Telocytes in Oral Biology

Telocytes in Oral Biology:

From Structural Networks to Regenerative Medicine

By

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TABLE OF CONTENTS

Chapter One 1
Introduction to Telocytes: A Novel Interstitial Cell Population

Chapter Two 20
Telocytes in Oral Tissues: Structural Networks and Distribution

Chapter Three 49
Functional Roles of Telocytes in Oral Homeostasis and Pathophysiology

Chapter Four 75
Telocytes in Oral Regenerative Medicine: Therapeutic Potential

Chapter Five 101
Key Findings and Future Perspectives

Chapter Six 113
Conclusion

References 115

CHAPTER ONE

INTRODUCTION TO TELOCYTES: A NOVEL INTERSTITIAL CELL POPULATION

Historical Overview and Discovery

The identification and characterization of telocytes (TCs) as a distinct interstitial cell population mark a significant step forward in understanding tissue microenvironments. At first, stromal cells with unique shapes were seen in various tissues, but their exact identity and role remained unclear for many years. Early histological studies described cells with long, thin processes in connective tissues, though these were often mistaken for fibroblasts or other stromal cells due to limitations in imaging techniques and marker specificity. The development of more advanced immunohistochemical methods, especially using CD34 as a marker, helped researchers differentiate TCs from other interstitial cells. Finding CD34+ stromal cells across different species provided strong evidence for this new cell type. A key feature of TCs is their extremely elongated and slender extensions called telopodes (TPs). These structures create complex networks within tissues, supporting extensive communication between cells and helping maintain tissue structure (Ez Elarab et al. 2025; El-Gendy et al. 2025). The identification of these features was made possible by advances in electron microscopy, which enabled detailed visualization of TPs and their spatial relationships with neighboring cells.

Over time, accumulating ultrastructural data confirmed that TCs are not merely passive structural components but actively participate in maintaining tissue homeostasis through dynamic interactions with other cell types (Kondo and Kaestner 2019). In oral tissues specifically, the discovery of TCs has been relatively recent compared to different organ systems. Investigations into the cellular composition of oral mucosa, salivary glands, periodontium, and dental pulp revealed the presence of cells exhibiting the characteristic morphology and marker expression profile associated with TCs (El-Gendy et al. 2025). Their distribution within these tissues suggested specialized roles in supporting epithelial

renewal, modulating immune responses, and orchestrating repair processes following injury. The functional implications assigned to TCs have evolved in tandem with their morphological characterization. While initial hypotheses regarding their roles were primarily based on proximity to stem cell niches or structural associations within tissues, subsequent research began to explore their involvement in signaling pathways and regenerative processes (Kondo and Kaestner 2019). For instance, studies have proposed that TCs contribute to tissue repair by mediating intercellular communication via extracellular vesicles and by influencing local stem cell behavior (Manole et al. 2024; Ez Elarab et al. 2025). Although much of this functional attribution remains under investigation, there is a growing consensus that TCs represent a unique component of the interstitial milieu, making multifaceted contributions to tissue physiology. The historical trajectory from initial observation to formal recognition underscores both the challenges and opportunities inherent in studying novel cell populations. As methodologies continue to improve and new markers are identified, further insights into the origins, heterogeneity, and functions of TCs are likely to emerge. This evolving understanding holds particular promise for regenerative medicine applications in oral health, where harnessing the properties of TCs could lead to innovative therapeutic strategies for tissue repair and disease management (Manole et al. 2024; Ez Elarab et al. 2025).

