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Review

Telocytes heterogeneity: From cellular morphology to functional evidence

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ABSTRACT

Telocytes (TCs), located ubiquitously in the internal organs of vertebrates, are a heterogeneous, recently described, cell population of the stromal space. Characterized by lengthy cytoplasmic extensions that can reach tens of microns and are called telopodes (Tps), TCs are difficult to see using conventional microscopes. It was the electron microscopy which led to their first identification and Popescu's team the first responsible for the reconstructions indicating TCs 'organization' in a three-dimensional (3D) network that is believed to be accountable for the complex roles of TCs. Gradually, it became increasingly evident that TCs are difficult to characterize in terms of immunophenotype and that their phenotype is different depending on the location and needs of the tissue at one time. This review discusses the growing body of evidence accumulated since TCs were discovered and highlights how the complex interplay between TCs and stem cells might be of importance for tissue engineering and regenerative medicine.

Contents

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1. Brief history of telocytes discovery

Telocytes (TCs) are a specialized type of stromal (interstitial) cells discovered through serendipity [1]. These cells form extensive networks in the interstitium of mammalian, birds and reptiles organs and are different from fibroblasts, mesenchymal stem cells and endothelial cells [2,3]. Their discovery is modern, taking place 10 years ago. In 2005 Popescu and his team in Bucharest observed, in human and rat pancreas, cells which shared common (morphological and immunohistochemical) characteristics with interstitial cells of Cajal (ICC) [4]. In the digestive tube ICCs were known as having the role of pacemaker because they are electrically coupled to smooth muscle cells (for review see Refs. [5–7]). Therefore, at that time it was considered that organs lacking visceral muscles also lack ICCs. The presence of some cells with apparently similar ultrastructural and immunohistochemical features to ICCs in the pancreas was considered as peculiar [8]. In the following years, Popescu's team extended their search for interstitial Cajal-like cells to other extra-digestive organs (uterus, fallopian tube, mammary gland, heart) [9–14]. After five years they realized (with the help of Faussone-Pellegrini in Florence, a recognized researcher in the field of ICC), that they discovered something new without looking for it. At that time Popescu suggested naming these serendipitously discovered cells as TELOCYTES based on their long extensions called telopodes (by using the Greek affix 'telos' = distance) [15]. He used to say "the shortest definition for a telocyte is a cell with telopodes". The term is considered to be suggestive of the TCs function of controlling the microenvironment locally or remotely, was quickly embraced by the scientific community of those who studies the stromal space and its cells. The uptrend that shows its use is illustrated by the chart displayed in Fig. 1. Nowadays, some people even consider that, for his discoveries, Popescu could have earned the Nobel Prize, if he had not passed too early [16,17]. Through hard work and perseverance, Popescu inspired numerous groups of researchers, nowadays TCs being studied all around the world as seen in Fig. 2.

2. Distribution, methods of investigation and morphology

2.1. Distribution

TCs reside in practically all organs that were searched for as we can visualize in Table 1. TCs are often located in close proximity to blood vessels and nerves, or underneath epithelia, or surrounding glandular structures [2].

2.2. Sample collection, culture and methods of investigation

Tissue samples are usually collected from humans, laboratory animals and agricultural animals under sterile conditions and in accordance with the International and Local Guidelines for the Care and Use of Mammals and in accordance with a protocol approved by the local Bioethics Committee after informed written consent from all human patients donating tissue samples. Samples are divided into appropriate-sized slices and used for different methods to identify TCs *in situ* or *in vitro*.

In situ methods are useful in pursuing the examination of TCs in the habitat where they naturally occur through various procedures: conventional and non-conventional histology, immunohistochemistry and electron microscopy [4,66]. These methods were initially used to identify and semi-quantitatively analyze these cell populations and are still used in any study regarding TCs [9,10]. Advances in electron microscopy imaging allowed to use in the study of TCs state-of-the-art microscopes and techniques *e.g.* electron tomography, focused ion beam scanning electron microscopy (FIB-SEM) tomography, to reveal the typical feature of TCs and their connection with other cells [79–81].

In vitro techniques use tissue samples within 30 min from harvesting which are collected into sterile tubes containing Dulbecco's Modified Eagle's Medium (DMEM), supplemented with 100 UI/ml penicillin, 0.1 mg/ml streptomycin, and 0.25 μg/ml amphotericin. These samples are then used either for tissue response experiments using complete tissue and organ bath – myograph systems or to obtain cell cultures. To investigate the involvement of TCs as possible pacemakers, the effect of imatinib mesylate (Glivec®) on the contractility pattern of human intestinal and myometrial specimens fragments was assessed by using standardized *in vitro* organ bath techniques [82,83].

The experimental protocol for cell cultures was described in detail in the first published articles on this topic [9,10]. Cells in culture are then observed and studied by techniques such as phase contrast microscopy, immunocytochemistry, immunofluorescence to identify their morphology and immunophenotype. Cultured TCs were also identified by flow-cytometric analysis and sorting. Fluorescent-activated cell sorting (FACS) with antibodies to CD34 and PDGFRα as the markers to identify and separate TCs was proved to be an efficient method to purify TCs [84]. TCs behavior in cell culture was observed by time-lapse videomicroscopy and showed in real-time the existing interactions between TCs and myocytes [48]. To identify some of the electrophysiological properties whole-cell patch voltage clamp and extracellular single unit recordings were used [10,48,85]. Laser capture microdissection performed on TCs in culture was used for RNA extraction, reverse-transcription and microRNA qPCR [86]. Using supernatants

Fig. 1. Diagram presenting the number of articles published in English retrieved by a search in the PubMed/Medline scientific database for entries 'telocytes in the title' or 'telocytes anywhere in text', for 2010–2016 period. For the 2016 total number of articles, a linear estimate using the first months was calculated.

Fig. 2. Mapping of the cities listed in authors affiliations in PubMed/Medline database of papers on telocytes topic as of August 2016. Geographic locations markers were placed on a Google map (Map data © 2016 Google, INEGI) using the free BatchGeo.com geocoding service (BatchGeo LLC, Seattle, WA, USA).

from cultured TCs their secretome was also analyzed by (i) high-sensitivity on-chip electrophoresis, (ii) surface-enhanced laser desorption/ionization time-of-flight mass spectrometry and (iii) multiplex analysis by Luminex-xMAP [87]. Also, proteins extracted from primary cultures of TCs were analyzed by automated 2-dimensional nano-electrospray ionization liquid chromatography tandem mass spectrometry (2D Nano-ESI LC–MS/MS) [88,89]. Gene Expression Array was used to analyze the gene expression profile of mouse lung TCs by comparison with mesenchymal stem cells and fibroblasts [90]. Cultivated TCs were similarly used for the investigation of features and patterns of TC-specific gene profiles and signatures in chromosomes 1–4,17,18,X. The functional and characteristic networks were identified and compared with other types of cells including mesenchymal stem cells, fibroblasts, alveolar type II cells, airway epithelial cells, and lymphocytes by bioinformatics tools [91–95].

