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Telocytes: Connective tissue repair and communication cells

The mechanotransduction features of fibroblasts are well established, with the potential for different degrees, durations frequency and direction of biomechanical loading (as in myofascial release) and unloading (as in counterstrain), having been shown, in in-vitro studies, to have predictable effects on tissue remodelling and inflammatory processes (as examples) (Zein-Hamoud and Standley, 2015).

Mechanosensitivity has now also been identified as a feature of telocytes - a highly versatile, newly identified, different category of connective tissue cell, that is also active in repair and regeneration, recently described and characterized by Popescu et al. (2011), in Bucharest, Romania. (Cretoiu, 2016).

The question therefore arises as to how, and to what degree, appropriately applied biomechanical load, associated with the therapeutic use of movement and manual treatment, may be capable of positively influencing these connective tissue cells in their known homeostatic roles?

1. Telocyte features (Cretoiu, 2016, Cretoiu et al. 2016; Edelstein, 2016)

Telocytes are specialised mechanosensitive connective-tissue cells, capable of organising and accomplishing - alone or together with stem cells, fibroblasts, macrophages and others - multiple tasks associated with facilitating cellular repair, regeneration and remodelling, throughout the body.

They have been shown to have the ability to initiate complex protein-synthesis processes, as well as being able to modify cellular gene expression via epigenetic interactions, as required, while also having the means to deliver essential materials to different varieties and types of cells, via self-produced nano-sized vesicles (exosomes).

Such diverse functions necessarily involve a range of forms of information transfer - featuring diverse communication mechanisms.

Surprisingly, it is only within the last decade or so that the extraordinary range of the integrated features of telocytes have been recognized!

2. Homeostasis and regeneration

As Cretoiu et al. (2016) explain:

- Telocytes are connective tissue cells, that are functionally distinct from stem cells and fibroblasts, that have roles in cell-signaling, tissue-homeostasis, remodelling, and angiogenesis
- Telocytes are distributed in the interstitial extracellular matrix of all body tissues.
- Telocytes have telopodes (see Fig. 1) involved in intercellular communication with other telocytes, as well as surrounding structures, such as blood vessels, nerve endings, smooth muscles, glandular elements, and those covering epithelia, by means of direct homo- and heterocellular junctions, or via extracellular vesicles.
- Extracellular vesicles, created by the telocytes, play important roles in stem cell maintenance, tissue repair, immune surveillance and vascular hemostasis - transporting and releasing lipids, proteins as well as nucleic acids - manufactured by telocytes to meet target-tissue requirements.

3. Telocyte structural features and functions

Dawidowicz et al. (2015), discussing telocytes in the tensor fascia lata, note that "The exact role of these cells within the fascia is unknown [but we] speculate that … telocytes … may be involved in regeneration, homeostasis and intracellular signaling."

They have described the cytoplasm of telocytes as containing a small Golgi complex, elements of rough and smooth endoplasmic reticulum, and cytoskeletal features, as well as a number of very long (up to hundreds of μm), thin, prolongations - telopodes. Apart from the axons of some neurons, telopodes are probably the longest cellular prolongations in the human body. Telopodes also contain even thinner features, podomeres, that in turn contain 'podoms'- small functional units capable of synthesizing protein, and interacting with target tissue cells epigenetically – or via bioelectric communication.

- For example: If a tissue cell is injured, it emits a chemical signal (e.g., hemoglobin in the case of a damaged blood vessel) - recognized by the telocyte's podom – causing it to synthesize appropriate proteins to repair the injury.
- Or - where the target cell is a smooth muscle cell, the podom may modulate the target cell's frequency of peristaltic contraction
- Or - When the target cell is a macrophage, or lymphocyte, the exosome transfer machinery would be specific to influencing immune reactions
- In these ways, complex tasks can be undertaken by simpler mechanisms, reducing the need for the telocyte to carry excessive equipment – because it can be manufactured locally, and automatically supplied via exosomes instead – so reducing the need for long distance, slow information, transfer (Edelstein, 2016).

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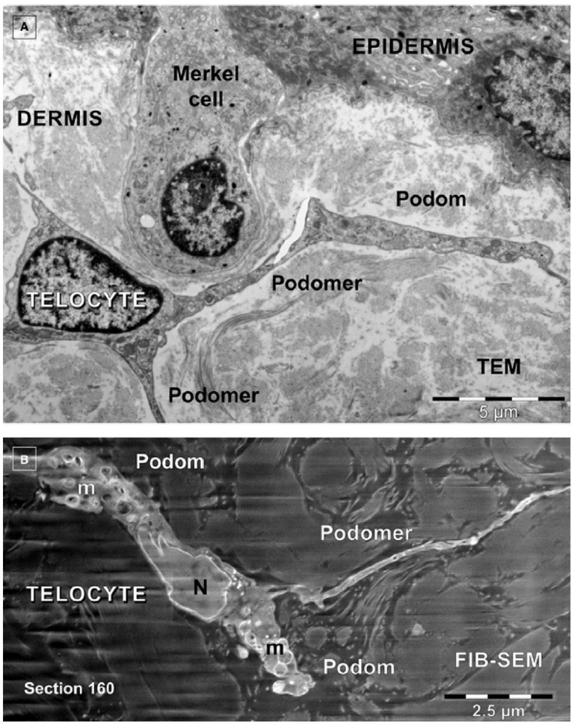