Unique Morphological Features

Structure and Ultrastructure of Telocytes

TCs are distinguished from other interstitial cells by their unique structural and ultrastructural characteristics, elucidated using advanced imaging techniques such as transmission electron microscopy (TEM) and immunofluorescence. The hallmark of TCs is their small cell body from which extremely long, slender TPs emerge. These TPs exhibit a moniliform, or bead-like, appearance due to the alternation of thin segments, called podomeres, and thicker, dilated regions, termed podoms. Podomeres are elongated and narrow, while podoms are more voluminous and house essential organelles such as mitochondria and elements of the endoplasmic reticulum, which support both metabolic activity and intracellular signaling processes (Alunno et al. 2015; Ez Elarab et al. 2025; Sasso-Cerri et al. 2024). The ultrastructure of TCs reveals that the podoms contain ribosomes and rough endoplasmic reticulum, indicating a capacity for protein synthesis and secretion. This is consistent with observations

across various tissues in which TCs have been identified, including the skin of reptiles such as the Greek tortoise, where TEM studies have confirmed the presence of these organelles within podoms (Ez Elarab et al. 2025). The alternating arrangement of podomeres and podoms along the TPs not only imparts a distinctive morphology but also facilitates specialized functions related to intercellular communication.

TCs form intricate three-dimensional networks within the extracellular matrix by extending their TPs over considerable distances relative to their small somatic volume. These networks enable direct physical contacts with a variety of neighboring cells, including fibroblasts, acinar cells in glands, myoepithelial cells, blood vessels, and immune cells (Ez Elarab et al. 2025; Sasso-Cerri et al. 2024). Such interactions are mediated both by direct membrane appositions and by the release of extracellular vesicles or nanovesicles from podoms. These vesicles serve as vehicles for signaling molecules that contribute to tissue maintenance, repair processes, and homeostasis (Ez Elarab et al. 2025; Sasso-Cerri et al. 2024). Morphologically, TCs can be differentiated from fibroblasts and other mesenchymal cells not only by their unique TPs architecture but also by their genic expression profiles and functional properties. While fibroblasts typically display shorter processes without the characteristic alternation of podomeres and podoms, TCs possess long branching extensions with dichotomous patterns that allow them to bridge distant cellular domains within tissues (Alunno et al. 2015; Kumar et al. 2024; Sasso-Cerri et al. 2024). In oral tissues specifically, this structural organization underpins their role in maintaining tissue integrity and facilitating dynamic responses to physiological or pathological stimuli. The presence of abundant mitochondria within podoms suggests that TCs are metabolically active cells capable of sustaining prolonged signaling activities.

Furthermore, the cytoskeletal framework within TPs supports both mechanical stability and adaptability in response to changes in tissue architecture or function (Kumar et al. 2024). The ability of TCs to form extensive contact points with multiple cell types positions them as central coordinators within stromal microenvironments. The structure and ultrastructure of TCs, characterized by a small cell body with exceptionally long moniliform TPs composed of alternating podomeres and podoms containing key organelles, underlie their distinctive identity among interstitial cells. Their spatial arrangement into complex networks allows for multifaceted roles in cellular communication, tissue homeostasis, and regeneration across diverse oral structures.

TPs and Their 3D Networks

TPs represent the most distinctive morphological hallmark of TCs, setting them apart from other interstitial cell types. These extremely long and slender cellular extensions can reach tens to hundreds of micrometers in length, yet maintain a remarkably thin profile, often below the resolution limit of conventional light microscopy. TPs exhibit a moniliform appearance, characterized by alternating thin segments (podomers) and dilated regions (podoms), which are readily visualized using specialized staining techniques such as methylene blue or toluidine blue. The podoms frequently house organelles, including mitochondria and endoplasmic reticulum, suggesting that TPs are not merely passive structures but actively participate in cellular processes (Cretoiu et al. 2017). The three-dimensional organization of TPs is fundamental to their function. Rather than existing as isolated projections, TPs form intricate networks within the interstitial spaces of tissues. This network architecture enables TCs to establish contact with a wide variety of neighboring cells, including immune cells, fibroblasts, endothelial cells, and stem/progenitor cells. Through these extensive contacts, TCs are thought to facilitate intercellular communication and coordinate tissue responses to physiological and pathological stimuli (Kondo and Kaestner 2019). The spatial arrangement of TPs allows for both short-range signaling via direct membrane contacts or gap junctions and long-range paracrine interactions through the release of extracellular vesicles.

