjögren's disease	77
Gastric antrum	Inflammatory fibroid polyp	43
Gallbladder	Gallstones	78
Pancreas	Extra-gastrointestinal stromal tumor.	79
Kidney	Uretero-pelvic junction obstruction.	80
Urinary bladder	Neurogenic detrusor over-activity	81
Lung	Fibrosis after pneumonia	82
Testis	Hyperplasia of the Leydig cells in undescended testes(cryptorchidism)	83
Prostate gland	Prostate cancer and benign prostate hyperplasia	84
Uterus	Leiomyomas	85
Fallopian tube	Endometriosis, tubal damage, and infertility	86
Ovary	Premature ovarian failure	87
Placenta	Preeclampsia	88
Breast	Breast cancer	45
Eye	Keratoconus	89
Heart	Heart failure and arrhythmia	90
Connective tissue	Various degenerative changes	91

The Immunohistochemical Features of the Subtypes of the Cutaneous TCs

The immunophenotypic features of the cutaneous TCs differ according to their subtype and distribution. Two subtypes of cutaneous TCs have similar morphology but different immunophenotyping features. The first subtype is the CD34 and vimentin-positive TCs, which reside in the reticular dermis around sebaceous glands, hair follicles, arrector pili muscles, and sweat glands (Fig. 1). The second subtype is the CD117 and vimentin-positive TCs, which reside around the hair follicles and the sweat glands (Fig. 2). Some PDGFRα positive TCs reside in the papillary dermis.[11]

The Ultrastructural Features of the Cutaneous TCs

The dermal TCs with their characteristic long extensions (Tps) have similar ultrastructural features to TCs described in the other organs. In the skin, the Tps exhibit alternating thin fibrillar-like segments (podomeres) and dilated, cistern-like segments (podoms), which contain the mitochondria, endoplasmic reticulum, and caveolae. The podomere/podom structure imparts a moniliform appearance on the Tps.[11] Examining the 3D configuration of the dermal TCs using focus ion beam scanning electron microscopy (FIBSEM) revealed some interesting findings. They indicated that the TCs can shed microvesicles (>100 nm) rather than exosomes (<100 nm), and the Tps appear as uneven tubular-like structures with irregular dilations or variable ribbon-like segments.[22]

The Cytokine Expression Profile of the Cutaneous TCs

The TCs represent a distinct cell population that can be separated from other dermal stromal interstitial cells such as fibroblasts, dendritic cells, myofibroblasts, Langerhans cells using some immunohistochemical markers (Table 6). There are high expression levels of the epithelial neutrophil activated peptide (78ENA-78) and the granulocyte chemotactic protein (2GCP-2) cytokines in the TCs as compared to the stromal fibroblasts. The expression of these cytokines in the dermal TCs supports their roles in cutaneous homeostasis, angiogenesis, immune modulation, intercellular signaling, and carcinogenesis. Alternatively, the expression values of the cytokines involved in wound healing are higher in the dermal fibroblasts than in the TCs.[46]

The Biological Functions of the Cutaneous TCs

Although the exact biological functions of cutaneous TCs are still unclear, several studies have proposed some roles for these cells. The 3D configuration of the TCs maintains the microarchitecture of the dermis by supporting the networks between dermal collagen and elastic fibers.[47] The TCs act as nursing cells for the epithelial and dermal mesenchymal stem cells; therefore, the dermal TCs are involved in skin repair and regeneration. This biological function is reasoned to the fact that the Tps of the TCs enwrap clusters of the dermal stem cells near the hair follicle bulge, and this direct interaction supports their role as nursing cells.[48] The TCs play roles in immune modulation through