Moreover, *in vivo* studies using rodents with experimental myocardial infarction following coronary ligation and injected intramyocardially with cardiac TCs were performed and are indicative of TCs involvement in the support and stimulation of the regenerative potential of the myocardium [96,97].

2.3. Cellular identification

2.3.1. Staining properties

At the beginning of their research, to demonstrate the presence of TCs both *in situ* and *in vitro*, Popescu and co-workers followed the original visualization methods described by Santiago Ramón y Cajal for ICC [5]. They proposed a diagnostic algorithm for TCs identification in four successive steps: (1) conventional light microscopy, after staining with methylene blue; (2) non-conventional light microscopy which involves semi-thin sections stained with Toluidine blue; (3) transmission electron microscopy (TEM) to reveal the criteria known as 'gold standard'; (4) immunohistochemistry for c-kit and CD34 [4]. A number of dyes have been used to observe and identify TCs *e.g.* methylene blue and Janus green B vital stainings, silver impregnation and crystal violet [9,10]. Methylene blue staining was a technique which allowed the observation of the "beads" of the moniliform Tps, while Janus green B and MitoTracker green FM were used to assess viability and localize mitochondria in TCs [9]. Silver impregnation is also useful in cell cultures, as well as are the vital dyes mentioned above [98].

Toluidine blue stained semi-thin sections have the advantage it can be examined under a standard light microscope. Spatial relationships between cellular components are better preserved and there are no significant overlapping structures, permitting a better observation with 100× objective (difficult in thin sections). Embedding in resins preserves cellular components better than paraffin embedding, offering a great definition of cellular details which is essential in the case of TCs. Light microscopy observation of a semi-thin section permits a precise determination of the area of interest. In our experience, a thickness between 0.5–1.5 μm is considered optimal for light microscopy examination due to an optimal ratio between thickness and staining (nor faint, nor excessive) and allowed good photomicrographs [13]. This technique is a problem-solving for picking areas of interest in the resin block before trimming down the block for ultra-thin sectioning and TEM examination.

2.3.2. Electron microscopy

TEM is essential to differentiate TCs from other types of interstitial cells [99]. The most common ultrastructural traits that define a telocyte are: (i) a tiny cell body (containing a small amount of cytoplasm and the nucleus) with variable shape depending on the number of Tps; (ii) several elongated slender Tps (tens to hundreds micrometers) with alternating regions of filamentous podomers and expanded podoms. However, other ultrastructural characteristics must be analyzed: the existence of an intermittent thin basal lamina; the existence of considerable amount of caveolae on the cell membrane (up to 2–3% on the cell body and an average of ~0.5 caveolae/μm of cell membrane); caveolae have a specific organization at podoms level where they form Ca^{2+} uptake/release units in association with endoplasmic reticulum and mitochondria; the existence within Tps or budding from their plasma membrane of small extracellular vesicles (exosomes or ectosomes, respectively) [48]. Moreover, Tps have a dichotomic branching pattern and form a labyrinthine network in the interstitial space [100].

Electron microscope tomography allows examination of 250-nm-thick sections. Its use favored the visualization of the "plug and socket" assembly connecting TCs in mouse parietal pleura (in a 0.5 μm^3 volume) [30]. With the aid of this technique details regarding homocellular communication between Tps (Fig. 3) and heterocellular contacts between Tps and stem cells and cardiomyocytes were elucidated [27,79].

FIB-SEM tomography is considered as a true revolution for ultrastructural volume 3D visualization and reconstruction. This technology was used to reconstruct a stack of 500 serial images corresponding to 10,908.57 μm^3 volume of human cardiac tissue and a stack of 275 serial images corresponding to 2270 μm^3 reconstructed volume of human dermis [80,81]. The 3D image of a telocyte revealed the fact that Tps actually look like very long, wavy and anfractuous ribbons [81].

Table 1
Anatomic locations of TCs.

System	Organ	References
Cardiovascular system	Heart (epicardium, myocardium, endocardium, valves)	[18–21]
	Vasculature (aorta, carotid artery, pulmonary veins, arterioles, venules and capillaries)	[22–25]
Respiratory system	Trachea and bronchi	[26]
	Lungs	[27–29]
	Pleura	[30]
Digestive system	Esophagus	[31,32]
	Stomach	[33]
	Duodenum	[34]
	Jejunum	[35]
	Colon	[36]
	Salivary glands	[37,38]
	Pancreas	[39,40]
	Gallbladder	[41,42]
	Liver	[43–45]
Reproductive system	Uterus	[46–48]
	Fallopian tube	[11,49–51]
	Ovary	[52]
	Placenta	[53,54]
	Mammary gland	[55,56]
	Testis	[57]
	Prostate	[58]
Urinary system	Kidney	[59,60]
	Renal pelvis	[61]
	Ureter & Urinary bladder	[62–64]
	Urethra	[61]
Musculoskeletal system	Striated muscle	[65,66]
	Neuromuscular spindle	[67]
	Fascia lata	[68]
	Temporomandibular joint disc	[69]
Integumentary system	Papillary dermis & reticular dermis	[70–72]
Visual system	Eye: Limbus & uvea	[73]
Nervous system	Meninges & choroid plexus	[74]
	Trigeminal ganglion	[75,76]
Hematopoietic system	Spleen	[77]
	Bone marrow	[78]

3. Immunophenotypic heterogeneity

Although no specific markers are known for TCs, the ultrastructural diagnosis is frequently complemented by immunohistochemistry. The most common markers expressed are CD34 and PDGFR, however, multiple immunophenotypes of TCs were described according to the organ and/or the animal species.

In the heart, TCs express CD34, vimentin, sca-1 and c-kit, Nanog and are CD34/PDGFR-α-double positive cells TCs enriched in rat cardiac interstitial cell populations [101,102]. Cardiac TCs are also positive for mesenchymal marker CD29 and negative for hematopoietic marker CD45 [103]. As most of the enumerated markers are also expressed in mesenchymal stem cells it was hypothesized that TCs might be a source of cardiac mesenchymal cells [103].

Pulmonary TCs were found to be double positive for c-kit and CD34 and also labeled for VEGF suggesting some implication in angiogenesis [27,104].