In oral tissues specifically, the three-dimensional networks formed by TPs are hypothesized to contribute significantly to tissue homeostasis and structural integrity. For example, in the dermal layer of reptilian skin, elongated TPs create an interconnected meshwork that supports the architectural framework of the tissue while simultaneously enabling dynamic interactions with adjacent cell populations. The presence of communication vesicles along these extensions further underscores their role in mediating complex signaling events essential for tissue repair and regeneration (Ez Elarab et al. 2025).

Such features have been observed not only in skin but also in oral mucosa and papillae, where TCs may influence epithelial renewal and sensory functions (El-Gendy et al. 2025).

The ability of TPs to form elaborate 3D networks is also relevant for their proposed involvement in stem cell niches. By enveloping or contacting stem/progenitor cells within tissues such as dental pulp or periodontium,

TCs may help regulate stem cell maintenance and differentiation through both physical support and molecular signaling (Nicolescu 2016a; Horch et al. 2016). This network-forming capacity is increasingly recognized as a key element underlying the regenerative potential attributed to TCs in various organs. Advanced imaging modalities have been instrumental in elucidating the ultrastructural details of TP networks. Techniques such as electron microscopy combined with digital colorization enhance contrast between cellular elements, allowing for precise morphometric analysis of TP length, branching patterns, and spatial relationships with other tissue components (Sayed et al. 2021). These studies reveal that the density and complexity of TP networks can vary depending on anatomical location and physiological state. The unique morphology of TPs, characterized by their extraordinary length, moniliform structure, and propensity for forming interconnected 3D networks, underpins many functional attributes assigned to TCs. Their strategic positioning within tissues enables them to act as sentinels for microenvironmental changes while orchestrating the multicellular responses necessary to maintain oral tissue health.

Comparative Morphology with Other Interstitial Cells

TCs are distinguished from other interstitial cells by their unique morphological characteristics, most notably the presence of extremely long and slender cellular extensions termed TPs. These TPs can extend for considerable distances relative to the cell body, forming intricate three-dimensional networks within tissues. This feature is not observed in classical interstitial cells, such as fibroblasts or pericytes, which typically exhibit shorter, less complex processes. The defining criterion for identifying TC is thus the presence of these TPs, which are much thinner and longer than the processes of other stromal cells (Horch et al. 2016). Gene expression profiles further differentiate TCs from fibroblasts, with specific genes such as Sh3glb1 and Tm4sf1 being highly expressed in TC but not in fibroblasts, suggesting functional divergence that is reflected at the morphological level (Xiao and Bei 2016). In oral tissues, TCs have been identified in various locations, including the lamina propria, papillae of the tongue, and dermal layers of reptilian skin. Their spindle-shaped morphology and the presence of TPs support their identification as a distinct population among interstitial cells (El-Gendy et al. 2025). Unlike fibroblasts, which primarily contribute to extracellular matrix production and structural support, TCs play dynamic roles in cellular communication and tissue homeostasis. The presence of communication vesicles along their TPs suggests an active participation in signaling with neighboring

cells, a feature less pronounced or absent in other interstitial cell types (Ez Elarab et al. 2025; El-Gendy et al. 2025). These vesicles may facilitate interactions crucial for maintaining tissue integrity and supporting repair mechanisms. Compared with TCs, fibroblasts reside within connective tissues but lack the extensive network-forming capacity of TPs. Fibroblast processes are generally shorter and do not form the same degree of intercellular connectivity observed with TCs (Horch et al. 2016).