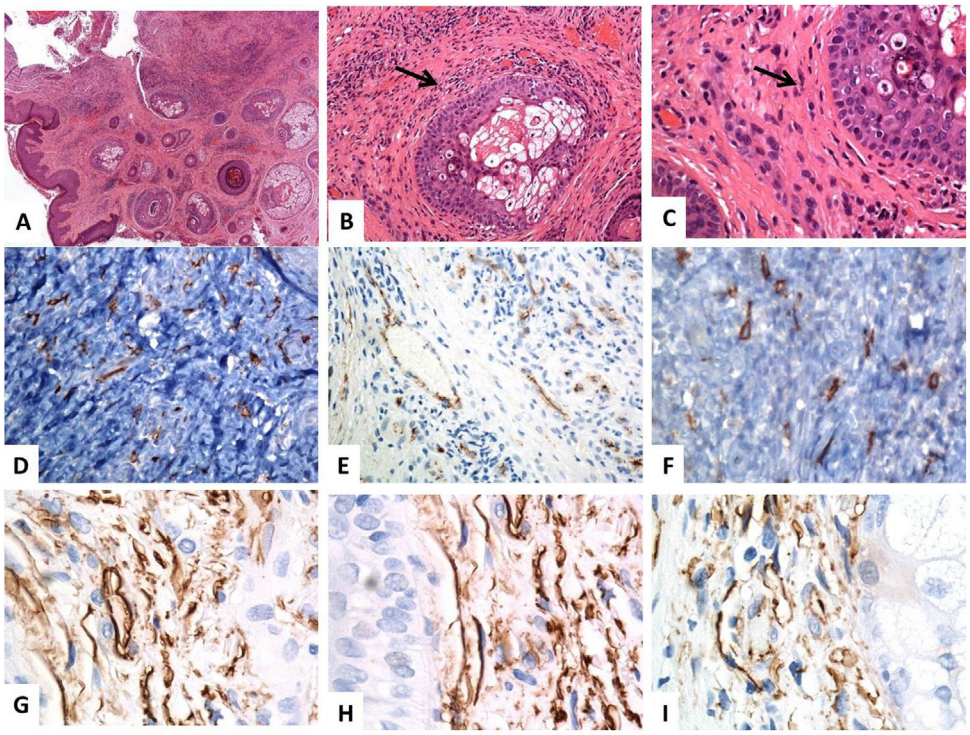


Figure 1 Histological and immunohistochemical (CD34) localization of the telocytes in normal skin. (A–C) Hematoxylin and eosin staining of the normal human skin, revealing unremarkable epidermis and dermal connective tissue. Within the dermal connective tissues, some spindle-shaped cells are finely distributed (arrows) throughout the dermis (original magnifications: A: ×40, B: ×200, C: ×400). (D–F) CD34 immunostain and the brown chromogendiaminobenzidine decorate the localization of several telocytes (TCs)/CD34-positive cells distributed throughout the dermis. The telocytes appear as spindle-shaped cells, having a nucleated oval or triangular cell body and thin, long, and varicose, moniliform tadpoles (original magnifications: D: ×400, E: ×400, F: ×600). (G–I) CD34-positive telocytes form an almost continuous layer around the basement membrane of the hair follicles (cells outer root sheath) and sebaceous glands (germinative layer) (original magnifications: G–I: ×1000, oil immersion).

Table 6 The Immunohistochemical Variations Among the Cutaneous TCs and the Surrounding Interstitial Cells.

Cell types	Immunohistochemical marker	References
Telocytes	PDGFRα and CD34	49
Fibroblasts	Procollagen-1	46
Endothelial cells	CD31	92
Myofibroblasts	αSMA	93
Pericytes	PDGFRβ, αSMA, CD146, NG2, and nestin	94
Macrophages	CD68, CD11c, CD11b, CD64, CD40, and CD14	95
Melanocytes	HMB45, S-100, and Melan-A	96
Langerhans cells	CD1a, S100, CD68, and Langerin	49
Stem cells	CD34, CD29, SCA-1, CD90, and CD44	97
Dermal dendritic cells	CD83, CD11c, and CD208	49
Plasmacytoid dendritic cells	CD205, CD11c, TNFα, and CD123	49
Inflammatory dendritic cells	CD209, CD11c, NOS, and CD14	49

the interaction of the dermal TCs through the heterocellular junctions with several dermal immune cells such as the macrophages and the mast cells. In support, the TCs are important immune modulators in some cutaneous allergic and autoimmune disorders.[11] The TCs support skin repair and regeneration. These cells can maintain vascular integrity and angiogenesis through their direct interactions with dermal endothelial cells.[49] Additionally, the TCs can modify the surrounding stromal cells. They control the fibroblasts's functions by secreting some paracrine signaling molecules such as microRNAs and shedding the extracellular vesicles.[11]

The Involvement of the Cutaneous TCs in Some Dermatoses

The TCs seem to be involved in the development of some dermatoses, such as psoriasis vulgaris and systemic