Fig. 1. **A** and **B**) Telocytes in human papillary dermis. (**A**) Transmission electron microscopy shows a telocyte with 3 telopodes edging a Merkel cell. (**B**) FIB-SEM backscattered electron imaging mode shows a telocyte with two telopodes in dermis (Cretoiu et al., 2015).

4. Communication and bioelectric signaling functions of '… *long, tenuous and sinuous cells'*

Telocytes differ from fibroblasts - the major connective tissue cells responsible for synthesizing the extracellular matrix and collagen – because telocyte function appears to largely involve inter-cellular signaling.

Edelstein (2016) discusses recent telocyte research evidence: "What were previously regarded as simple connective tissue cells, proved to be miniature communication devices now known as telocytes, long, tenuous and sinuous cells that use elaborate electrical, chemical and epigenetic mechanisms, including the exchange of exosomes, to integrate many activities within and between nearly all types of cells in tissues and organs."

As Bei et al. (2015) explain: "Telocytes [are found in] skeletal muscle interstitium [close to] capillaries, nerve fibres, satellite cells and myocytes." - and - "Functionally telocytes form a 3D interstitial network by homocellular and heterocellular communication […..] through close associations with fibroblasts, smooth muscle cells, endothelial cells, immunoreactive cells and nerve endings, which suggests conventional roles of telocytes in mechanical support, immune surveillance and intercellular communication and signaling […] involved in the maintenance of tissue homeostasis."

Cretoiu et al. (2012, 2016) further summarize some telocyte communication attributes:

- They appear to be cellular mechano-transducers, when in smooth muscle tissue, that are able to sense and translate stretch information for the cell-nucleus, and activate genes responsible for protein synthesis – so influencing surrounding cells.
- Telocytes may also be '*hormonal sensors*' since they have been shown to express estrogen and progesterone receptors in vitro, possibly involved in myogenic contractility modulation. Recent evidence also suggests that telocytes may play a role in neo-angiogenesis.

Edelstein and Smythies (2014) have discussed the possible role of telocytes in pathology; "[They transmit] integrated signals to neighboring cells …. their interrelationship with neural stem cells and neurogenesis in the context of neurodegenerative disease is just beginning to be explored."

"The consensus is that telocytes could form an extensive intercellular information transmission and executive system …. utilizing electric currents, small molecules, exosomes—and possibly electrical events within the cytoskeleton—to modulate homeostasis stem cell activity, tissue repair, peristalsis, anticancer activity and other complex functions in many organs."

5. Telocyte presence is reduced in pathological settings

And what happens when telocytes 'go wrong'? (Wollheim, 2016)

- In systemic sclerosis there is a progressive decrease in telocyte numbers. Tissue anoxia may trigger this decrease, since areas adjacent to obliterated vessels seem most severely affected?
- One hypothesis is that telocytes prevent formation of aggressive myofibroblasts, such as occur in inflammatory bowel diseases, since ample numbers of telocytes are present in normal areas of the gut, but are reduced in areas of fibrosis
- Numbers of telocytes are seen to decrease, with interrupted telopodes and networks, in the glands of patients with Sjögren's syndrome
- "The connection … with fibrosis makes one curious regarding conditions like inflammatory myositis, pancreatitis, thyroiditis, and IgG4 related diseases. Clearly telocyte dysfunction is involved in the pathogenesis of inflammatory and fibrotic diseases, as well as aging … [and]… may become future therapeutic agents."
- In contrast, telocytes are abundant in experimental regeneration of the liver, where it is assumed that they act as 'nursing cells' for stem cells.

6. Can we beneficially influence telocytes biomechanically?

Humphrey et al. (2014) have observed – in relation to fascial homeostasis:

"Soft connective tissues resident cells continually read and respond to environmental cues to promote homeostasis, including maintenance of mechanical properties of the extracellular matrix (ECM) - fundamental to cellular and tissue health."

Since telocytes are known to be mechanosensitive, what practitioners who use manual and exercise based therapies need to know - from those engaged in basic science research into these remarkable cells - is if and how telocytes may be therapeutically influenced by movement (or lack of it) and by externally applied mechanical loading (or unloading) procedures?

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