Furthermore, immunophenotypic markers provide additional means for distinguishing these populations: CD34 is commonly used to identify TCs across species, whereas fibroblasts typically do not express this marker at significant levels (Ez Elarab et al. 2025). In addition to CD34, PDGFRα expression has been associated with TCs populations in oral papillae, further supporting their distinction from other stromal cells (El-Gendy et al. 2025). The functional implications of these morphological differences are substantial. TCs' ability to form extensive networks via their TPs positions them as central coordinators within tissue microenvironments. They likely serve as hubs for intercellular communication, modulating responses to injury or physiological changes more efficiently than classical interstitial cells (Horch et al. 2016). This network-forming property may underlie their proposed regenerative potential and involvement in stem cell niches. When comparing TCs to other interstitial cell types, such as fibroblasts or pericytes, within oral tissues and beyond, several key morphological distinctions emerge: the extraordinary length and thinness of their processes (TPs), their network-forming capacity, distinctive immunophenotypic markers like CD34 and PDGFRα, and specialized structures such as communication vesicles. These features collectively underpin their unique roles in tissue organization, signaling, and regeneration, functions that set them apart from more traditional stromal cell populations.

Identification and Characterization of Telocytes

Transmission Electron Microscopy Techniques

TEM has emerged as the gold standard for the identification and ultrastructural characterization of TCs within various tissues, including oral and skin environments. The unique morphological features of TCs, particularly their extremely long and slender cellular extensions known as TPs, are best visualized using TEM due to its high spatial resolution and ability to reveal subcellular details that are not discernible with conventional light microscopy. These TPs exhibit a moniliform appearance,

characterized by alternating thick segments (podoms) and thin segments (podomeres), which together form a distinctive beaded structure. This ultrastructural hallmark is critical for distinguishing TCs from other interstitial or stromal cells, such as fibroblasts or pericytes, which lack such specialized projections (Ez Elarab et al. 2025). The application of TEM allows for the direct observation of additional features that further support the identification of TCs. For instance, TEM imaging reveals the presence of extracellular vesicles budding from the plasma membrane of TPs, suggesting active participation in intercellular communication through paracrine signaling mechanisms (Zhao et al. 2022). These vesicles may play roles in modulating the local microenvironment, influencing neighboring cells such as stem cells or immune cells, and contributing to tissue homeostasis and repair processes.

In oral tissues specifically, where cellular heterogeneity is pronounced due to the presence of diverse cell types within structures like salivary glands, mucosa, periodontium, and dental pulp, TEM provides an indispensable tool for unambiguous identification. While immunohistochemical markers such as CD34 and PDGFRα have been employed to label TCs in situ, these markers are not absolutely specific; they can also be expressed by hematopoietic stem cells or other stromal populations (Butucescu et al. 2020). Therefore, reliance on immunophenotyping alone may lead to misidentification. Combining immunofluorescence with TEM enhances specificity: immunolabeling can guide the localization of candidate cells within tissue sections, while subsequent TEM analysis confirms their identity based on ultrastructural criteria (Ez Elarab et al. 2025). Furthermore, studies utilizing TEM have clarified that TCs establish extensive three-dimensional networks via their TPs. These networks facilitate direct physical contacts with adjacent cell types, including epithelial cells, immune cells, nerve fibers, and vascular elements, supporting hypotheses regarding their involvement in structural organization and dynamic regulation of tissue architecture (Zhao et al. 2022). In addition to structural roles, these contacts likely underpin functional contributions to cell signaling pathways essential for tissue maintenance and regeneration. Despite advances in imaging modalities such as confocal microscopy or super-resolution techniques, none match the resolving power of TEM for visualizing the fine details necessary for definitive telocyte identification. This is particularly relevant when investigating tissues where TCs have not previously been described or where their existence remains controversial. For example, recent investigations into reptilian skin utilized a combination of light microscopy and TEM to provide the first detailed description of TC morphology in these species. Such studies underscore the necessity of

TEM-based approaches when expanding our understanding of TC distribution across phylogenetically diverse organisms.