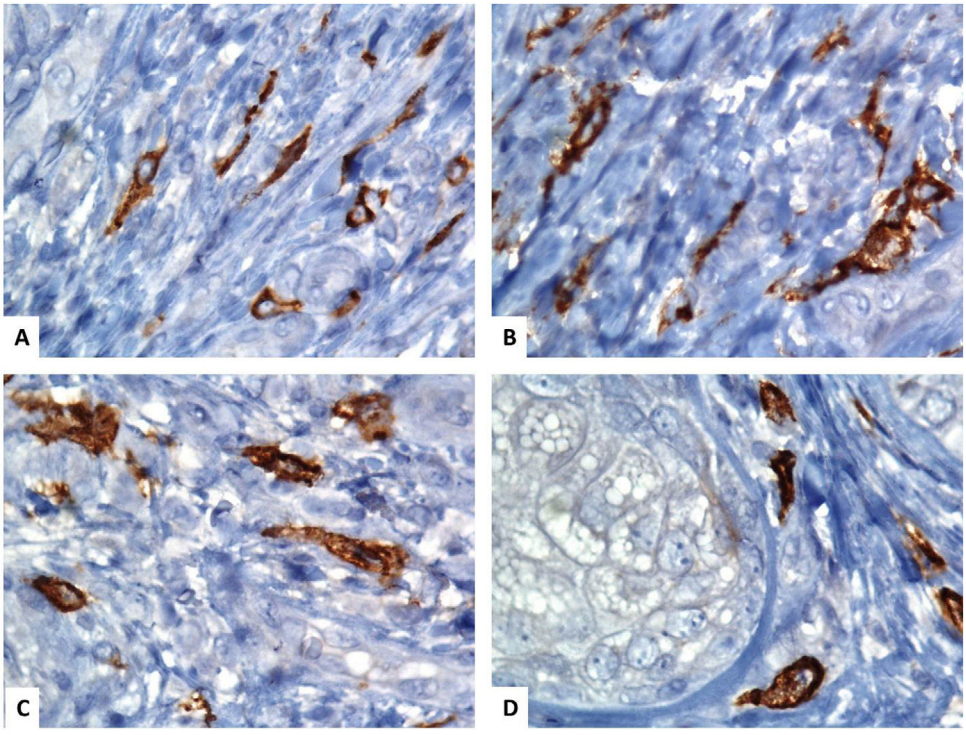


Figure 2 Immunohistochemical localization of the telocytes in the human normal skin using CD117 (C-KIT). (A–D) spindle-shaped telocytes (TCs) are stained by CD117and the brown chromogendiaminobenzidine. The TCs can be easily separated from the surrounding other stromal cells. The TCs have an elongated appearance with oval or triangular nuclei (counterstained with Mayer's hematoxylin) and long, varicose tadpole-like processes extending from their cell bodies (original magnification, ×1000, oil immersion).

sclerosis.[49,50] These disorders are associated with the dystrophy of the TCs and the reduction of their density in the lesional skin. In the psoriatic skin, there is dystrophy and a severe decrease in the number of TCs. Ultrastructurally, there are apoptotic nuclei, cytoplasmic disintegration, interrupted basement membranes, fragmented Tps, and loss of the homocellular junctions between TCs. The TCs in perilesional normal skin is structurally and numerically normal.[49] In psoriasis vulgaris, there is a papillary dermal vascular ectasia (vascularized dermal papillae) due to the loss of the contractile function of the vascular smooth muscle cells. The loss of the TCs around the blood vessels is implicated in this vascular ectasia and the characteristic ''Auspitz's sign'' seen in psoriasis. The disruption of the basement membrane of TCs in psoriasis facilitates the migration of the Langerhans cells from the epidermis to the dermis resulting in the activation of T cells. The alterations of the interactions between the TCs network and the T-cell mediated immune reaction are essential in the initiation and progression of psoriasis.[49,50]

Systemic sclerosis is a multi-organ disease characterized by excessive fibrosis, inflammation, and vasculopathy (due to endothelial cell injury). It involves the skin, heart, lung, esophagus, and kidney.[47] In systemic sclerosis, there is a loss of TCs and extensive fibrosis that disrupts the microanatomy of the dermis. The alterations of the TCs in systemic sclerosis include cytoplasmic vacuolation, swollen mitochondria, and lipofuscin bodies. These changes are reasoned to the ischemic damage of TCs resulting from the injury of the endothelial cells and oxygen deprivation. In the early phases of systemic sclerosis, the density of the TCs around hair follicles, sebaceous glands, arterioles, and nerves are reduced in the reticular dermis and are absent in the papillary dermis. The disease progression is associated with the loss of most dermal TCs except for a few cells around the eccrine sweat glands. The loss of TCs is reasoned to the associated ischemic changes.[47] The TCs enwrap collagen and elastic fibers in the dermis, and therefore the alterations of the TCs also affect the extracellular matrix since TCs enwrap collagen and elastic fibers.[47]

The Involvement of the TCs in Cutaneous Squamous and Basal Cell Carcinomas

To date, our knowledge about the roles of the TCs in cutaneous carcinogenesis is largely unknown. It is well-known that a limitation of cell-cell contact is the hallmark of invasive carcinomas. Several observations support the roles of TCs in the development of cutaneous carcinomas. For instance, the presence of TCs in the tumor stroma of the cutaneous squamous cell carcinoma and basal cell carcinoma.[51] In these carcinomas, there is a decreased density of the heterocellular junctions among the TCs and the peritumoral stromal cells. Alternatively, the homocellular junctions are preserved. The TCs-mast cell junctions are also lost, which results in the loss of control over the secretion of the mast's cell granules and the overexpression of inflammatory mediators in the tumor stroma.

