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# Telocytes in skeletal muscle: Emerging players in homeostasis and repair/regeneration

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# Telocytes in skeletal muscle: Emerging players in homeostasis and repair/regeneration

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**Running title:** *Telocytes in skeletal muscle*

**Summary**

Telocytes (TCs) have recently emerged as novel components of the skeletal muscle interstitium. They are distinguished from other stromal cells by their immunophenotypic profiles and, especially, unique ultrastructural traits. Specifically, TCs feature a small cell body and very long, thin telopodes with a moniliform appearance conferred by the alternation of slender segments (podomers) and small dilated portions (podoms). Experimental evidence suggests that, as part of the skeletal muscle stem cell niche, TCs may be involved in orchestrating satellite cell activation and myogenic differentiation through both direct physical interactions and paracrine signaling. Yet, further in-depth research is needed to uncover specific immunophenotypic signatures for skeletal muscle TCs within the niche, as well as to identify the signaling pathways by which they influence neighboring satellite cells and, possibly, other cellular components of the niche. In the present review, particular emphasis is placed on the putative strategic role of TCs in maintaining skeletal muscle tissue homeostasis, their involvement in muscle pathological alterations, and, most importantly, their possible role in the coordination of the regenerative response following injury. In perspective, the promising therapeutic potential of TC-based strategies to enhance skeletal muscle tissue repair/regeneration and restrain post-injury fibrosis is also discussed.

**Keywords**

Telocytes, Stromal cells, Skeletal muscle, Stem cell niche, Satellite cells, Tissue repair/regeneration



## Morphology, immunophenotype, and putative functions of telocytes

In the last decades, telocytes (TCs) have been thoroughly described as a distinct type of interstitial (stromal) cell in a large number of tissues and organs across different species (Cretoiu et al., 2019; Rosa et al., 2021; Dolbnya et al., 2025). Their unique ultrastructural

traits, immunophenotypic features, gene expression, proteomic profiles, and microRNA signatures provide compelling evidence that TCs differ from "classical" fibroblasts and other interstitial cell types (Faussone Pellegrini and Popescu, 2011; Cretoiu and Popescu, 2014; Díaz-Flores et al., 2014; Song et al., 2016; Cretoiu et al., 2017; Marini et al., 2017a; Dolbnya et al., 2025).

By means of transmission electron microscopy (TEM), TCs are ultrastructurally distinguished by a small cell body giving rise to extremely thin, long, and sinuous prolongations called telopodes (Tps) (Popescu and Faussone-Pellegrini, 2010; Faussone Pellegrini and Popescu, 2011; Cretoiu and Popescu, 2014; Cretoiu et al., 2020; Dolbnya et al., 2025). These Tps exhibit a moniliform aspect, defined by the alternation of slender segments (podomers) and dilated regions (podoms) containing mitochondria, caveolae, and endoplasmic reticulum (Popescu and Faussone-Pellegrini, 2010; Faussone Pellegrini and Popescu, 2011; Cretoiu and Popescu, 2014; Cretoiu et al., 2020). In addition, TCs possess a large euchromatic nucleus with clusters of peripheral heterochromatin encircled by a small amount of cytoplasm containing mitochondria, sparse endoplasmic reticulum, and a small Golgi apparatus (Popescu and Faussone-Pellegrini, 2010; Faussone Pellegrini and Popescu, 2011; Cretoiu and Popescu, 2014; Cretoiu et al., 2020).

Although TEM remains the gold standard technique for the identification of TCs, immunohistochemical staining and light microscopy techniques are also commonly used to detect these cells within the interstitium of different organs (Cretoiu and Popescu, 2014; Díaz-Flores et al., 2014; Marini et al., 2018b; Rosa et al., 2018, 2021; Cretoiu et al., 2020). First, it must be emphasized that currently, no single specific marker for TCs exists. In this context, TCs have been extensively demonstrated to be immunophenotypically defined by CD34 antigen expression, being thus frequently referred to as TCs/CD34$^+$ stromal cells (Díaz-Flores et al., 2014, 2020a, 2020b; Romano et al., 2020). Nevertheless, CD34-based identification has intrinsic limitations, as this surface marker is expressed by different cell

populations. In particular, considering that CD34 positivity is also shared by vascular endothelial cells in the stromal compartment, the combination of CD34 and CD31 immunostaining has been largely applied to clearly discriminate $CD34^{+}CD31^{-}$ TCs from the surrounding $CD34^{+}CD31^{+}$ vascular structures, especially thin-walled blood capillary vessels (Marini et al., 2018c; Rosa et al., 2019; Cretoiu et al., 2020; Romano et al., 2020). Double immunolabeling for CD34 and α-smooth muscle actin (α-SMA) is instead useful to distinguish TCs from other adjacent stromal cells, including myofibroblasts, myoid cells, periglandular myoepithelial cells, smooth muscle cells, and pericytes, which indeed express α-SMA but not CD34 (Marini et al., 2018b; Rosa et al., 2019, 2021). In addition, since double positivity for CD34 and platelet-derived growth factor receptor-α (PDGFR-α) has been found to immunophenotypically characterize TCs from many tissues and organs, PDGFR-α is an additional frequently used TC marker (Cretoiu and Popescu, 2014; Marini et al., 2017b; Rosa et al., 2018, 2021). Similar to CD34, even PDGFR-α cannot be considered TC-specific, as it is a common marker for various mesenchymal stromal cells and tissue-resident fibroblasts (Muhl et al., 2020). Taken together, it has been proposed that TCs may be identified as $CD34^{+}PDGFR\text{-}\alpha^{+}CD31^{-}$ stromal cells to differentiate them from both $CD34^{+}CD31^{+}$ endothelial cells and $CD34^{-}PDGFR\text{-}\alpha^{+}$ “classical” fibroblasts (Romano et al., 2020). More recently, the mesenchymal transcription factor FOXL1 and the G-protein-coupled receptor LGR5 have been identified as markers for intestinal TCs, but their possible usefulness to identify TCs in other organs is still to be proven (Kondo and Kaestner, 2019; Rosa et al., 2021). Yet, the identification of TC-specific markers remains a topic of particular interest for future research. Evidence also suggests that, rather than being a uniform cellular population, TCs may constitute a heterogeneous system with distinct TC subtypes identifiable in different organs or even coexisting within the same organ (Cretoiu et al., 2017). Moreover, it appears that in pathological or highly dynamic regenerative states, these

cells may undergo a phenotypic shift with changes in their markers (Díaz-Flores et al., 2014, 2015, 2016).