Nevertheless, TEM remains an essential technique for identifying and characterizing TCs within oral tissues and beyond. Its capacity to resolve ultrastructural features, such as moniliform TPs and extracellular vesicle formation, enables researchers to distinguish these novel interstitial cells from morphologically similar populations. When integrated with complementary methods like immunofluorescence labeling, TEM provides a robust framework for advancing knowledge about TC biology and their potential therapeutic applications in regenerative medicine.

Immunohistochemical Markers in Telocyte Research

Immunohistochemical markers have become indispensable tools in the identification and characterization of TCs, particularly within oral tissues. The unique morphological features of TCs, such as their small cell bodies and extremely long, slender prolongations known as TPs, necessitate the use of specific molecular markers to distinguish them from other cells, including interstitial cells. However, the immunophenotypic profile of TCs remains a subject of ongoing investigation due to considerable heterogeneity in marker expression across different tissues and species (Kondo and Kaestner 2019). A central challenge in TC research is the lack of a single definitive marker. Instead, researchers rely on combinations of immunohistochemical markers to identify these cells. Commonly used markers include CD34, PDGFRα, and vimentin. CD34 is frequently employed due to its expression in various stromal cell populations, including TCs, but it is not exclusive to them; endothelial cells also express CD34, which can complicate interpretation (Ez Elarab et al. 2025; Kondo and Kaestner 2019).

To address this limitation, double-immunofluorescence approaches are often utilized. For example, combining CD34 with CD31 allows for differentiation between TCs and endothelial cells since CD31 is a well-established marker for endothelial and hematopoietic cells but does not label TCs. This combinatorial strategy enhances specificity in identifying TC populations within complex tissue environments. Vimentin, a type III intermediate filament protein typically found in mesenchymal-derived cells such as fibroblasts and endothelial cells, is another marker commonly associated with TCs (Nicolescu et al. 2012). Its presence supports the mesenchymal origin of these cells and their involvement in maintaining tissue integrity. In studies on reptilian dermis, vimentin-positive cells were

distributed predominantly in regions with high densities of fibroblasts and mesenchymal elements, suggesting that vimentin expression may correlate with areas where TCs contribute to structural support and tissue homeostasis (Ez Elarab et al. 2025). However, since vimentin is broadly expressed among mesenchymal cells, its utility as a sole marker for TCs is limited. The literature also highlights that the expression patterns of these markers can vary significantly depending on the tissue context. For instance, while CD34 and PDGFRα are often co-expressed in human cardiac or skin TCs, their expression may differ in oral tissues or across species (Kondo and Kaestner 2019; Horch et al. 2016). This variability underscores the importance of integrating ultrastructural analysis, such as electron microscopy, with immunohistochemical staining to confirm the identity of TCs based on both molecular and morphological criteria (Horch et al. 2016; Manole et al. 2022). Despite advances in marker-based identification strategies, ambiguities persist regarding which combination of markers best defines TCs. Current knowledge points toward minimal shared features among TCs from different tissues beyond their ultrastructural characteristics (Kondo and Kaestner 2019). Therefore, future research should focus on comprehensive gene expression profiling and lineage tracing to refine our understanding of TC identity. Thus, immunohistochemical identification of TC relies on a panel of markers, most notably CD34 (excluding CD31+ endothelial cells), PDGFRα, and vimentin, combined with detailed morphological assessment. The integration of these approaches has enabled more precise mapping of TC distribution within oral tissues such as salivary glands and mucosa while highlighting their potential roles in tissue homeostasis and regeneration. As research progresses, refining marker panels through molecular profiling will be crucial for advancing both basic science and clinical applications involving this intriguing interstitial cell population.