Furthermore, TCs-endothelial cell junctions are lost in these tumors. The loss of the heterocellular junctions of TCs result from the loss of TCs functions in the tumor stroma. The TCs can exert paracrine function by shedding extracellular microvesicles in these tumors.[51] These microvesicles transfer signals are required for cancer cell motility, tumor progression, and metastasis. Therefore, the TCs are involved in tumor development and progression.[51,52]

The Implications of TCs As a Targeted Therapy

The TCs play important roles in tissue repair, homeostasis, and regeneration through their communication with stem and progenitor cells. The TCs express stem cell markers (Sca-1, c-kit, and Oct 4), and as such, they represent promising future players in the field of regenerative medicine.[9,53] The TCs also express VEGF and PDGFR-β, which promote angiogenesis during tissue repair processes.[53] Therefore, the TCs represent a novel therapeutic target.[54] Several observations support this notion. In a murine model of the partial hepatectomy, the TCs stimulate the proliferation and regeneration of hepatocytes and progenitor cells to restore liver size.[55] The transplantation of TCs in an experimental model of asthma can improve airway hyper-responsiveness and inflammation through suppression of Th2 cell differentiation and stimulation of Th1 cells and their related cytokines. Therefore, transplantation of these TCs represents a new therapeutic strategy in bronchial asthma.[56] In the experimental models of the myocardial infarction, the direct injection of the TCs into the damaged cardiac muscle was associated with regeneration and a decrease in the size of the infracted areas.[57]

To conclude, the TCs are novel interstitial cells widely distributed not only in the gut but also in most human organs. They have specific immunohistochemical and ultrastructural features that help separate them from other interstitial cells.

Several research issues should be addressed by future research such as (i) whether TCs represent a homogeneous population of cells or heterogeneous subpopulations of cells specific for each organ; (ii) what are the specific immunohistochemical markers of the TC to facilitate its identification; (iii) what is the exact role of TCs in the neoplastic and non-neoplastic conditions, and (iv) what are the therapeutic implications of TCs in human diseases. An improved understanding of these issues will help use the TCs as novel therapeutic targets in the future.

Conflict of Interests

The authors declare that they have no conflict of interest.

References

1. Ramón y Cajal S. Histologie du système nerveux de l'homme & des vertébrés. In: Ed. française rev. & mise à jour par l'auteur, tr. de l'espagnol par L. Azoulay. Maloine: edn. Paris; 1911.
2. Faussone Pellegrini MS, Cortesini C, Romagnoli P. Ultrastructure of the tunica muscularis of the cardial portion of the human esophagus and stomach, with special reference to the so-called Cajal's interstitial cells. Arch Ital Anat Embriol – Ital J Anat Embryol. 1977;82:157–77.
3. Lecoin L, Gabella G, Le Douarin N. Origin of the c-kit-positive interstitial cells in the avian bowel. Development. 1996;122:725–33.
4. Popescu LM, Hinescu ME, Ionescu N, Ciontea SM, Cretoiu D, Ardelean C. Interstitial cells of Cajal in pancreas. J Cell Mol Med. 2005;9:169–90.
5. Popescu LM, Faussone-Pellegrini MS. Telocytes – a case of serendipity: the winding way from interstitial cells of Cajal (ICC), via interstitial Cajal-like cells (ICLC) to telocytes. J Cell Mol Med. 2010;14:729–40.
6. Vannucchi MG, Traini C, Manetti M, Ibba-Manneschi L, Faussone-Pellegrini MS. Telocytes express PDGFRα in the human gastrointestinal tract. J Cell Mol Med. 2013;17:1099–108.
7. Gherghiceanu M, Manole CG, Popescu LM. Telocytes in endocardium: electron microscope evidence. J Cell Mol Med. 2010;14:2330–4.
8. Zhang H-Q, Lu S-S, Xu T, Feng Y-L, Li H, Ge J-B. Morphological evidence of telocytes in mice aorta. Chin Med J. 2015;128:348–52.
9. Popescu LM, Gherghiceanu M, Suciu LC, Manole CG, Hinescu ME. Telocytes and putative stem cells in the lungs: electron microscopy, electron tomography and laser scanning microscopy. Cell Tissue Res. 2011;345:391–403.
10. Popescu BO, Gherghiceanu M, Kostin S, Ceafalan L, Popescu LM. Telocytes in meninges and choroid plexus. Neurosci Lett. 2012;516:265–9.
11. Ceafalan L, Gherghiceanu M, Popescu LM, Simionescu O. Telocytes in human skin – are they involved in skin regeneration? J Cell Mol Med. 2012;16:1405–20.
12. Nicolescu MI, Bucur A, Dinca O, Rusu MC, Popescu LM. Telocytes in parotid glands. Anat Rec. 2012;295:378–85.
13. Hinescu ME, Ardeleanu C, Gherghiceanu M, Popescu LM. Interstitial Cajal-like cells in human gallbladder. J Mol Histol. 2007;38:275–84.
14. Ciontea SM, Radu E, Regalia T, Ceafalan L, Cretoiu D, Gherghiceanu M, et al. C-kit immunopositive interstitial cells (Cajal-type) in human myometrium. J Cell Mol Med. 2005;9:407–20.
15. Gherghiceanu M, Popescu LM. Interstitial Cajal-like cells (ICLC) in human resting mammary gland stroma. Transmission electron microscope (TEM) identification. J Cell Mol Med. 2005;9:893–910.
16. Li H, Zhang H, Yang L, Lu S, Ge J. Telocytes in mice bone marrow: electron microscope evidence. J Cell Mol Med. 2014;18:975–8.
17. Popescu LM, Ciontea SM, Cretoiu D. Interstitial Cajal-like cells in human uterus and fallopian tube. Ann N Y Acad Sci. 2007;1101:139–65.
18. Suciu L, Popescu LM, Gherghiceanu M, Regalia T, Nicolescu MI, Hinescu ME, et al. Telocytes in human term placenta: morphology and phenotype. Cells Tissues Organs. 2010;192:325–39.
19. Zheng Y, Zhu T, Lin M, Wu D, Wang X. Telocytes in the urinary system. J Transl Med. 2012;10:188.
20. Cretoiu D, Hummel E, Zimmermann H, Gherghiceanu M, Popescu LM. Human cardiac telocytes: 3D imaging by FIB-SEM tomography. J Cell Mol Med. 2014;18:2157–64.
21. Albulescu R, Tanase C, Codrici E, Popescu DI, Cretoiu SM, Popescu LM. The secretome of myocardial telocytes modulates the activity of cardiac stem cells. J Cell Mol Med. 2015;19:1783–94.
22. Cretoiu D, Gherghiceanu M, Hummel E, Zimmermann H, Simionescu O, Popescu LM. FIB-SEM tomography of human skin telocytes and their extracellular vesicles. J Cell Mol Med. 2015;19:714–22.
23. Roatesi I, Radu BM, Cretoiu D, Cretoiu SM. Uterine telocytes: a review of current knowledge. Biol Reprod. 2015;93:10.