Although TC roles have not yet been completely unraveled, increasing literature suggests that they might exert both general and location-specific functions (Cretoiu et al., 2017; Kondo and Kaestner, 2019). Indeed, by means of their long-distance Tps, TCs generate extremely intricate three-dimensional networks thought to provide an essential scaffold able not only to orchestrate proper tissue organization during development and preserve postnatal tissue and organ structural integrity/functionality, but also to facilitate both homo- and heterocellular communications (Faussone Pellegrini and Popescu, 2011; Cretoiu and Popescu, 2014; Cantarero et al., 2016; Cretoiu, 2016; Díaz-Flores et al., 2016; Faussone-Pellegrini and Gherghiceanu, 2016; Cretoiu et al., 2020). Of note, the hypothesis that TCs may locally function as important homeostatic regulators is further corroborated by the several TC network anomalies that have been described in different pathological tissues (Díaz-Flores et al., 2014, 2016, 2020a, 2020b; Ibba-Manneschi et al., 2016a). In addition, TCs seem to perform paracrine tasks, as demonstrated by their capability to transmit genetic information and molecular signals to other cells through the release of various extracellular vesicles, including exosomes, ectosomes, and multivesicular cargos (Cretoiu et al., 2016; Marini et al., 2017a; Rosa et al., 2021). Because of the aforementioned spatial and paracrine relationships with various cell types, TCs are hence generally regarded as "connecting cells", able to transform the interstitial microenvironment into an integrated system that aids in both proper organ morphogenesis and subsequent maintenance of local tissue homeostasis (Ibba-Manneschi et al., 2016a; Wollheim, 2016). Furthermore, by interacting with immune cells, TCs appear to play a role in the modulation of local immune responses, while by regulating tissue-resident stem/progenitor cell survival, proliferation, differentiation, maturation, and guidance, they seem to be involved in organ repair and regeneration (Díaz-Flores et al., 2014, 2015, 2016; Ibba-Manneschi et al., 2016a, 2016b; Song et al., 2016;

Marini et al., 2017a; Kondo and Kaestner, 2019). In this regard, based on their colocalization with tissue-resident stem cells and their ability to release extracellular vesicles and crosstalk with stem cells, TCs have been hypothesized to potentially represent an essential player in the stem cell niche milieu of different organs, including the intestine, heart, lung, skin, eye, and skeletal muscle (Gherghiceanu and Popescu, 2010; Bojin et al., 2011; Popescu et al., 2011a; Luesma et al., 2013; Albulescu et al., 2015; Bei et al., 2015; Cismaşiu and Popescu, 2015; Díaz-Flores et al., 2016; El Maadawi, 2016; Kondo and Kaestner, 2019). Finally, as in some tissue locations TCs have been found to express stem cell markers—including c-kit/CD117, stem cell antigen-1 (Sca-1), and Oct-4—it has also been suggested that they may represent a subset of mesenchymal stem cells with differentiation potential and, thus, directly involved in tissue regenerative processes (Bojin et al., 2011; Galiger et al., 2014; Bei et al., 2015; Díaz-Flores et al., 2016).

On these bases, the present review aims to recapitulate current evidence positioning TCs as active and essential components of the skeletal muscle interstitial compartment and stem cell niche. A particular focus is placed on the putative strategic role of TCs in maintaining skeletal muscle tissue homeostasis, their involvement in muscle pathological alterations, and, most importantly, their coordination of the regenerative response following injury. Hence, this review underscores that these cells should no longer be considered mere bystanders, but integral participants in the muscle tissue repair process. Additionally, we will discuss the promising therapeutic potential of TC-based strategies to promote skeletal muscle tissue repair/regeneration and limit post-injury fibrosis.

**Telocytes as emerging components of the skeletal muscle interstitial compartment and stem cell niche**

Skeletal muscle represents a highly plastic tissue endowed with a remarkable regenerative capacity, largely attributable to the presence of stem cells, which are commonly referred to as satellite cells due to their position just outside the myofiber plasma membrane (Morrison and Spradling, 2008; Chang and Rudnicki, 2014; Almeida et al., 2016; Fuchs and Blau, 2020; Koike et al., 2022; Yeh et al., 2023; Byun et al., 2024; Jiang et al., 2024). These cells, which reside within specialized niches scattered throughout the tissue and located between the sarcolemma of myofibers and the surrounding basal lamina, sustain regenerative processes throughout most of adult life by providing myogenic progenitors (myoblasts) capable of restoring damaged muscle tissue (Morrison and Spradling, 2008; Chang and Rudnicki, 2014; Almeida et al., 2016; Fuchs and Blau, 2020; Rosa et al., 2021; Koike et al., 2022; Yeh et al., 2023; Byun et al., 2024; Jiang et al., 2024). Under physiological conditions, satellite cells reside in a reversible state of cell cycle arrest primarily maintained by Notch signaling; however, upon appropriate stimuli—such as mechanical loading (intense physical activity) or tissue damage—they break quiescence, re-enter the cell cycle, and upregulate transcription factors, such as myogenic factor 5 (Myf5) and myoblast determination protein 1 (MyoD), eventually expressing myogenin as they differentiate and fuse to form new myofibers or to repair damaged myofibers (Almeida et al., 2016; Manetti et al., 2019; Koike et al., 2022; Yeh et al., 2023; Byun et al., 2024; Jiang et al., 2024). Accumulating evidence indicates that even if satellite cells are the primary and indispensable drivers of myogenesis, effective muscle repair is a multifaceted process that requires the coordinated crosstalk between these cells and various interstitial cell populations, which together form the skeletal muscle stem cell niche (Dinulovic et al., 2017; Koike et al., 2022; Johnson et al., 2023; Koopmans et al., 2023; Byun et al., 2024; Jiang et al., 2024). Indeed,

satellite cell activation, self-renewal, and commitment are orchestrated by a cascade of signaling pathways that are dynamically regulated by extrinsic, niche-derived factors (Dinulovic et al., 2017; Koike et al., 2022; Johnson et al., 2023; Koopmans et al., 2023; Byun et al., 2024; Jiang et al., 2024).