Emerging Methods for Telocytes Detection

Emerging methods for TCs detection have advanced significantly, driven by the need to distinguish these cells from other interstitial populations and to clarify their roles in tissue architecture and function. The identification of TCs relies heavily on specific immunohistochemical markers, with CD34 and PDGFRα currently regarded as the most reliable combination for their detection across various tissues, including oral structures. This dual-marker approach enables researchers to differentiate TCs from other stromal or endothelial cells that may express only one of these markers or display distinct morphological characteristics (El-Gendy et al. 2025;

Manole and Simionescu 2016). In particular, the co-expression of PDGFRα and CD34 in the connective tissue of the papillae within the Egyptian tortoise tongue has provided compelling evidence for the presence of TCs, supporting their identification as a unique interstitial cell type with specialized functions (El-Gendy et al. 2025). The specificity of these markers is further supported by studies in other tissues, such as skin, where PDGFα-positive TC form intricate three-dimensional networks essential for maintaining tissue integrity and facilitating repair processes (Butucescu et al. 2020; Ez Elarab et al. 2025; Manole and Simionescu 2016). The use of polyclonal antibodies against PDGFRα has been validated across multiple investigations, reinforcing its utility as a core marker for TC identification (Butucescu et al. 2020). However, despite this progress, there remains an ongoing debate regarding the absolute specificity of these markers. Some studies have noted that c-kit/CD117, another marker previously used to identify interstitial cells, can exhibit nonspecific binding to epithelial cells, highlighting the necessity for more refined and exclusive markers to avoid misidentification (Nicolescu et al. 2012). Recent technological advancements are set to overcome these limitations. Single-cell RNA sequencing (scRNA-seq) and sequential RNA fluorescent in situ hybridization (RNA-FISH) are powerful tools for dissecting cellular heterogeneity at unprecedented resolution. These approaches allow for comprehensive transcriptomic profiling of individual cells within complex tissues, thereby enabling the discovery of novel marker sets that may be unique to TCs regardless of tissue context. For example, mining large-scale scRNA-seq datasets has revealed stromal cell populations expressing gene signatures consistent with those identified in mouse TC, such as BMP5, BMP2, and WNT5A. Such findings suggest that future research could leverage these datasets to pinpoint more definitive protein markers for TC identification (Kondo and Kaestner 2019). In addition to molecular profiling techniques, immunofluorescence analysis using panels of multiple antibodies has become increasingly important. By employing a combination of six distinct antibodies targeting various cellular components within tongue tissue, researchers have been able to elucidate not only the presence but also the spatial organization and potential interactions of TCs with neighboring cells (El-Gendy et al. 2025). This multi-faceted approach enhances confidence in cell-type assignment and provides insights into how TCs integrate into broader tissue networks. Flow cytometry-based methods also contribute to emerging detection strategies. For instance, fluorescence-activated cell sorting (FACS) using fluorescently conjugated antibodies against CD34 and CD31 enables precise separation and quantification of specific cell

populations from dissociated tissues (Zhao et al. 2022). While CD31 is primarily used to identify endothelial cells, its exclusion alongside positive selection for CD34 can help enrich for non-endothelial stromal populations such as TCs. Despite these advances, challenges persist due to overlapping marker expression among different stromal cell types. The field recognizes an urgent need for a marker or set of markers uniquely expressed by TCs across all tissue types. Until such markers are identified through integrative approaches combining transcriptomics, proteomics, and advanced imaging modalities, current best practices recommend using a combination of established immunohistochemical markers alongside morphological assessment via electron microscopy or high-resolution light microscopy (Manole and Simionescu 2016; Kondo and Kaestner 2019; El-Gendy et al. 2025). Collectively, these emerging methods underscore a dynamic landscape in TC research. The integration of molecular profiling technologies with traditional immunohistochemistry is expected to refine our ability to accurately detect and characterize TCs in oral tissues and beyond. As new data accumulate from both animal models and human specimens, such as those derived from paraffin-embedded tongue samples, our understanding of TC biology will continue to deepen (El-Gendy et al. 2025; Rosa et al. 2019). This progress holds promise not only for fundamental science but also for translational applications in regenerative medicine targeting oral health.