24. Kondo A, Kaestner KH. Emerging diverse roles of telocytes. Development. 2019;146:dev175018.
25. Enciu AM, Popescu LM. Telopodes of telocytes are influenced in vitro by redox conditions and ageing. Mol Cell Biochem. 2015;410:165–74.
26. Vannucchi MG. The telocytes: ten years after their introduction in the scientific literature. An update on their morphology, distribution, and potential roles in the gut. Int J Mol Sci. 2020;21:4478.
27. Manole CG, Simionescu O. The cutaneous telocytes. Adv Exp Med Biol. 2016;913:303–23.
28. Cretoiu SM, Popescu LM. Telocytes revisited. Biomol Concepts. 2014;5:353–69.
29. Popescu LM, Manole E, Serboiu CS, Manole CG, Suciu LC, Gherghiceanu M, et al. Identification of telocytes in skeletal muscle interstitium: implication for muscle regeneration. J Cell Mol Med. 2011;15:1379–92.
30. Cretoiu SM, Cretoiu D, Suciu L, Popescu LM. Interstitial Cajal-like cells of human Fallopian tube express estrogen and progesterone receptors. J Mol Histol. 2009;40:387–94.
31. Gevaert T, De Vos R, Van Der Aa F, Joniau S, van den Oord J, Roskams T, et al. Identification of telocytes in the upper lamina propria of the human urinary tract. J Cell Mol Med. 2012;16:2085–93.
32. Shoshkes-Carmel M, Wang YJ, Wangensteen KJ, Tóth B, Kondo A, Massasa EE, et al. Subepithelial telocytes are an important source of Wnts that supports intestinal crypts. Nature. 2018;557:242–6.
33. Zhang B, Yang C, Qiao L, Li Q, Wang C, Yan X, et al. Telocytes: a potential defender in the spleen of Npc1 mutant mice. J Cell Mol Med. 2017;21:848–59.
34. Bei Y, Zhou Q, Fu S, Lv D, Chen P, Chen Y, et al. Cardiac telocytes and fibroblasts in primary culture: different morphologies and immunophenotypes. PLOS ONE. 2015;10:e0115991.
35. Zhou Q, Wei L, Zhong C, Fu S, Bei Y, Huică RI, et al. Cardiac telocytes are double positive for CD34/PDGFR-α. J Cell Mol Med. 2015;19:2036–42.
36. Song D, Cretoiu D, Zheng M, Qian M, Zhang M, Cretoiu SM, et al. Comparison of Chromosome 4 gene expression profile between lung telocytes and other local cell types. J Cell Mol Med. 2016;20:71–80.
37. Cismașiu VB, Popescu LM. Telocytes transfer extracellular vesicles loaded with microRNAs to stem cells. J Cell Mol Med. 2015;19:351–8.
38. Cismasiu VB, Radu E, Popescu LM. miR-193 expression differentiates telocytes from other stromal cells. J Cell Mol Med. 2011;15:1071–4.
39. Varga I, Polak S, Kyselovic J, Kachlik D, Danisovic L, Klein M. Recently discovered interstitial cell population of telocytes: distinguishing facts from fiction regarding their role in the pathogenesis of diverse diseases called ''telocytopathies''. Medicina (Kaunas, Lithuania). 2019;55(2.).
40. Ricci R, Giustiniani MC, Gessi M, Lanza P, Castri F, Biondi A, et al. Telocytes are the physiological counterpart of inflammatory fibroid polyps and PDGFRA-mutant GISTs. J Cell Mol Med. 2018;22:4856–62.
41. Padhi S, Nayak HK. Primary extragastrointestinal stromal tumours in the hepatobiliary tree and telocytes. Adv Exp Med Biol. 2016;913:207–28.
42. You YH, Zhang Y. Primary prostatic extragastrointestinal stromal tumor: a case report and literature review. J Int Med Res. 2018;46:4343–9.
43. Peitsidis P, Zarganis P, Trichia H, Vorgias G, Smith JR, Akrivos T. Extragastrointestinal stromal tumor mimicking a uterine tumor. A rare clinical entity. Int J Gynecol Cancer. 2008;18:1115–8.
44. Liu QY, Kan YZ, Zhang MY, Sun TY, Kong LF. Primary extragastrointestinal stromal tumor arising in the vaginal wall: significant clinicopathological characteristics of a rare aggressive soft tissue neoplasm. World J Clin Cases. 2016;4:118–23.