In the digestive system, TCs were demonstrated to be unequivocally different from the ICCs by immuno-electron microscopy

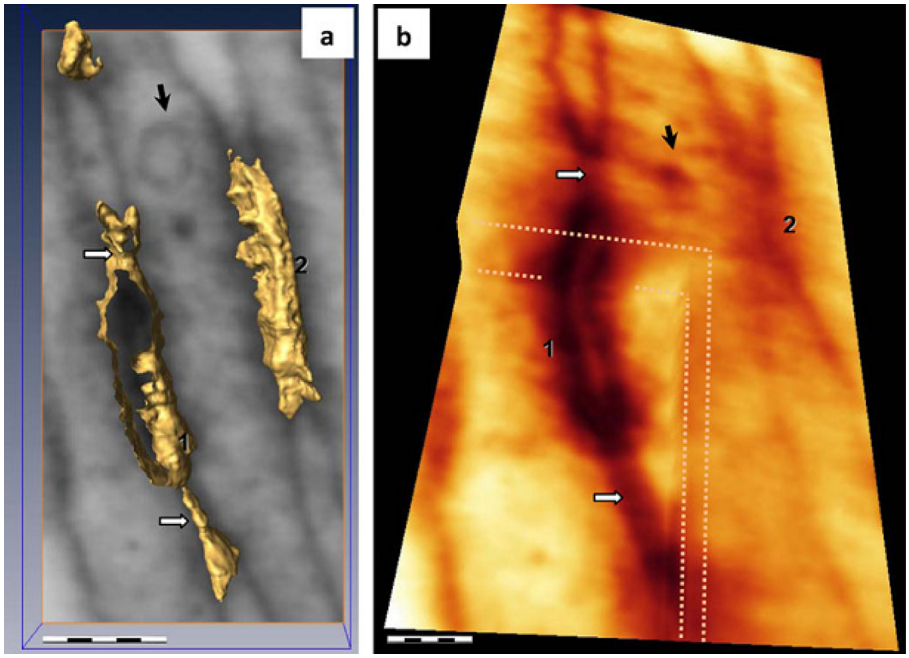

Fig. 3. Details of electron tomography in TCs junctional complex in mouse parietal pleura (*black arrow*-vesicle visible in one telopode involved in the junctional complex). (a) Top view of the 3D isosurface reconstruction shows an intercellular cleft (about 20 nm wide) between tight connecting lines (*white arrows*). (b) Cropped corner of the reconstructed volume showing the tight peripheral connecting lines (*white arrows*) in different planes. Bars 0.5 μm (a), 0.2 μm (b). Reproduced with permission from [30].

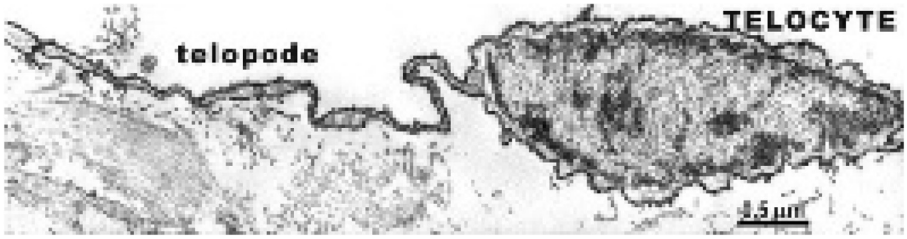

Fig. 4. CD34-immunoelectro-labeling: small intestine. CD34-immunoelectro-labelling is present on the surface of a telocyte. The labelling appears as an electron-dense material distributed all along the plasma membrane, from which spherules protrude outside. Reproduced with permission from [105].

(Fig. 4) [105]. In addition, TCs are CD34/PDGFR-α double-positive in the human esophagus, all gastric regions, and large and small intestine [36]. Hepatic TCs also displayed the same phenotype: CD34/PDGFR-α double positive [43,45].

TCs in the female reproductive system express in various degrees: c-kit receptor, CD34, PDGFRα, estrogen and progesterone receptors and T-type Ca^{2+}channels (CaV3.1 and CaV3.2 isoforms) [9,98,106,107]. Some of the cultured TCs from the placental villi are double positive for c-kit and iNOS and some for c-kit and VEGF [53]. This subject was recently reviewed by us and therefore will not be extensively discussed here (see [3,108]).

Skin TCs were positive for CD34 or c-kit/CD117, mainly in the reticular dermis, while those in the papillary dermis were mainly PDGFRα positive. A double positive reaction for CD117/vimentin was detected for TCs situated in the dermis surrounding hair follicles and sweat glands [70]. These TCs do not express CD1a, mast cell tryptase, α-SMA, procollagen or CD90 [72].

In the urinary system, the immunophenotype palette is wider and while the TCs in the bladder submucosa and detrusor are CD34-positive and PDGFRα-negative, those in the lamina propria of the mucosa are PDGFRα-positive and CD34-negative and sometimes αSMA-positive [63].

As it was suggested before, this heterogeneous cell population of TCs might represent, in fact, adult progenitor cells capable of adapting and transforming according to their location and in response to the functional demand existing in one specific tissue [3]. Their phenotype might fluctuate under the influence of the locally received signaling molecules and why not, TCs might even change their secreted factors accordingly. Diaz-Flores et al. also suggested that TCs are a source of progenitor cells during repair [109–111].

4. Genomic and proteomic characterization

As already emphasized in the immunophenotypic description of TCs, among the most common markers are CD34 and PDGFR. However, it is very important to point out that CD34 was described as a marker for hematopoietic progenitor and stem cells [112,113], (myo)fibroblasts [114,115], endothelial cells [116,117], immune cells [118,119], *etc*. Therefore, a detailed genomic and proteomic characterization of TCs is very important in order to establish the

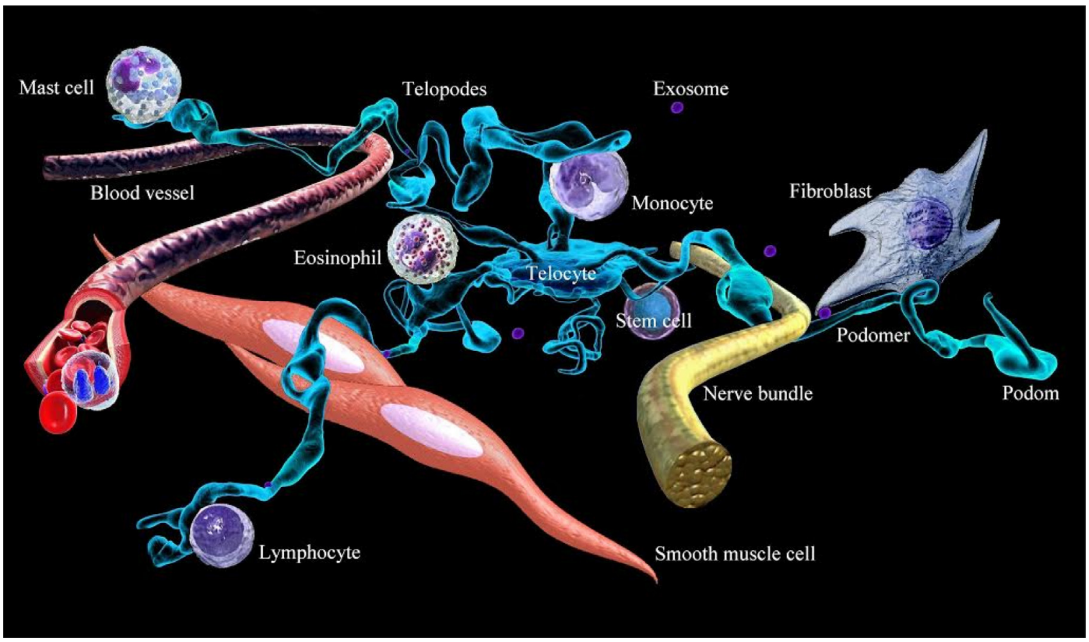

Fig. 5. Artistic representation of a 3 D view of the contacts of a telocyte. TCs are regarded as interconnection devices due to their homo- and heterocellular junctions, as well as to their proximity to structures like blood vessels, nerve fibers and muscle fibers. Image courtesy of Iurie Roatesi.