General Functional Significance

Cell-to-Cell Communication Mechanisms

TCs are distinguished by their remarkable ability to participate in cell-to-cell communication, a property that underpins their functional importance within oral tissues. Their unique morphology, characterized by extremely long and thin TPs facilitates the formation of extensive three-dimensional networks throughout the interstitial spaces. These networks enable TCs to interact with a variety of neighboring cells, including fibroblasts, immune cells, endothelial cells, and stem cells, thereby orchestrating complex signaling events essential for tissue homeostasis and repair. The mechanisms behind TC-mediated communication are multifaceted. One prominent mode involves direct physical contact through specialized junctions formed between TPs and adjacent cells. These junctions can include gap junctions, adherens junctions, and other intercellular connections that allow the exchange of ions, small molecules, and signaling mediators. Such structural connectivity supports synchronized

responses across cellular populations and contributes to the maintenance of tissue integrity (Manole et al. 2022; El Maadawi 2016). These intercellular contacts are not merely passive; they actively participate in modulating the local microenvironment. In addition to direct contact-dependent mechanisms, TCs exert paracrine effects by secreting extracellular vesicles (EVs), including exosomes and microvesicles. These vesicles encapsulate a diverse array of bioactive molecules, such as proteins, lipids, and nucleic acids, that can influence the behavior of recipient cells at both short and long distances. The release of EVs allows TCs to modulate immune responses, promote angiogenesis, and regulate stem cell activity within their niche (Manole et al. 2022). Proteomic analyses have shown dynamic changes in the secretome profile of cultured human dermal TCs compared to fibroblasts or endothelial cells, emphasizing their distinct capacity for paracrine signaling (Ratajczak et al. 2016). Additionally, TCs are believed to play roles in mechano-transduction within the interstitium. Their strategic positioning and structural features suggest they can detect mechanical cues from the extracellular matrix (ECM) or neighboring cells and transduce these signals into biochemical responses that coordinate tissue adaptation or repair (Manole et al. 2022). This function is particularly relevant in oral tissues where mechanical forces from mastication or speech constantly exert stress on cellular components. The involvement of TCs in stem cell niches further exemplifies their communicative versatility. In these specialized microenvironments, TCs help regulate stem cell fate decisions by providing both structural support and molecular cues essential for self-renewal or differentiation. The spatial arrangement of TCs at tissue interfaces allows them to mediate interactions between stem cells and other niche components, such as blood vessels or nerve endings. Through both juxtacrine (contact-dependent) and paracrine mechanisms, TCs contribute to maintaining an optimal balance between quiescence and activation in resident stem cell populations (El Maadawi 2016). Overall, these diverse communication strategies position TCs as central coordinators within oral tissues. Their ability to integrate signals from multiple sources ensures quick adaptation to physiological demands or injury. By influencing processes such as wound healing, immune modulation, and tissue regeneration through complex cell-to-cell communication networks, TCs emerge as key players in maintaining oral health and hold promising potential for regenerative therapies.