Recent single-cell transcriptomic studies offered new insights into the heterogeneous composition of the adult skeletal muscle interstitium and stem cell niche, highlighting the presence of a variety of cellular populations, including satellite cells, fibro-adipogenic progenitors (FAPs), immune cells (B cells, T cells, macrophages, and neutrophils), endothelial cells, pericytes, neural cells, tenocytes, and smooth muscle-mesenchymal cells (Giordani et al., 2019; Koike et al., 2022). However, further functional analysis is required to reveal how each of these populations may regulate skeletal muscle regeneration, leading to a better understanding of the pathophysiology of muscle disorders like sarcopenia and fibrosis caused by regeneration defects (Koike et al., 2022). In this regard, spatial transcriptomics is rapidly emerging as a groundbreaking technology with great potential to accelerate our understanding of the cellular interactions that regulate satellite cell responses in skeletal muscle injury and regeneration (Virtanen et al., 2025). Hence, such an advancement is essential to characterize the fundamental mechanisms of muscle repair and identify aberrant signaling pathways underlying chronic injury or impaired regeneration (Virtanen et al., 2025). At present, several soluble mediators released in the niche have been shown to influence satellite cell behavior, regulating their maintenance in a quiescent state or inducing myogenic cell differentiation (Koike et al., 2022). For instance, multiple cytokines—such as fibroblast growth factor, insulin-like growth factor-1, PDGF, hepatocyte growth factor (HGF), tumor necrosis factor-α, vascular endothelial growth factor (VEGF), interleukin (IL)-6, and IL-10—have been identified to promote the activation, proliferation, and differentiation processes of satellite cells, whereas transforming growth factor-β has been reported to inhibit these processes (Koike et al., 2022; Yeh et al., 2023). Furthermore,

microRNAs have recently emerged as addition mediators implicated in the control of satellite cell function in the adult skeletal muscle (Koopmans et al., 2023). In addition, different downstream signaling pathways contribute to the temporal and spatial regulation of satellite cells from quiescence to different stages of the myogenic process, particularly Notch, Wnt, and Eph/ephrin signaling (Stark et al., 2011; Arnold et al., 2020; Koike et al., 2022; Yeh et al., 2023).

Within this intricate cellular landscape, TCs deserve particular attention, as they represent a distinct population of interstitial cells widely distributed within the perimysial and endomysial compartments of the adult skeletal muscle (Figs. 1 and 2), where they express a plethora of markers, including CD34 (Fig. 1a−c), PDGFR-β, caveolin-1, c-kit/CD117, vimentin, and VEGF (Bojin et al., 2011; Popescu et al., 2011b; Suciu et al., 2012; Arafat, 2016; Marini et al., 2018c; Manetti et al., 2019; Henrot et al., 2023). It has been shown that the immunophenotypic profiles of skeletal muscle TCs, together with their unique ultrastructural features (Fig. 1d), distinguish them from both fibroblasts, which are indeed negative to both CD34 and c-kit/CD117, and satellite cells, which are characterized by the expression of the Pax7 transcription factor (Bojin et al., 2011; Popescu et al., 2011b; Suciu et al., 2012; Arafat, 2016; Marini et al., 2018c; Manetti et al., 2019). Skeletal muscle TCs are typically oriented parallel to myofibers and frequently extend their Tps into small invaginations at the myofiber periphery (Popescu et al., 2011b; Arafat, 2016). Moreover, close spatial relationships between Tps and satellite cells could be highlighted by TEM or double immunostaining for CD34 and Pax7 (Fig. 1d,e) (Manetti et al., 2019). In addition, by laminin immunolabeling, TCs have been demonstrated to exhibit a perivascular localization within the muscle interstitium, as, in contrast to vascular mural cells, they are not surrounded by a basal lamina (Popescu et al., 2011b; Suciu et al., 2012). Notably, the position of TCs outside the basal lamina of capillary vessels clearly differentiates them from pericytes, which are largely acknowledged as components of the skeletal muscle stem cell niche (Koike et

al., 2022; Johnson et al., 2023). Such a distribution of the endomysial network of $CD34^+CD31^-$ TCs around $CD34^+CD31^+$ capillary vessels has been further confirmed by double immunofluorescence staining (Fig. 1c) (Marini et al., 2018c; Manetti et al., 2019).

Although the precise functional roles of TCs in skeletal muscle physiology still remain to be fully elucidated, accumulating evidence suggests that these interstitial cells may constitute previously unrecognized components of the skeletal muscle stem cell niche and may actively contribute to tissue repair and regeneration (Bojin et al., 2011; Ceafalan et al., 2014; Manetti et al., 2019; Rosa et al., 2021). Furthermore, as already mentioned above, based on their expression of the stemness marker c-kit/CD117, skeletal muscle TCs have even been hypothesized to represent a distinct progenitor-like cell population within the stem cell niche (Bojin et al., 2011). Based on their morphology, TCs have been proposed to play a role in the skeletal muscle stem cell niche by establishing long-distance intercellular connections *via* their Tps, thus functioning as integrative hubs coordinating the diverse signals required for skeletal muscle homeostasis, remodeling, and regeneration (Bojin et al., 2011; Ceafalan et al., 2014). Moreover, the TC network surrounding myofibers has been suggested to provide not only a physical scaffold guiding the migration and spatial organization of myogenic progenitors after activation, but also a relevant source of paracrine regulatory signals within the niche (Bojin et al., 2011; Ceafalan et al., 2014). Consistent with this notion, skeletal muscle TCs have been shown to express high levels of VEGF, a trophic factor known to exert important regulatory effects on both microvasculature and satellite cells within the muscle stem cell niche (Popescu et al., 2011b; Sassoli et al., 2012; Manetti et al., 2019). These assumptions have been substantiated by recent experimental studies that, investigating TC distribution and behavior in an *ex vivo* mouse model of skeletal muscle injury induced by forced eccentric contraction, highlighted the TC capability to establish important morphofunctional interactions with satellite cells (Manetti et al., 2019; Squecco et al., 2021). Compared with uninjured control muscles, indeed, damaged muscles displayed

a markedly expanded network of $CD34^{+}CD31^{-}$ TCs throughout the myofiber endomysium, with Tps preferentially arranged around activated satellite cells exhibiting nuclear MyoD positivity (Manetti et al., 2019). Physical intimate interactions between TCs and satellite cells following injury-induced activation were further revealed by TEM, as evidenced by the presence of Tps traversing disrupted regions of the myofiber basal lamina and establishing direct contacts with the underlying activated satellite cells (Fig. 2) (Manetti et al., 2019). Basal lamina degradation represents a crucial step that enables satellite cell migration toward the injury site, a process to which satellite cells themselves contribute through the secretion of proteolytic enzymes, including matrix metalloproteinase-2 and -9, along with their specific tissue inhibitors (Sassoli et al., 2011; Thomas et al., 2015). Notably, as TCs also express matrix metalloproteinases (Zheng et al., 2013), it has been proposed that they may cooperate with satellite cells in basal lamina remodeling and potentially facilitate the release of promyogenic factors from the extracellular matrix, thereby actively supporting satellite cell activation (Manetti et al., 2019). Consistent with these observations, analyses of TCs and satellite cells isolated from intact single myofibers surrounded by their endomysial sheath confirmed the preferential physical interaction between these cells and revealed an upregulation of VEGF expression in TCs derived from damaged muscles (Manetti et al., 2019).