45. Mou Y, Wang Y, Li J, Lü S, Duan C, Du Z, et al. Immunohistochemical characterization and functional identification of mammary gland telocytes in the self-assembly of reconstituted breast cancer tissue in vitro. J Cell Mol Med. 2013;17:65–75.
46. Kang Y, Zhu Z, Zheng Y, Wan W, Manole CG, Zhang Q. Skin telocytes versus fibroblasts: two distinct dermal cell populations. J Cell Mol Med. 2015;19:2530–9.
47. Manetti M, Guiducci S, Ruffo M, Rosa I, Faussone-Pellegrini MS, Matucci-Cerinic M, et al. Evidence for progressive reduction and loss of telocytes in the dermal cellular network of systemic sclerosis. J Cell Mol Med. 2013;17:482–96.
48. Manole CG, Simionescu O. The cutaneous telocytes. In: Wang X, Cretoiu D, editors. Telocytes: connecting cells. Singapore: Springer Singapore; 2016. p. 303–23.
49. Manole CG, Gherghiceanu M, Simionescu O. Telocyte dynamics in psoriasis. J Cell Mol Med. 2015;19:1504–19.
50. Tirumalae R. Psoriasiform dermatoses: microscopic approach. Indian J Dermatol. 2013;58:290–3.
51. Mirancea N, Morosanu AM, Mirancea GV, Juravle FD, Manoiu VS. Infrastructure of the telocytes from tumor stroma in the skin basal and squamous cell carcinomas. Rom J Morphol Embryol. 2013;54:1025–37.
52. Smythies J. Intercellular signaling in cancer – the SMT and TOFT hypotheses, exosomes, telocytes and metastases: is the messenger in the message? J Cancer. 2015;6:604–9.
53. Bei Y, Wang F, Yang C, Xiao J. Telocytes in regenerative medicine. J Cell Mol Med. 2015;19:1441–54.
54. Boos AM, Weigand A, Brodbeck R, Beier JP, Arkudas A, Horch RE. The potential role of telocytes in tissue engineering and regenerative medicine. Semin Cell Dev Biol. 2016;55:70–8.
55. Wang F, Song Y, Bei Y, Zhao Y, Xiao J, Yang C. Telocytes in liver regeneration: possible roles. J Cell Mol Med. 2014;18:1720–6.
56. Ye L, Song D, Jin M, Wang X. Therapeutic roles of telocytes in OVA-induced acute asthma in mice. J Cell Mol Med. 2017;21:2863–71.
57. Zhao B, Chen S, Liu J, Yuan Z, Qi X, Qin J, et al. Cardiac telocytes were decreased during myocardial infarction and their therapeutic effects for ischaemic heart in rat. J Cell Mol Med. 2013;17:123–33.
58. Yang Y, Sun W, Wu SM, Xiao J, Kong X. Telocytes in human heart valves. J Cell Mol Med. 2014;18:759–65.
59. Luesma MJ, Gherghiceanu M, Popescu LM. Telocytes and stem cells in limbus and uvea of mouse eye. J Cell Mol Med. 2013;17:1016–24.
60. Chen X, Zheng Y, Manole CG, Wang X, Wang Q. Telocytes in human oesophagus. J Cell Mol Med. 2013;17:1506–12.
61. Cretoiu D, Cretoiu S, Simionescu AA, Popescu L. Telocytes, a distinct type of cell among the stromal cells present in the lamina propria of jejunum. Histol Histopathol. 2012;27:1067–78.
62. Corradi LS, Jesus MM, Fochi RA, Vilamaior PSL, Justulin LA, Góes RM, et al. Structural and ultrastructural evidence for telocytes in prostate stroma. J Cell Mol Med. 2013;17:398–406.
63. Greicius G, Kabiri Z, Sigmundsson K, Liang C, Bunte R, Singh MK, et al. PDGFRα(+) pericryptal stromal cells are the critical source of Wnts and RSPO3 for murine intestinal stem cells in vivo. Proc Natl Acad Sci U S A. 2018;115:E3173–81.
64. Karpus ON, Westendorp BF, Vermeulen JLM, Meisner S, Koster J, Muncan V, et al. Colonic CD90+ crypt fibroblasts secrete semaphorins to support epithelial growth. Cell Rep. 2019;26, 3698–3708.e5.
65. Nicolescu MI, Popescu LM. Telocytes in the interstitium of human exocrine pancreas: ultrastructural evidence. Pancreas. 2012;41:949–56.
66. Cretoiu SM, Cretoiu D, Marin A, Radu BM, Popescu LM. Telocytes: ultrastructural, immunohistochemical and electrophysiological