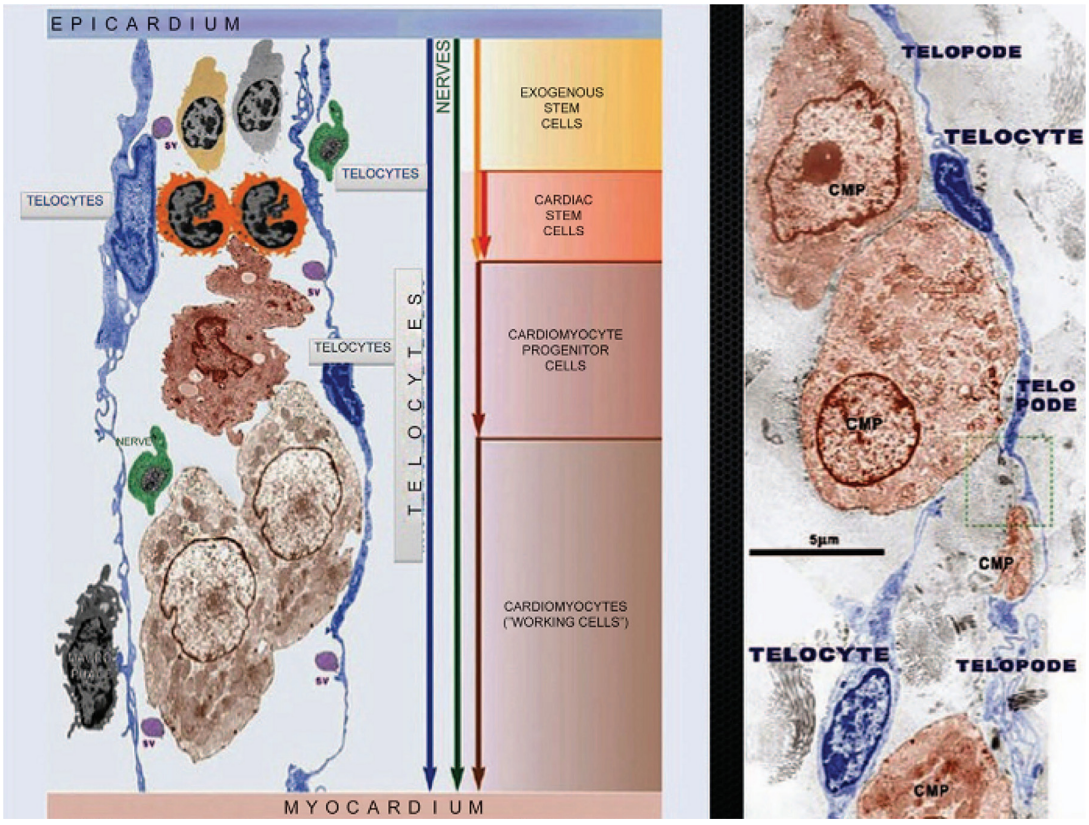

Fig. 6. Schematic representation shows that TCs network is a prerequisite for myocardial cellular homeostasis shaping the scaffold required to activate exogenous and endogenous stem cells and to guide the migration of cardiomyocyte progenitors. Cardiomyocyte progenitors communicate at distance with nurse TCs from epicardial niches and which deliver information 'packages' via shed vesicles (sv). Macrophages and nerves assist the TCs to monitor the cardiac renewing (Reproduced with permission from [122]).

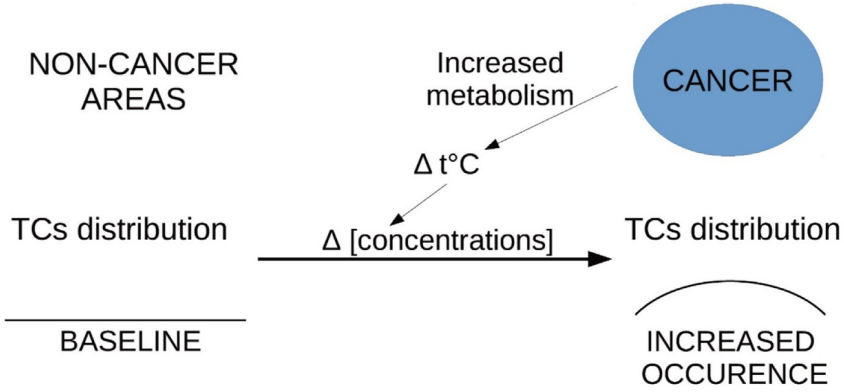

Fig. 7. Proposed model for explaining the signaling mechanisms involved in local growth of TCs number due to raised tumor metabolism which leads to an apparent increase in local metabolite's concentrations and to TCs migration based on concentration gradients.

specific gene/protein profile of these cells, but also their physiological role.

4.1. Genomic characterization of TCs

Studies of genetic comparison between mouse lung TCs and mesenchymal stem cells or fibroblasts, using an Agilent Mouse 4× 44K Gene Expression Array, evidenced that over 2000 and 4000 different genes were upregulated and downregulated, respectively. Among the upregulated genes one can enumerate *Ctgf, Mmp10, Mmp3, Col4a4, Col4a6, Col4a5, Unc13b, Mapk13, lgsf9, Glipr1, Clic5, Myh14, etc* [90]. As can be seen, some regulators of the vascular basement membrane are highly expressed in TCs (*e.g.* Nidogen, Collagen type IV and Tissue Inhibitor of Metalloproteinase 3 −TIMP3, matrix metalloproteases Mmp3 and Mmp10) [90]. Considering the vicinity of TCs with the lung microvasculature, some role of TCs in *de novo* vessel formation and in the regulation of the extracellular matrix during vascular branching were hypothesized by Zheng et al. [90].