Overall, these data support the hypothesis that TCs constitute a novel and functionally relevant component of the skeletal muscle stem cell niche, exhibiting “nursing cell” properties that promote satellite cell activation and myogenic differentiation through both direct cell-to-cell interactions and paracrine mechanisms (Manetti et al., 2019). Besides VEGF- and matrix metalloproteinase-mediated effects, further studies are necessary to more comprehensively uncover the mechanisms by which TCs might influence muscle satellite cells (Fig. 2). In this regard, a number of factors and signaling pathways that have currently been related to TCs in tissues other than the skeletal muscle but are known to

control satellite cell behavior may be worthy of investigation (Fig. 2). In particular, it is important to mention that TCs have been reported to secrete HGF, which is a crucial mediator of satellite cell activation, proliferation, and differentiation (Zhao et al., 2022; Yeh et al., 2023; Zhang et al., 2023). Moreover, TCs have been identified as an important source of other cytokines, such as IL-6 and IL-10, microRNAs, and Wnt proteins, which are all prominently implicated in myogenesis and muscle repair processes (Shoshkes-Carmel et al., 2018; Kondo and Kaestner, 2019; Rosa et al., 2021; Koike et al., 2022; Koopmans et al., 2023; Yeh et al., 2023; Porcu et al., 2024). Of note, the secretome of myocardial TCs was found to be particularly enriched in IL-6 and to modulate the activity of cardiac stem cells (Albulescu et al., 2015). Another study found that TCs are capable of transferring extracellular vesicles loaded with microRNAs to cardiac stem cells (Cismaşiu and Popescu, 2015). Furthermore, a very recent investigation demonstrated that TCs deliver essential Wnt proteins directly to intestinal stem cells *via* synapse-like intercellular contacts (Greicius et al., 2025). Interestingly, the evidence that after damage, TCs establish direct intercellular contacts with activated satellite cells may suggest the implication of similar Wnt-mediated mechanisms during muscle repair (Manetti et al., 2019). Likewise, the possible contribution of TCs to juxtacrine signaling pathways involved in the regulation of muscle satellite cells, mainly Notch and Eph/ephrin, may be worth investigating (Stark et al., 2011; Arnold et al., 2020; Koike et al., 2022; Yeh et al., 2023). Finally, considering the well-known contribution of TCs to intercellular signaling *via* both cell-to-cell contacts and release of extracellular vesicles, it is conceivable that they are engaged in crosstalk not only with satellite cells but also with other cellular components of the skeletal muscle niche, such as with microvascular cells, neural cells, FAPs, and immune cells (Fig. 3) (Cretoiu et al., 2012, 2016, 2020; Cretoiu and Popescu, 2014; Faussone-Pellegrini and Gherghiceanu, 2016; Kondo and Kaestner, 2019; Rosa et al., 2021).

Further insights into the possible functions of skeletal muscle TCs have emerged from a study that focused on human fetal skeletal muscle development (Marini et al., 2018a). When examining TCs in lower-limb fetal muscle tissue, indeed, the authors found that their distribution varied across gestational stages, suggesting that these cells may play a prominent role during early myogenesis, contributing to tissue organization, compartmentalization, angiogenesis, and myotube maturation (Marini et al., 2018a). Specifically, from 9 to 11.5 weeks of gestation, the number of TCs was markedly increased, with Tps forming an extensive reticular network closely associated with primary and secondary myotubes undergoing maturation, while at approximately 12 weeks of gestation, coinciding with the appearance of more mature myotubes, the number of TCs was significantly reduced (Marini et al., 2018a). Taken together, current observations suggest that TCs residing within the skeletal muscle stem cell niche may exert promyogenic functions not only during postnatal muscle repair and regeneration, but also throughout morphogenesis and fetal development (Marini et al., 2018a; Manetti et al., 2019).

In addition to satellite cells, the skeletal muscle interstitium harbors several other non-satellite progenitor populations with differentiation potential, including bone marrow-derived mesenchymal stem cells, pericytes, vessel-associated mesodermal progenitors known as mesoangioblasts, and $CD133^+$ cells, although their quantitative contribution to the myoblast pool appears to be relatively limited (Sambasivan and Tajbakhsh, 2015; Ambrosi et al., 2019; Fuchs and Blau, 2020; Rosa et al., 2021; Koike et al., 2022). Another well-characterized interstitial population with muscle regenerative potential is represented by FAPs, namely cells expressing PDGFR-α, Sca-1, and CD34 markers that support satellite cell function but are capable of differentiating into fibroblastic or adipogenic lineages when homeostasis fails (Joe et al., 2010; Uezumi et al., 2014; Parker and Hamrick, 2021; Koike et al., 2022; Henrot et al., 2023; Byun et al., 2024; Jiang et al., 2024). In fact, in some pathological settings, including muscular dystrophies or chronic injury, the extracellular

microenvironment has been shown to shift the activity of FAPs toward detrimental outcomes, leading to the replacement of functional muscle with non-contractile fibrotic and adipose tissue (Parker and Hamrick, 2021; Giuliani et al., 2022; Henrot et al., 2023; Johnson et al., 2023; Jiang et al., 2024). Interestingly, given that PDGFR-α and CD34 are amongst the most used markers for TC identification, and considering that TCs have been reported to express the stem cell-associated marker Sca-1 in certain tissues, it is conceivable that TCs represent a morphologically and functionally specialized subset of FAPs (Cretoiu and Popescu, 2014; Díaz-Flores et al., 2016; Marini et al., 2018c). Indeed, it is important to consider that TCs are primarily defined by their unique ultrastructural morphology (*i.e.*, cells with Tps), and that skeletal muscle TCs also express c-kit/CD117, a marker that has never been described in FAPs (Bojin et al., 2011; Cretoiu and Popescu, 2014). Exploring the possibility that in the skeletal muscle TCs may express additional markers, such as FOXL1 and LGR5, could help to better classify them as a distinct subset of FAPs (Kondo and Kaestner, 2019; Rosa et al., 2021). It is also worth noting that Bojin et al., who first identified and characterized TCs within the human skeletal muscle stem cell niche, had already reported that muscle TCs exhibit high proliferative activity and pluripotent potential, thus providing the first evidence supporting a possible FAP-like role for TCs in muscle repair and regeneration (Bojin et al., 2011). In addition, similar to FAPs, TCs have been widely demonstrated to exhibit progenitor properties across multiple tissue repair processes and pathological conditions (Díaz-Flores et al., 2014, 2015, 2016). Collectively, it can be hypothesized that within the same muscle interstitial niche, “classical” FAPs might mainly serve as a general reservoir of mesenchymal progenitors, while TCs might constitute a FAP subpopulation preferentially behaving as effector cells, specifically tasked with niche maintenance and “nursing” satellite cells through direct physical contact and extracellular vesicle release. Finally, it is worth mentioning that, by performing an immunohistochemical analysis with a panel of progenitor cell markers on human skeletal muscle, Hejbøl et al. have identified an endomysial interstitial cell population