characteristics in human myometrium. Reproduction (Cambridge, England). 2013;145:357–70.
67. Vannucchi MG, Traini C, Guasti D, Del Popolo G, Faussone-Pellegrini MS. Telocytes subtypes in human urinary bladder. J Cell Mol Med. 2014;18:2000–8.
68. Qi G, Lin M, Xu M, Manole CG, Wang X, Zhu T. Telocytes in the human kidney cortex. J Cell Mol Med. 2012;16:3116–22.
69. diaz-flores L, Gutiérrez R, Garcia MP, González M, Sáez F, Aparicio F, et al. Human resident CD34+ stromal cells/telocytes have progenitor capacity and are a source of αSMA+ cells during repair. Histol Histopathol. 2014:30.
70. Vannucchi MG, Bani D, Faussone-Pellegrini MS. Telocytes contribute as cell progenitors and differentiation inductors in tissue regeneration. Curr Stem Cell Res Ther. 2016;11:383–9.
71. Diaz-Flores L, Gutierrez R, Garcia MP, Saez FJ, Aparicio F, Diaz-Flores L Jr, et al. Uptake and intracytoplasmic storage of pigmented particles by human CD34+ stromal cells/telocytes: endocytic property of telocytes. J Cell Mol Med. 2014;18:2478–87.
72. Diaz-Flores L, Gutierrez R, Garcia MP, Saez FJ, Diaz-Flores L Jr, Valladares F, et al. CD34+ stromal cells/fibroblasts/fibrocytes/telocytes as a tissue reserve and a principal source of mesenchymal cells. Location, morphology, function and role in pathology. Histol Histopathol. 2014;29:831–70.
73. Chi C, Jiang XJ, Su L, Shen ZJ, Yang XJ. In vitro morphology, viability and cytokine secretion of uterine telocyte-activated mouse peritoneal macrophages. J Cell Mol Med. 2015;19:2741–50.
74. Aleksandrovych V, Pasternak A, Basta P, Sajewicz M, Walocha JA, Gil K. Telocytes: facts, speculations and myths (review article). Folia Med Cracov. 2017;57:5–22.
75. Manetti M, Rosa I, Messerini L, Ibba-Manneschi L. Telocytes are reduced during fibrotic remodelling of the colonic wall in ulcerative colitis. J Cell Mol Med. 2015;19:62–73.
76. Wang XY, Zarate N, Soderholm JD, Bourgeois JM, Liu LW, Huizinga JD. Ultrastructural injury to interstitial cells of Cajal and communication with mast cells in Crohn's disease. Neurogastroenterol Motil. 2007;19:349–64.
77. Alunno A, Ibba-Manneschi L, Bistoni O, Rosa I, Caterbi S, Gerli R, et al. Telocytes in minor salivary glands of primary Sjögren's syndrome: association with the extent of inflammation and ectopic lymphoid neogenesis. J Cell Mol Med. 2015.
78. Matyja A, Gil K, Pasternak A, Sztefko K, Gajda M, Tomaszewski KA, et al. Telocytes: new insight into the pathogenesis of gallstone disease. J Cell Mol Med. 2013;17:734–42.
79. Padhi S, Sarangi R, Mallick S. Pancreatic extragastrointestinal stromal tumors, interstitial cajal like cells, and telocytes. JOP: Journal of the pancreas. 2013;14:1–14.
80. Mehrazma M, Tanzifi P, Rakhshani N. Changes in structure, interstitial Cajal-like cells and apoptosis of smooth muscle cells in congenital ureteropelvic junction obstruction. Iran J Pediatr. 2014;24:105–10.
81. Gevaert T, De Vos R, Everaerts W, Libbrecht L, Van Der Aa F, van den Oord J, et al. Characterization of upper lamina propria interstitial cells in bladders from patients with neurogenic detrusor overactivity and bladder pain syndrome. J Cell Mol Med. 2011;15:2586–93.