Next studies have proposed to determine the patterns of mouse lung TC-specific gene profiles when compared to other types of cells including mesenchymal stem cells, fibroblasts, alveolar type II cells, airway epithelial cells, and lymphocytes. String Network analysis (www.string-db.org) was used to analyze the physical and functional associations of selected genes of TCs. The chromosome 1 profile in lung TCs with respect to the previously indicated cells revealed 25% up-regulated and 70% down-regulated genes (>1 fold), where *Capn2, Fhl2* and *Qsox1* genes were upregulated indicating the role of TCs in morphogenesis and local tissue homeostasis [91]. Moreover, same genetic comparison of chromosomes 2 and 3 gene expression profiles in pulmonary TCs highlighted 26 and 80 genes on chromosome 2 and 13 or 59 genes, up- or down-regulated, respectively in chromosome 3 [92]. Overexpression of *Myl9* gene in chromosome 2 may indicate inhibition or reduction of inflammation in the lung, and overexpression of *Sh3glb1, Tm4sf1* or *Csf1* genes in chromosome 3 was associated with tumour promotion in lung cancer, while down-expression of *Pde5g* gene in chromosome 3 may be suggestive for the development of pulmonary fibrosis and other acute and chronic interstitial lung diseases [92]. Further analysis of chromosome 4 genes profile in murine lung TCs was done in comparison with the same local cells, and indicated the upregulation of 17 genes, mainly *Akap2, Gpr153, Sdc3* and *Tbc1d2* (1–4 fold), and the downregulation of 56 genes, the most important being *Svep1* (>4 fold), and pointed out TCs involvement in cellular signalling, regulation of tissue inflammation and cell expansion and movement [95]. Another study focused on the analysis of chromosome 17 and 18 genes in murine lung TCs in comparison with mesenchymal stem cells, fibroblasts, alveolar type II cells, airway epithelial cells, and lymphocytes, and gave an important functional outcome: (i) *Mapk14* and *Trem2* were up-regulated and were correlated with the biological function of TCs in immune regulation; (ii) *Mcfd2* was upregulated while E4f1 and *Pdcd2* down-regulated, being associated with the role of TCs in tissue homeostasis, and (iii) *Dpysl3* was upregulated, probably indicating the role of TCs in self-proliferation and cell–cell network forming [94]. The genomic profile in the chromosome X of murine pulmonary TCs was performed by comparison with the above-mentioned cells and 31 chromosome X genes were selected as the TC-specific or dominated genes, among which 8 were up-regulated (*Flna, Msn, Cfp, Col4a5, Mum1l1, Rnf128, Syn1,* and *Srpx2*) and 23 were down-regulated (*Abcb7, Atf1, Ddx26b, Drp2, Fam122b, Gyk, Irak1, Lamp2, Mecp2, Ndufb11, Ogt, Pdha1, Pola1, Rab9, Rbmx2, Rhox9, Thoc2, Vbp1, Dkc1, Nkrf, Piga, Tmlhe* and *Tsr2*) [93].

4.2. Proteomic characterization of TCs

Proteomics analysis showed clear different profiles of TCs compared to microvascular endothelial cells (ECs) in human lungs [89]. To date, in the 5th day of culture, TCs present the upregulation of 38 proteins compared to ECs, especially Myosin-14 (18.84-fold), superoxide dismutase (SOD2; 14.59-fold), acid ceramidase (AC; 7.63-fold), envoplakin and epiplakin (∼6-fold each), and the downregulation of 60 proteins, especially cell surface glycoprotein MUC18 (15.54-fold), Ras-interacting protein 1 (13.42-fold), BTB/POZ domain-containing protein (7.26-fold), peptidyl prolyl cis/trans isomerase (6.65-fold) and nestin (5.92-fold) and von Willebrand factor (5.74-fold). It should be highlighted that the highly expressed proteins in TCs have been identified to be involved in important molecular functions (*e.g.* catalytic activity, structural molecule activity), biological processes (*e.g.* metabolic processes), cellular processes (*e.g.* cell communication, cytokinesis, cellular component movement, cell cycle), developmental processes (*e.g.* anatomical structure morphogenesis, mesoderm development, system development, ectoderm development), and localization processes (*e.g.* vesicle-mediated transport, protein transport, ion transport). These proteins classes present in TCs belong to cytoskeletal proteins, oxidoreductase, structural proteins, transferase, and the upregulated proteins are mainly associated to the following pathways: nicotinic acetylcholine receptor, inflammation mediated by chemokines, de novo purine biosynthesis, cytoskeletal regulation by Rho GTPase, TCA cycle, Parkinson disease, integrin signalling and blood coagulation [89].

The same authors identified in TCs on the 10th day of culture 26 proteins upregulated compared to ECs, especially prostacyclin synthase (8.93-fold), epiplakin (4.78-fold) and superoxide dismutase (4.50-fold), and 56 proteins downregulated, especially microtubule-associated protein RP/EB family member 1 (100-fold), cysteine-rich protein 2 (100-fold), von Willebrand factor (15.89-fold) and platelet endothelial cell adhesion molecule (13.31-fold) peptidyl prolyl cis/trans isomerase (10.53-fold) and cell surface glycoprotein MUC18 (9.31-fold).

Similarly, a proteomic comparative profile was done between TCs and fibroblasts from human lung. Zheng at al. found 39 proteins, including especially Myosin-14 (15.72-fold) to be upregulated in lung TCs cultured for 5 days, while 25 proteins, especially collagen alfa 3(VI) chain (4.71-fold), secernin-1 (3.73-fold) and fascin (3.25-fold) were downregulated, relative to fibroblasts [88]. The proteins are involved mainly in metabolic processes, cellular processes, development processes, cellular component organization, precursor metabolites and energy generation, immune system processes, cell communication, transport, cell adhesion, cell cycle, system processes, homeostatic processes, biological processes regulation, and responses to stimulus [88]. Sine myosin-14 remained overexpressed in TCs after 10 days in cell culture TCs were considered as candidates for a mechanical sensing and mechanochemical conversion task [88].

5. Electrophysiological aspects

TCs heterogeneity implies the existence of transmembrane proteins with specific biophysical characteristics and the ability to be modulated by various factors. Several groups of researchers have managed to put in evidence through electrophysiological methods the presence of these ion channels [48,85,107,120]. Their functions depend on the organs in which TCs are found. In human myometrium, our research group revealed the existence of hyperpolarisation-activated chloride inward currents with calcium dependence, T-type and L-type voltage-gated calcium channels [48,107] and we have shown for the first time their involvement in Tps growth guided by mechanical forces [121]. Moreover, these ion channels are possibly involved in the modulation of rhythmic contraction of the smooth muscles and heart [122,123]. We previously reported the electrophysiological characteristics (membrane capacitance, input resistance, membrane resting potential, or the presence/absence of different outward and inward currents) of TCs versus those of smooth muscle fibers in uterine myometrium [99]. Small-conductance calcium-activated potassium channels were identified by immunohistochemistry and molecular biology in human myometrium and has been shown that agonists reduce uterine contractility [120]. Patch-clamp studies have confirmed the presence of cardiac large conductance Ca^{2+}-activated potassium currents (BK_{Ca}) and inwardly rectifying potassium currents (K_{ir}) but not the outward potassium currents (Ito) nor the ATP-sensitive potassium currents (K_{ATP}) [85]. Moreover, inwardly rectifying potassium currents are modulated by Transforming Growth Factor-β1 (TGF-β1) and down-regulated by hydrogen sulfide. Given that TGF-β1 may contribute to tumor maintenance and progression it can be extrapolated that TCs are able to detect tumors. Due to TCs involvement in detecting mechanical stimuli through calcium channels and the fact that uterine fibroids are often arranged concentrically, suggest that fibroids are organized according to mechanical stimuli. It is not clear whether TCs are involved in the formation of fibroids or are just a response of the body.