co-expressing CD10, CD34, CD271, and PDGFR-α (Hejbøl et al., 2019). Interestingly, since these cells were not only $CD34^+PDGFR\text{-}\alpha^+$, but also displayed the characteristic TC ultrastructural hallmarks when observed by immunoelectron microscopy for CD10 positivity, the authors proposed that they correspond to TCs (Hejbøl et al., 2019). In the same study, $CD10^+$ endomysial interstitial cells/TCs were found to increase in muscle lesions and to display proliferative activity, suggesting a role in myogenesis and muscle regeneration (Hejbøl et al., 2019). Their phenotype was also dynamically regulated by injury severity: focal damage was associated with CD10, CD34, and CD271 upregulation and reduced PDGFR-α expression, whereas severe lesions showed loss of CD34 and increased PDGFR-α positivity (Hejbøl et al., 2019). Differential CD10 expression around atrophic *vs*. hypertrophic myofibers further highlighted the marked plasticity of these cells, supporting their involvement in skeletal muscle repair (Hejbøl et al., 2019).

In a study investigating TC distribution in the tibialis anterior muscle of healthy rats displaying muscle hypertrophy after an endurance training protocol (*i.e.*, treadmill running) compared with sedentary rats, which conversely showed muscle atrophy, TCs were found to be significantly reduced in sedentary rats, while in trained animals the TC population remained stable (Ravalli et al., 2021). Based on these findings, the authors proposed that physical activity prevents TC depletion and promotes remodeling processes that preserve the muscle interstitial niche. This association between skeletal muscle TCs and exercise highlights their potential relevance in regenerative medicine and provides novel perspectives for the treatment of sarcopenia and other musculoskeletal disorders (Ravalli et al., 2021).

TCs have also been investigated in two distinct forms of muscular dystrophy, namely Ullrich congenital muscular dystrophy and dysferlinopathy (Sabatelli et al., 2022; Chekmareva et al., 2025). In Ullrich congenital muscular dystrophy, collagen VI deficiency was found to be associated with a marked expansion of $CD34^+$ TCs within the deep fascia

and muscle interstitium, where they formed an extensive cellular network interfacing with myofibers, adipocytes, and vascular structures (Sabatelli et al., 2022). Such a redistribution led the authors to hypothesize that TCs may act as a compensatory mechanism in response to satellite cell dysfunction and impaired muscle regeneration (Sabatelli et al., 2022). Conversely, in dysferlinopathy, which arises from mutations in the gene encoding dysferlin, a transmembrane protein involved in skeletal muscle regeneration, ultrastructural analyses revealed necrosis of both satellite cells and TCs, indicating a direct impairment of the niche components essential for muscle repair (Chekmareva et al., 2025). All together, these findings support the notion that TCs are not merely passive stromal elements but are dynamically involved in maintaining skeletal muscle homeostasis, and that their dysfunction or aberrant activation may contribute to defective regeneration and disease progression in muscular dystrophies (Sabatelli et al., 2022; Chekmareva et al., 2025).

Within the skeletal muscle, cells exhibiting TC-characteristic ultrastructural features have also been identified in neuromuscular spindles, where they may contribute to the regulation of muscle tone and motor activity (Díaz-Flores et al., 2013). In particular, TCs have been reported to form the innermost layer and, in part, the outermost layer of the external neuromuscular spindle capsule, as well as the entire internal capsule, where their Tps are arranged in a dense network surrounding intrafusal striated myofibers, nerve fibers, and blood microvessels (Díaz-Flores et al., 2013). This organization suggests both passive and active roles of these cells in the modulation of neuromuscular spindle function, potentially *via* cell-to-cell signaling, as suggested by the frequent detection of shed vesicles and exosomes released from, and in close proximity to, Tps (Díaz-Flores et al., 2013). TCs have also been proposed to participate in neuromuscular spindle development, since TCs and perineural cells in human fetuses at 22-23 weeks of gestation appear to form a sheath likely serving as a guiding structure for the organization of intrafusal components (Díaz-Flores et al., 2013). Finally, neuromuscular spindle TCs have been proposed to be involved

in some skeletal muscle pathological conditions, as suggested by the increased number of $CD34^+$ TCs found in residual neuromuscular spindles adjacent to infiltrative musculoaponeurotic fibromatosis, together with the variable TC distribution in neuromuscular spindles surrounded by lymphocytic infiltrates in inflammatory myopathies (Díaz-Flores et al., 2013). From an immunohistochemical standpoint, neuromuscular spindle TCs were found to express CD34 and vimentin, while c-kit/CD117 has been only occasionally detected (Díaz-Flores et al., 2013).

Recent studies also described TCs within the rat myotendinous junction (site of contractile force transmission from the muscle to the tendon), where they have been described to form a niche by establishing intimate structural relationships with both myofiber plasma membrane invaginations and satellite cells (Pimentel Neto et al., 2020, 2024; Rocha et al., 2021). Interestingly, physical aquatic training following joint immobilization and consequent skeletal myofiber atrophy and reduced myotendinous interface was found not only to restore the myotendinous junction perimeter and nuclear density, but also to significantly promote functional and structural remodeling of the TC niche, thus facilitating tissue plasticity and regeneration through TC paracrine signaling and release of extracellular vesicles (Rocha et al., 2021). Collectively, these findings indicate that TCs may act as key modulators of myotendinous junction structural integrity and recovery in response to mechanical unloading and subsequent reloading (Rocha et al., 2021).