82. Sun X, Zheng M, Zhang M, Qian M, Zheng Y, Li M, et al. Differences in the expression of chromosome 1 genes between lung telocytes and other cells: mesenchymal stem cells, fibroblasts, alveolar type II cells, airway epithelial cells and lymphocytes. J Cell Mol Med. 2014;18:801–10.
83. Díaz-Flores L, Gutiérrez R, Díaz-Flores L Jr, Goméz MG, Sáez FJ, Madrid JF. Behaviour of telocytes during physiopathological activation. Semin Cell Dev Biol. 2016;55:50–61.
84. Gevaert T, Lerut E, Joniau S, Franken J, Roskams T, De Ridder D. Characterization of subepithelial interstitial cells in normal and pathological human prostate. Histopathology. 2014;65:418–28.
85. Varga I, Klein M, Urban L, Danihel L Jr, Polak S, Danihel L Sr. Recently discovered interstitial cells ''telocytes'' as players in the pathogenesis of uterine leiomyomas. Med Hypotheses. 2018;110:64–7.
86. Klein M, Lapides L, Fecmanova D, Varga I. From telocytes to telocytopathies. Do recently described interstitial cells play a role in female idiopathic infertility? Medicina (Kaunas, Lithuania). 2020;56.
87. Liu T, Wang S, Li Q, Huang Y, Chen C, Zheng J. Telocytes as potential targets in a cyclophosphamide-induced animal model of premature ovarian failure. Mol Med Rep. 2016;14:2415–22.
88. Bosco C, Diaz E, Gutiérrez R, González Montero J, Parra-Cordero M, Rodrigo R, et al. A putative role for telocytes in placental barrier impairment during preeclampsia. Med Hypotheses. 2014:84.
89. Marini M, Mencucci R, Rosa I, Favuzza E, Guasti D, Ibba-Manneschi L, et al. Telocytes in normal and keratoconic human cornea: an immunohistochemical and transmission electron microscopy study. J Cell Mol Med. 2017;21:3602–11.
90. Richter M, Kostin S. The failing human heart is characterized by decreased numbers of telocytes as result of apoptosis and altered extracellular matrix composition. J Cell Mol Med. 2015;19:2597–606.
91. Szotek S, Dawidowicz J, Eyden B, Matysiak N, Czogalla A, Dudzik G, et al. Morphological features of fascia lata in relation to fascia diseases. Ultrastruct Pathol. 2016;40:297–310.
92. Lertkiatmongkol P, Liao D, Mei H, Hu Y, Newman PJ. Endothelial functions of platelet/endothelial cell adhesion molecule-1 (CD31). Curr Opin Hematol. 2016;23:253–9.
93. Ehrlich HP, Allison GM, Leggett M. The myofibroblast, cadherin, alpha smooth muscle actin and the collagen effect. Cell Biochem Funct. 2006;24:63–70.
94. Nakagawa S, Miki Y, Miyashita M, Hata S, Takahashi Y, Rai Y, et al. Tumor microenvironment in invasive lobular carcinoma: possible therapeutic targets. Breast Cancer Res Treat. 2016;155:65–75.
95. Misharin AV, Morales-Nebreda L, Mutlu GM, Budinger GR, Perlman H. Flow cytometric analysis of macrophages and dendritic cell subsets in the mouse lung. Am J Respir Cell Mol Biol. 2013;49:503–10.
96. Orchard GE. Comparison of immunohistochemical labelling of melanocyte differentiation antibodies melan-A, tyrosinase and HMB 45 with NKIC3 and S100 protein in the evaluation of benign naevi and malignant melanoma. Histochem J. 2000;32:475–81.
97. Lui PP. Markers for the identification of tendon-derived stem cells in vitro and tendon stem cells in situ – update and future development. Stem Cell Res Ther. 2015;6:106.