6. Functional significance of telocytes

6.1. Telocytes as a part of a complex system of communication

Communication between a cell and extracellular environment can be mediated by junctional complexes, by cell secretion or by the transfer of genetic information (via extracellular vesicles). These ways are valid for TCs since they are lately considered as connecting cells. Their capability as connecting devices can be subdivided into two major categories: (1) capability to form mechanical and electrochemical communications between them or with adjacent cells with the aid of homocellular and heterocellular junctions (for details see review [124]); (2) capability to receive outside-in and send inside-out informative signals. Diaz-Flores et al. demonstrated the endocytic and storage properties of TCs [125]. They described in the colonic wall TCs loaded with India ink particles which were stored around the nucleus and in the Tps while other stromal cells in did not show uptake or storage of India ink, except for a few ICCs. In other locations like skin and periodontal tissues TCs are also able to store naturally-produced pigments such hemosiderin, melanin and some components of dental amalgam, respectively [125]. The TCs capacity to release extracellular vesicles represents an antagonistic way of communication that closes this circle of informational exchange [126].

6.1.1. Contacts of telocytes

Tps make junctional contacts between them and with a whole variety of distinct cell types: stem cells, immune cells, muscle cells, Schwan cells, myofibroblasts, ICC, *etc*. and thus a 3D network is formed (Fig. 5) [35,63,127].

Homocellular junctions are established between cells of the same type. In the case of TCs, their existence between Tps allows the formation of the labyrinthine three-dimensional network. The presence of homocellular junctions was detected as a constant characteristic of TCs regardless of location or animal species. In their latest review, Faussone-Pellegrini & Gherghiceanu classify these junctions as: (i) simple appositions of the plasma membranes (*puncta adhaerentia minima, processus adhaerens, recessus adhaerens* or *manubria adhaerentia*) and (ii) complex junctional areas (*nexuses*). While the first are responsible for a mechanical function, the others realize functional intercellular exchanges [124].

Heterocellular junctions are established between different types of cells. TCs often contact the surrounding cells: immunocytes (macrophages, mast cells, lymphocytes, plasma cells, eosinophils, basophils, neutrophils), stem cells, ICC or tissue-specific cells (cardiomyocytes, smooth muscle fibers, Schwann cells) [35,48,63,128–130]. These junctions can be classified as (i) minute junctions (point contacts, nanocontacts and planar contacts) having a 10–30 nm space between plasma membranes and (ii) simple appositions [124].

The existence of this three-dimensional network has certainly functional implications. TCs' involvement as mechanical support is provided by the existence of simple homocellular junctions between Tps [99]. In addition, a mechanical sensing and mechanochemical conversion task were suggested for TCs [88].

Heterocellular contacts with immunoreactive cells plead for a role in immune surveillance, while those established with cardiomyocytes and cardiac stem cells qualify TCs as "nurse cells" [131]. Moreover, the role of TCs in immunomodulation and immunosurveillance was hypothesized since the initial description of the interactions between TCs and immune cells when a special type of "juxtacrine synapse" – the stromal synapse was proposed [128]. Sun et al. also suggested their involvement in the immune

response where TCs might contribute by acting like 'local data suppliers' [91].

6.1.2. Secretome of telocytes

The protein secretory profile of TCs was analyzed by different research groups using the supernatant from cultured TCs. Albulescu et al. determined the mouse and rat cardiac TC secretory profile and found that interleukin (IL)-6, VEGF, macrophage inflammatory protein 1α (MIP-1α), MIP-2 and MCP-1 are present in the supernatants of cultured cardiac TCs, while rat cardiac TCs secrete a slightly greater number of cytokines (IL-2, IL-10, IL-13) and some chemokines (growth-related oncogene/keratinocyte-derived chemokine GRO-KC) [87]. They also analyzed how these secreted factors could influence cardiac stem cells and concluded that TCs might "sense and re-direct the cellular microenvironment to increase the renewal capacity of cardiac stem cells" [87]. Kang et al. performed a comparative analysis of the supernatants from cultured dermal TCs and fibroblasts and found that two cytokines were expressed 1.5 times higher in TCs: neutrophil-activating peptide 78 (ENA-78) and granulocyte chemotactic protein-2 (GCP-2) [72]. Both proteins are suggestive for a possible involvement of TCs in (neo)angiogenesis [72].

6.1.3. Extracellular vesicles of telocytes

Several studies point out that TCs release three types of extracellular vesicles (EVs): exosomes, ectosomes and multivesicular bodies [48,132]. EVs defined as a family of nano-sized membrane-surrounded structures derived from the endosomal compartment or shed from the plasma membrane. The importance of EVs in accomplishing the role of TCs has been recently reviewed [126]. Usually, EVs carry receptors, bioactive lipids, proteins, and, most importantly, nucleic acids, such as mRNA, microRNA (miRNA), and non-coding RNAs and therefore it is considered that TCs play an important role in the horizontal transfer of information between cells both locally and remotely [126].

6.2. Telocytes in ontogeny

Although TCs involvement in developmental processes (~13%) such as structure morphogenesis (~41%) holds a significant share according to bioinformatic analyses of the identified proteins [88] there are few studies addressing to TCs during prenatal development of organs. Faussone-Pellegrini and Bani showed that TCs are present since the early developmental stages of cardiac development and are negative for c-kit and CD34. It appears that TCs acquire CD34 positivity after birth [133]. They also suggested in a subsequent study that TCs might be responsible for the re-activation of dormant myocardial precursors during the repair of the adult heart [134] while in embryonic life they behave as inductors/regulators of differentiation during morphogenesis [135]. Moreover, in fetal life, the presence of T-type Ca^{2+}channels in cardiac myocytes regulate their size and are involved in the exit of cardiomyocytes from the cell cycle after birth [136]. Such T-type Ca^{2+}channels were also reported in TCs [107] and might also have a contribution in tissue bioelectrical signaling [137].

Another study evaluated the number of uterine TCs based on immunohistochemical markers [138]. Numerically, the immature rat uteri have the lowest number of TCs, which became significantly increased in adult uteri [138]. However, results are questionable since only the c-kit positivity was considered.

6.3. Telocytes in homeostasis maintenance

Homeostasis can be shortly defined as an equilibrium between cells produced and cells discarded in a specific tissue/organ in a constant and propitious microenvironment that supports them. Defined by extremely long, tortuous, and overlapping Tps, the TCs are interconnected in a 3D network. There are several properties which enable us to believe that TCs may function as a scaffold to define the correct tissue organization. Firstly, there are some differentially expressed genes, Capn2, Fhl2, and Qsox1, overexpressed in TCs in comparison with mesenchymal stem cells, fibroblasts, alveolar type II cells, airway epithelial cells, and lymphocytes and indicative for an involvement in morphogenesis and local tissue homeostasis. Secondly, the extracellular vesicles derived from TCs are loaded with microRNAs and since nearly 60% genes are regulated by miRNAs we cannot exclude the participation of TCs in tissue homeostasis maintenance. Lastly, but certainly not least, TCs close relationship with stem cells is definitely not haphazardous and aimless but, in fact, they might contribute to support the proliferation and differentiation of stem cells. Morphological changes in TCs ultrastructural features and disruption of the network integrity is frequently reported in pathologic conditions.