Preliminary studies have identified TCs as integral components also of the deep muscular fascia, a three-dimensional continuum of soft, collagen-containing fibrous tissues that attaches, encloses, and separates skeletal muscles and internal organs, allowing all systems to operate in an integrated manner (Dawidowicz et al., 2016; Fede et al., 2021). In particular, TCs have been identified in the fascia lata, crural, plantar, and thoracolumbar fasciae, where they might contribute to tissue repair, regeneration, remodeling, immune modulation, and intercellular communication, thereby possibly playing a regulatory role in

myofascial homeostasis, myofascial pain, and fascia-related disorders (Dawidowicz et al., 2016; Fede et al., 2021).

To conclude, even if TCs have been extensively studied in mammals, and particularly in humans and rodents, recent research has established their presence also in lower vertebrates such as the common carp, where they have been identified within the gill stroma, surrounding and partially enveloping undifferentiated stem cells, and establishing single or multi-point contacts with skeletal myofibers (Emeish et al., 2023; Massoud et al., 2024). In particular, TCs have been demonstrated to be highly sensitive to environmental changes (Emeish et al., 2023; Massoud et al., 2024). Specifically, in response to salinity stress, they displayed adaptive changes, including an increase in the release of secretory vesicles that might promote the organization of myofilament proteins in myoblasts, thus contributing to the hypertrophy of skeletal myofibers (Emeish et al., 2023; Massoud et al., 2024).

**Conclusions and future perspectives**

Over the last fifteen years, TCs have been consistently identified within the skeletal muscle perimysium and endomysium, where their long Tps establish close spatial relationships with myofibers, capillaries, and nerve endings, forming an extensive and interconnected interstitial network (Fig. 2) (Bojin et al., 2011; Popescu et al., 2011b; Suciu et al., 2012; Arafat, 2016; Marini et al., 2018c; Manetti et al., 2019). Besides merely behaving as passive structural elements, TCs are now increasingly recognized as active regulators of skeletal muscle homeostasis and key coordinators of regenerative responses within the stem cell niche (Fig. 3), a highly dynamic microenvironment in which tightly orchestrated cellular interactions and signaling cues govern satellite cell quiescence, activation, self-renewal, and differentiation (Bojin et al., 2011; Ceafalan et al., 2014; Manetti et al., 2019; Rosa et al., 2021; Koike et al., 2022; Yeh et al., 2023). Current evidence, indeed, suggests

that TCs may function as "nursing cells" for satellite cells, contributing to myogenesis by paracrine signaling mechanisms, such as the release of extracellular vesicles and the upregulation of promyogenic factors like VEGF (Popescu et al., 2011b; Sassoli et al., 2012; Manetti et al., 2019). Moreover, it has been proposed that, after muscle tissue damage, TCs may participate in the active remodeling of the stem cell niche by means of matrix metalloproteinases, which create a “permissive gateway” through the basal lamina, allowing activated satellite cells to migrate to the site of injury (Manetti et al., 2019; Rosa et al., 2021). Based on the current knowledge of TCs from different tissues and organs, it can be hypothesized that a number of additional paracrine and juxtacrine signaling pathways may mediate muscle TC-satellite cell communications, which deserve to be addressed in depth by future studies. In this scenario, it is worth mentioning that the characterization of the skeletal muscle interstitium has been significantly advanced by recent single-cell transcriptomic studies (Giordani et al., 2019; Koike et al., 2022). Indeed, such cutting-edge studies have unraveled new resident populations, including specific stromal subsets that likely encompass or overlap with the TC population, and mapped their dynamic interactions (Giordani et al., 2019; Koike et al., 2022). Hopefully, spatial transcriptomics will further contribute to the understanding of the muscle interstitium, helping to definitively clarify whether TCs may represent a unique, morphologically and functionally specialized subset of FAPs (Virtanen et al., 2025). Furthermore, single-cell RNA sequencing and other omics applied to muscle injury models have great potential to unravel transcriptomic and metabolic shifts in TCs and other cellular components of the stem cell niche, strengthening the view that they function as dynamic regulators during muscle repair/regeneration.

Accordingly, TCs are expected to gain growing attention as potential targets or tools in the fields of tissue engineering and regenerative medicine for the skeletal muscle, whose capacity to regenerate is high after minor, transient damage but limited following severe injuries. Looking forward, the identification of TCs as active players within the skeletal

muscle stem cell niche opens significant avenues for the exploration of new TC-based therapeutic strategies in the preclinical setting. Indeed, a primary goal of future *in vitro* and *in vivo* research could be testing the TC secretome, particularly TC-derived extracellular vesicles such as exosomes, to deliver promyogenic molecular signals directly to damaged skeletal muscle tissue. This approach may hold immense potential for the treatment of sarcopenia, severe muscle injuries, and other disorders characterized by impaired tissue regeneration. Moreover, it is important to consider that after skeletal muscle injury, fibrosis often manifests, leading to aberrant regeneration and incomplete functional recovery (Garg et al., 2015). Of note, to date, a number of *in vitro* and *in vivo* studies have demonstrated significant antifibrotic effects of TC secretome, TC-derived exosomes, or TC transplantation in a variety of organs ( Zhao et al., 2014; Zheng et al., 2018; Chen et al., 2023; Zhang et al., 2023; Rosa et al., 2025, 2026). However, the actual TC-mediated antifibrotic effects remain to be specifically proved in skeletal muscle. In addition, it must be acknowledged that TC-based therapeutic approaches may clearly face several practical challenges, including cell isolation, purification, expansion, and delivery, as well as safety concerns (Li et al., 2016; Romano et al., 2020; Sanches et al., 2024). In this regard, considering that, like FAPs, TCs might preferentially shift toward profibrotic lineages in pathological microenvironments (Díaz-Flores et al., 2014, 2015, 2016), TC-derived secretome/exosomes might be preferable to TC transplantation as a cell-free therapeutic tool. Collectively, despite obvious limitations, current evidence and hypotheses provide a strong rationale for further exploring the potential of TC-based strategies to concurrently enhance skeletal muscle tissue repair/regeneration and restrain post-injury fibrosis.

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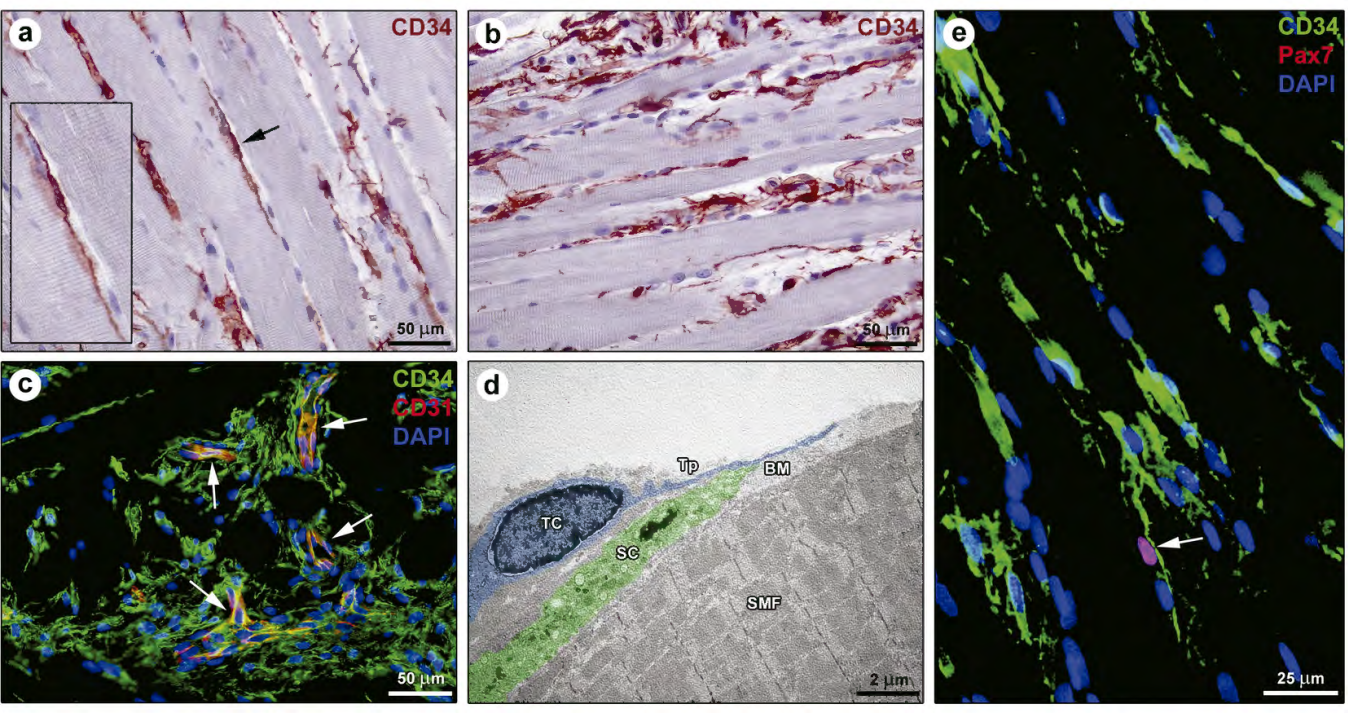
## Figure captions

**Fig. 1.** Localization of skeletal muscle-resident telocytes. **(a-c)** Photomicrographs of human skeletal muscle tissue sections immunostained for CD34 (brownish red) with hematoxylin nuclear counterstain **(a, b)**, or double immunostained for CD34 (green) and CD31 (red) with 4',6-diamidino-2-phenylindole (DAPI; blue) nuclear counterstain **(c)**. $CD34^+$ telocytes displaying very long and thin moniliform processes (telopodes) are in close proximity to myofibers and microvessels within the endomysial stromal compartment **(a-c)**. Inset in **(a)**: higher magnification view of a telocyte (arrow) that extends its telopodes along a myofiber. Telocytes are $CD34^+CD31^-$, while vascular endothelial cells (arrows) are $CD34^+CD31^+$ **(c)**. **(d)** Transmission electron microscopy photomicrograph illustrating a telocyte (TC, digitally colored in blue) extending a telopode (Tp) along the basement membrane (BM) of a skeletal myofiber (SMF) in the close vicinity of a satellite cell (SC, digitally colored in green). **(e)** Photomicrograph of human skeletal muscle tissue section double immunostained for CD34 (green) and satellite cell nuclear-expressed marker Pax7 (red) with DAPI (blue) nuclear counterstain. The telopode of a $CD34^+$ telocyte is adjacent to a $Pax7^+$ satellite cell (arrow) at the periphery of a myofiber **(e)**. Scale bars: 2 μm **(d)**, 25 μm **(e)**, 50 μm **(a-c)**.

**Fig. 2.** Schematic depiction of a skeletal muscle bundle consisting of myofibers wrapped around by the endomysium, a thin layer of highly vascularized and innervated connective tissue populated by different stromal cell types, including telocytes. By means of their prolongations (telopodes), telocytes are arranged to build networks within the endomysial stromal compartment, where they may be engaged in intercellular communication through both direct cell-to-cell contacts and release of extracellular vesicles. Telopodes intimately border the skeletal myofiber basement membrane that completely covers quiescent satellite cells. Upon tissue damage, telocytes may support satellite cell activation, contributing to skeletal muscle tissue repair/regeneration *via* both releasing paracrine signals and spreading their telopodes through a fragmented basement membrane to establish direct contact with the underlying satellite cells. According to current evidence and hypotheses, a number of mediators and signaling pathways by which telocytes might influence satellite cells are indicated. Abbreviations: HGF, hepatocyte growth factor; IL, interleukin; MMPs, matrix metalloproteinases; VEGF, vascular endothelial growth factor.

**Fig. 3.** Schematic representation of the network of telocytes as part of the skeletal muscle interstitial niche. The different cellular components of the niche identified by recent single-

cell transcriptomic studies are shown. Abbreviations: EVs, extracellular vesicles; FAPs, fibro-adipogenic progenitors; SMMCs, smooth muscle-mesenchymal cells; TCs, telocytes. Created in part with BioRender.com.