6.4. Telocytes in regeneration and repair

Since the beginning of their study, TCs were seen as having an important role in processes of regeneration possibly by forming a tandem with the stem cells [139]. TCs are frequently reported to be associated with the stem cell niche [27,122]. Interestingly, diverse experiments performed to verify this hypothesis are indicating a role for TCs in tissue engineering and regenerative medicine. We mention here some of the most suggestive ones. For example, in the heart, it was shown that TCs accompany stem cells both in situ and in situ in primary cultures [129,140]. Moreover, a special interrelation exists between TCs and cardiac stem cells: one established by the exchange of information with the aid of extracellular vesicles which shuttle miRNA bidirectionally and the other by direct connections through typical and atypical junctions (Fig. 6) [79,141]. Much more, *in vitro* assessment of TCs secretome effect on the faith of cardiac stem cells showed that this might enhance their proliferation and differentiation [87]. In an experimental model of myocardial infarction in rats it was shown that TCs are decreased and undetectable in the central infarcted zone and that intramyocardial transplantation of cardiac TCs improved cardiac function by reducing the infarcted area size and cardiac fibrosis [96,97]. A study designed to construct engineered heart tissue highlights the significance of TCs in the 3D architectural organization of the cardiomyocytes and underline the concept that TCs play a vital role in the regeneration process [142].

7. Telocytes in pathology

7.1. Pathological implications of TCs in cavitary organs

7.1.1. Uterus and fallopian tube

Previous work done on human myometrium revealed the importance of mechanical forces in modulating TCs signaling mechanisms. Using low-level laser stimulation (LLLS) the growth of Tps was achieved by applying localized optical forces. The growth process was inhibited by mibefradil, an inhibitor of T-type voltage-gated calcium channels which have a degree of mechanosensitivity [121]. In order to identify the possible roles of mechanoreception in TCs signaling it is important to identify, in areas with significant mechanical forces, the different pathologies associated or not with the presence of TCs. These areas can be represented by the cavitary organs where the forces are distributed across reduced wall width or where the mechanical force dictates the motility and organ functionality.

These findings on the importance of mechanical forces in the human myometrium may be involved in uniform width growth of

uterus wall during pregnancy. Pathologies involved in the uneven increase of uterine wall and more profound implantation of the placenta can lead to the development of areas with thin walls in which the mechanical forces resulting from physiological contractions are higher per unit area in the concerned cross section and consecutively in the TCs. Uterine TCs functioning as mechanical stress sensor can result in local compensatory hypertrophy of the uterine wall. This guidance of uniform thickness uterine growth by mechanical stimuli could be extrapolated to other cavitary organs due to various TCs distribution. Adjustment of mechanosensitive function can be achieved by pharmacological modulation of the ion channels involved and of lipid metabolism resulting in small changes in membrane fluidity. This last aspect is mainly due to the small size of Tps. In this context, it is necessary a reassessment of the safety level for therapeutic drugs, used in pregnancy, that target the calcium channels and statins that modulate cholesterol metabolism.

In the oviduct, TCs are small in number in endometriosis and acute salpingitis [51,143]. TCs destruction is accompanied by an alteration of the 3D architecture with possible implications in impaired fertility [51].

Uterine leiomyoma also referred to as fibromyoma is a benign, hormone-dependent, tumor in the uterine wall. Menstrual irregularities due to fibroids are hypothesized to be secondary to the loss of symmetric uterine contractions [144]. Of late interest in this area is the description of a large number of TCs in uterine leiomyoma [145]. Although surprising, the description of a large number of TCs with ultrastructural features suggestive of increased cellular activity (loss of the heterochromatin clumps, extremely long telopodes, large numbers of mitochondria, dilated rough endoplasmic reticulum cisternae, and clusters of shed vesicle) [145]. We would have expected a reduced number of TCs in correlation with the events that happen in fibrosis [17], however, a large number of TCs cannot be excluded given the fact that TCs might be hormone sensors since they express estrogen and progesterone receptors [99].

7.1.2. Lungs

Another organ where mechanical forces are valuable in physiological functioning is the lung, due to thinness of the alveolar wall and of increased alveolar distension which occurs during respiration. In this case, the analysis has to be done from the pathology to the possible implications needed for mechanism identification, starting from the premise that the large number of existing lung TCs are useful in architectural conservation. An important pathology correlated with alveolar distension and destruction is emphysema.

An important cause of this pathology is represented by pollution in large cities associated with an unhealthy lifestyle (*e.g.* smoking).

Nitric oxide produced in internal combustion engines of motor vehicles can influence L and N-types of calcium channels, process modulated by increased cGMP that activates cGMP-dependent protein kinase which in turn stimulates calcium channels [146]. Patch clamp experiments on rat ventricular myocytes have shown that SO2 derivatives, like bisulfite and sulfite, potentiate the L-type voltage-gated calcium channels influencing the biophysical properties of these channels with possible implications in cardiac distress [147]. Extrapolating these data to lung TCs, these can be influenced by SO2 by hyperactivation. Both pollutants can influence the activation of these cells due to their increased membrane solubility.

Alveoli are arranged in parallel (with specific air resistance) and impaired alveolar structures of hypertrophy of the alveolar wall mainly result in adjacent alveoli expansion, a mechanism that could explain the occurrence of emphysema in the presence of contaminants. Ozone, which is a major component of smog, can stiffen and increase membrane fluidity through a dose-dependent mechanism [148]. By influencing membrane fluidity, ozone can subsequently modify the mechanoreceptor function and may contribute to the pathophysiological mechanism in the evolution of emphysema. Channel blockers, involved in mechanical sensitivity of TCs and drugs that increase the membrane fluidity could be useful in decreasing the rate of change of emphysema caused by pollution. Due to the mechanism described above, both channel agonists and antagonists may be useful, dependent on drug distribution in the target tissue and on application pathways.

Idiopathic interstitial pneumonia are characterized by inflammation and fibrosis that result from lung parenchyma damage. Although the mechanisms triggering the incipit of the fibrotic process in idiopathic interstitial pneumonia should be still clarified, several risk factors have been associated with the developing of this disease, *e.g.* cigarette smoking, environmental/occupational pollutants, microbial agents, chronic microaspiration secondary to gastroesophageal reflux, and genetic abnormalities [149–151]. Recently, TCs have been proposed to contribute to different lung diseases, including idiopathic interstitial pneumonia, asthma and chronic obstructive pulmonary disease, pulmonary cancer, acute lung injury [29].

7.1.3. Heart

TCs were investigated during different cardiac diseases (see reviews [131,152,153]). During myocardial infarction in experimental conditions TCs were significantly increased in the border zone of infarction at 30 days after coronary ligation and were suggested to play a role in the angiogenesis process [96]. Moreover, in cardiac infarction areas induced in mice, by injecting iPSC, the number of TCs increases suggesting a functional connection between these two cell types [154]. Richter and Kostin characterized and quantified the structure and number of TCs in human heart failure as a consequence of different forms of cardiomyopathies and found a decreased number of TCs as a result of apoptosis and altered extracellular matrix composition [155]. In addition, TCs are more likely to prevent amyloid deposits dissemination in the heart [156]. The loss of TCs was also reported in the aging heart while in myocardial fibrotic areas of myocardial infarction and systemic sclerosis TCs are almost completely absent [130,157]. We can conclude that impaired functioning of TCs may cause fibrosis [157,158] and this may be extrapolated to the heart as a lack of TCs mechanical stimulation as a positive feedback mechanism which leads to a decrease in the function of TCs.