a
CD34
50 μm
b
CD34
50 μm
c
CD34
CD31
DAPI
50 μm
d
Tp
BM
TC
SC
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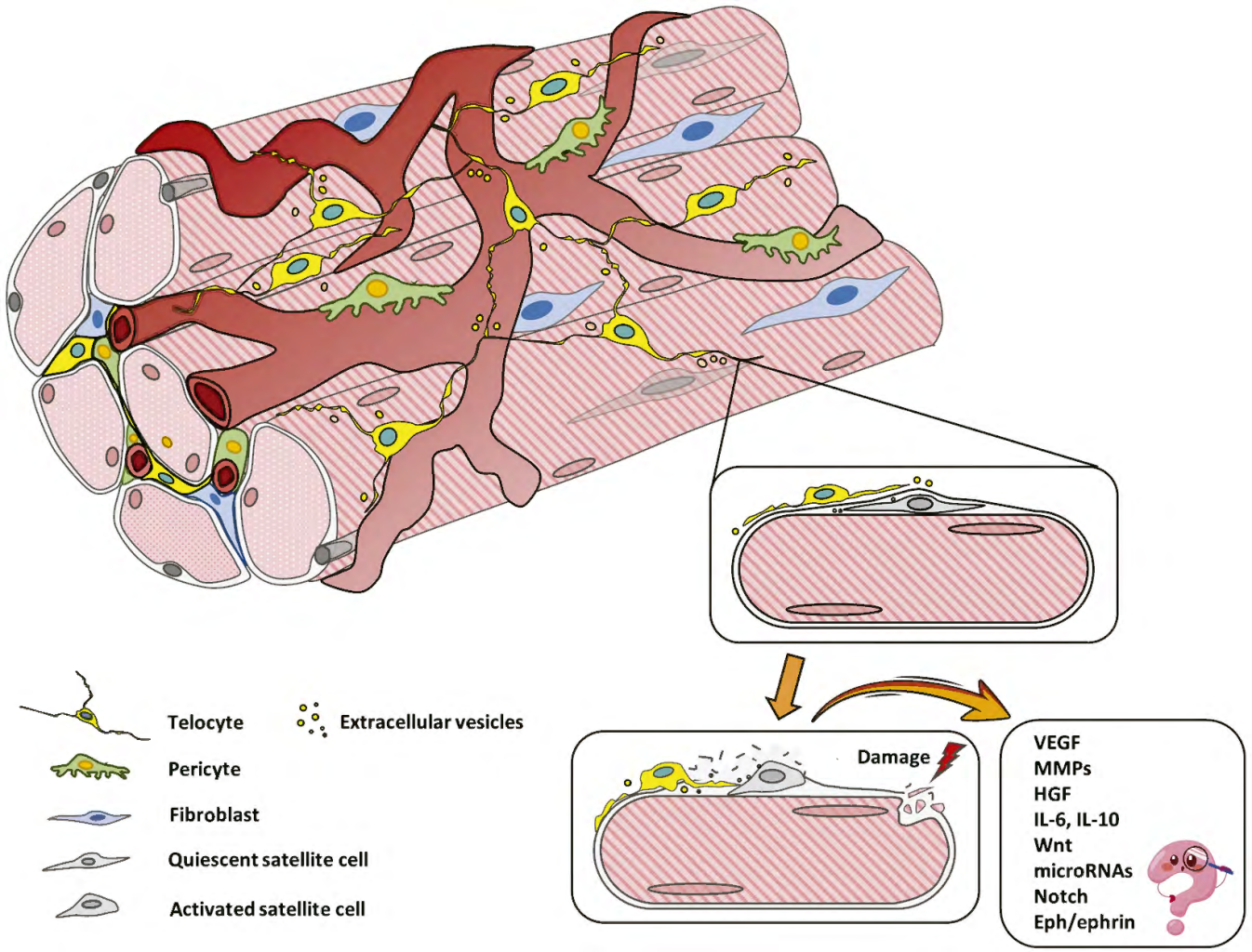
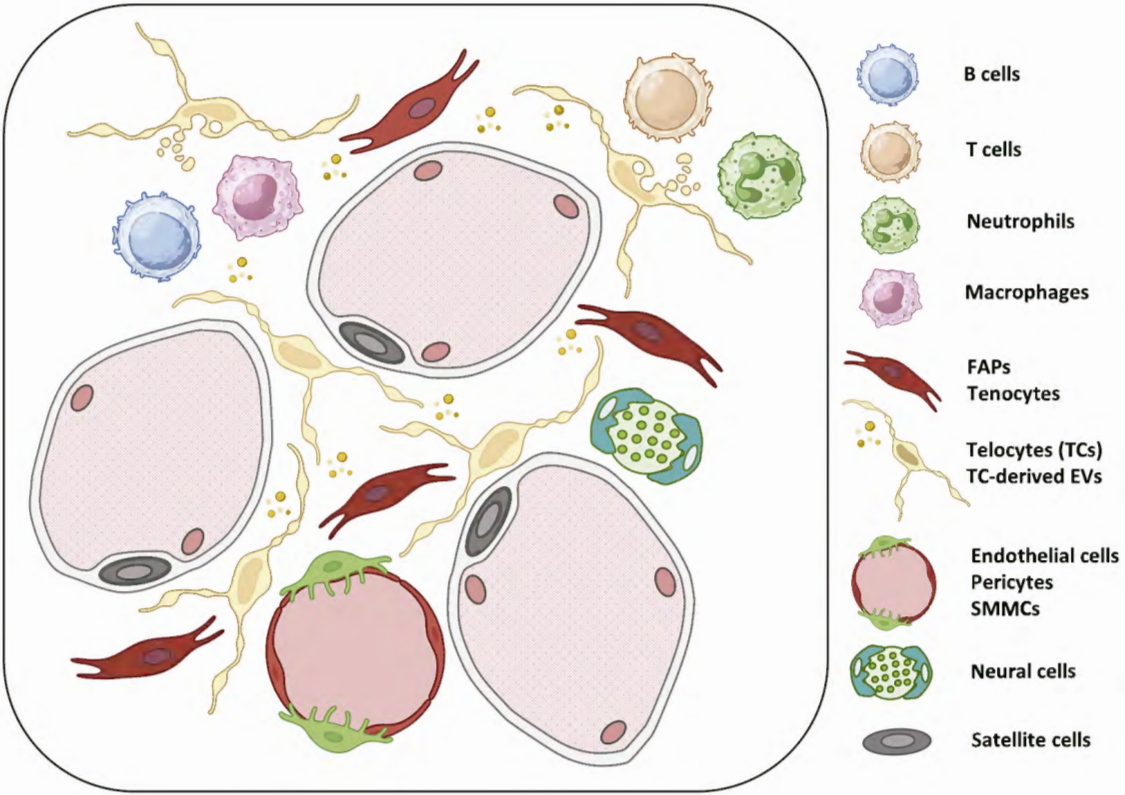
2 μm
e
CD34
Pax7
DAPI
25 μm


Telocyte
Extracellular vesicles
Pericyte
Fibroblast
Quiescent satellite cell
Activated satellite cell
Damage
VEGF
MMPs
HGF
IL-6, IL-10
Wnt
microRNAs
Notch
Eph/ephrin


B cells
T cells
Neutrophils
Macrophages
FAPs
Tenocytes
Telocytes (TCs)
TC-derived EVs
Endothelial cells
Pericytes
SMMCs
Neural cells
Satellite cells