7.1.4. Gastrointestinal tract

Gastrointestinal tract integrity is important for its proper functionality. Sanders et al. described the so-called SIP syncytium made of ICCs and PDGFRα+ cells which are electrically coupled to the intestinal smooth muscle cells [123], suggesting that these two interstitial cell populations might establish intercellular communication. Most probably the PDGFRα+ cells are likely to be TCs. Reduction in TCs number correlated with fibrosis was observed in the muscularis propria and myenteric plexus of patients with Crohn disease [159]. In ulcerative colitis, a decrease of TCs was observed associated with fibrotic remodeling of the colonic wall [160]. TCs are also found in the gallbladder and extrahepatic bile ducts and have been associated with gallbladder motility and possibly are in correlation with the lithogenicity of bile [42,161,162].

7.2. Pathological implications of TCs in non-cavitary organs

7.2.1. Liver

The existence of long Tps has raised many controversies regarding their roles. TCs involvement in signaling and mobility guided by various factors raised questions about using Tps length in chemical signals transduction in order to modulate the function of TCs by various chemical gradients. Liver, a parenchymatous organ,

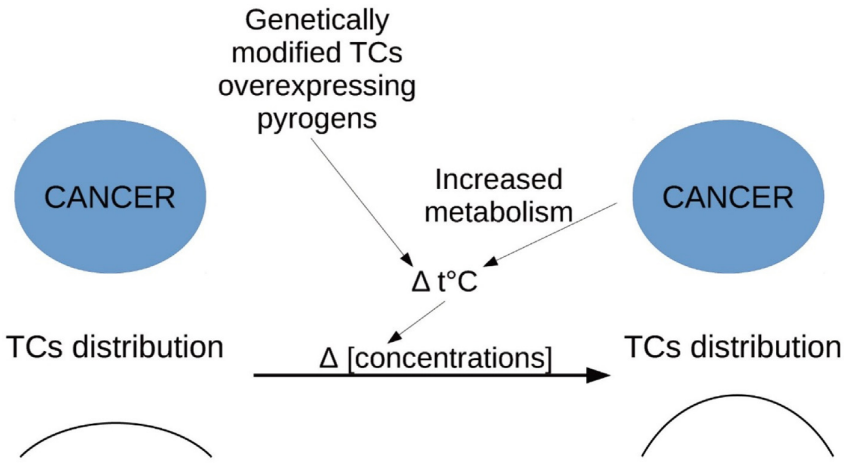

Fig. 8. Proposed therapy model for cancers leading to increased local number of TCs modulated by elevated temperature gradient using autologous TCs genetically modified to overexpress pyrogenic substances. The same TCs can be genetically modified to overexpress pro-inflammatory or antineoplastic factors for therapeutic purposes.

with an easily predictable chemical gradient, has a dual circulation, nutritional and functional. Growth and hypertrophy of the liver after resection is a way of assessing the growth distance between the functional and nutritional areas. Hypertrophy after limited resection and further hypertrophy after secondary resection as compensatory hypertrophy is a feature that preserves liver functionality, validated in clinical practice [163]. To assess the TCs involved in liver regeneration, experiments were performed on mice and, after hepatic resection, an increase in the number of TCs occurred in response to the need for liver hypertrophy [164].

Due to the fact that the function of TCs might be modulated by ion channels that show a degree of mechanical sensitivity [121] and the fact that estrogen may change membrane fluidity, modulating recovery after partial hepatectomy might be possible with the help of TCs, which have been shown to be increased in number and further proliferate together with hepatocytes during pregnancy [44]. This correlation may lead to the conclusion that the length of Tps is involved in the detection of chemical mediators gradients. Moreover, decreased TCs function is correlated with liver fibrosis and an additional number of TCs or modulation of their function could prevent liver fibrosis [165].

7.2.2. *Exocrine glands*

To evaluate the role of functional asymmetry and distribution of chemical mediators in the function of Tps as sensors of various chemical gradients, it is interesting to note TCs distribution networks in exocrine glands. TCs prevail in the pancreas periductal area [39], in contrast to the parotid and the submandibular glands where TCs are present predominantly in the acinar area [37]. This difference between the two patterns of distribution may be a consequence of differences in the presence of various mediators. In minor salivary glands, TCs are also represented among the stromal cells and are shown to be specifically reduced in focal lymphocytic sialadenitis and primary Sjögren's syndrome [38].

7.2.3. *Skin*

In the skin, TCs represent an architecture with a large specific surface area of Tps [81]. This could have the effect of amplifying the signals that modulate the function of TCs. These function modulating factors may be of mechanical nature as previously suggested [121], and therefore TCs differ from other dermal cells which are guided by growth factors [72]. It is noteworthy that an abnormality of TCs is correlated with systemic sclerosis [158] and psoriasis [166]. It is difficult to estimate signaling cascade in these pathologies. For this purpose, it is necessary to develop animal models of these diseases by modulating the number or functions of TCs.

8. Future therapeutic insights

Identifying the signaling mechanisms in the function modulation of TCs by mechanical factors and chemical concentration gradients of various mediators opens a new path in understanding the TCs involvement in cancer. It is worth noting that in malignancies TCs are present and this could be as a consequence of the TCs involvement in cancer formation, or, more likely, in the body defensive response against neoplasia.

In favor of the first hypothesis one could argue TCs implication in the modulation of stem cells [154] and neoplastic stem cells involvement in cancer development [55,167]. As an argument against this mechanism, it may be brought into question the large number of genetic mutations that correlate with different malignancies, making it unlikely that a common signaling mechanism of cancer cells with TCs can be maintained.

In order to elucidate the mechanisms of TCs involvement in the body's reaction to cancer, the ability of these cells to identify the chemical concentration gradients can be used, based on increased metabolism of cancer cells compared to the surrounding tissue. This could explain the migration of TCs in the tumor, making fewer heterocellular junctions with an increase in local concentration of TCs [168]. Moreover, the enhanced metabolism in the affected area may lead to the existence of a slight thermal gradient between the tumor and the unaffected adjacent areas, followed by an apparent increase in local metabolite's concentrations in the neoplastic zone due to changes induced by temperature on binding constants between various substances involved in signaling (Fig. 7).

This perspective of using TCs in antineoplastic therapy requires the existence of effective isolation methods of TCs from less important areas with the scope to transfect the mRNA for pyrogenic and specific anticancer substances. Adipose tissue and skin excess can represent potential sources for harvesting TCs. Another possible approach can be represented by using TCs cell line with induced genetic mutations that lead to migration of TCs in the neoplastic area. In this case, it is necessary to inject the genetically modified cells close to the tumor for preventing an autoimmune response. Possibly, by stimulating the immune response against the modified TCs cell line it can be triggered an immune response against cancer cells (Fig. 8).

These multiple perspectives in cancer therapy, using TCs as therapeutic vectors, opens a new age in the study of TCs with increased potential for obtaining spectacular results.

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