Extracellular Vesicle Dynamics

EVs dynamics represent a fundamental aspect of TC biology, underpinning their capacity for intercellular communication and modulation of tissue microenvironments. TCs are characterized by their extensive three-dimensional networks formed through long, slender prolongations that facilitate contact with a variety of resident and non-resident cells within the interstitium. These contacts are not limited to direct physical junctions but are also mediated by the release and uptake of extracellular vesicles, which serve as vehicles for the horizontal transfer of macromolecules, including proteins, various RNAs, and microRNAs (Pomerleau et al. 2023). The repertoire of extracellular vesicles released by telocytes is diverse. Electron microscopy studies have revealed that telocytes can produce exosomes, which originate from the endosomal compartment; ectosomes, which bud directly from the plasma membrane; and multivesicular cargoes containing multiple endomembrane-bound vesicles. The release of these distinct vesicle types suggests a sophisticated system for delivering molecular signals over both short and potentially longer distances within tissues. While the exact functional effects of these vesicle-mediated interactions are not fully understood, evidence suggests they may influence differentiation programs in nearby cells. TC-derived vesicles could influence cardiomyocyte differentiation during cardiac development, although this hypothesis awaits experimental confirmation (Kondo and Kaestner 2019). The structural orientation of fibroblasts contrasts with the more functionally oriented TCs, whose primary role appears to be facilitating intercellular communication via their 3D networks and EV-mediated signaling (Pomerleau et al. 2023). This distinction underscores the unique contribution of TCs to tissue homeostasis beyond mere structural support. The ability of TCs to form virtual networks through branching prolongations enables them to act as hubs for signal dissemination across complex tissue landscapes. Proteomic analyses further highlight the dynamic nature of TC EV biology. In lung TCs, differential expression of proteins involved in metabolic processes, cellular organization, immune responses, cell communication, and homeostatic regulation has been observed when compared to fibroblasts (Ratajczak et al. 2016). Such findings imply that extracellular vesicle content is tailored to support a broad spectrum of biological processes relevant to tissue maintenance and adaptation. In oral tissues specifically, where TCs are distributed across structures such as salivary glands, mucosa, periodontium, and dental pulp, their EV-mediated interactions likely contribute significantly to local tissue repair mechanisms and stem cell niche regulation. By transferring regulatory molecules via extracellular

vesicles, telocytes may orchestrate responses to injury or inflammation and maintain epithelial or stromal homeostasis. Taken together, current evidence positions extracellular vesicle dynamics at the core of TC function in oral tissues. Through both direct contact and EV-mediated signaling pathways, TCs integrate structural connectivity with molecular communication strategies that are essential for maintaining tissue integrity and responding adaptively to physiological challenges.

Electrophysiological Properties

Electrophysiological properties of TCs have garnered increasing attention due to their potential implications for tissue homeostasis, intercellular communication, and organ function. The unique morphology of TCs, characterized by their extremely long and thin TPs, suggests a specialized role in mediating electrical and chemical signals within the interstitial compartment. These processes facilitate extensive contacts with neighboring cells, including myocytes, immune cells, and stem cells, thereby positioning TCs as an integral component in the orchestration of local tissue responses. Recent investigations have focused on identifying the ion channels expressed by TCs and understanding how these channels contribute to their physiological functions. The distribution of TCs across various tissues influences both the repertoire of ion channels present and their activation profiles. For instance, the presence of long cellular extensions and dynamic motility may necessitate specific ion channel types that support rapid signal propagation and modulation of local microenvironments. Patch-clamp studies have begun to elucidate the electrophysiological landscape of TCs from different organs, revealing that these cells can generate pacemaker-like potentials. This property is particularly relevant in tissues where rhythmic contractile activity is essential, such as the gastrointestinal tract or uterus. The functional expression of ion channels in TCs is not uniform but rather context-dependent. Factors such as tissue type, developmental stage, species differences, and experimental conditions (in vitro versus in vivo) all contribute to variability in electrophysiological characteristics. This heterogeneity complicates direct comparisons across studies but also underscores the adaptability of TCs to distinct physiological demands. For example, in uterine tissue, it has been hypothesized that TCs participate in feedback loops that control myometrial contractions during delivery. Here, hormonal fluctuations modulate membrane fluidity and consequently influence TC activity and their interactions with surrounding smooth muscle cells. Such findings highlight a potential mechanistic link between

endocrine signaling and TC-mediated modulation of tissue contractility. Despite advances in characterizing TC electrophysiology, significant knowledge gaps remain. The dynamic changes observed in cultured TCs pose challenges for consistent electrophysiological analysis. Furthermore, limitations in clinical sample availability restrict comprehensive studies on human tissues. Nevertheless, accumulating evidence supports the notion that TCs are not passive structural elements but active participants in electrical signaling networks within oral tissues and beyond. In summary, the electrophysiological properties of telocytes are defined by a complex interplay between their morphological features, ion channel expression profiles, and responsiveness to local biochemical cues. These attributes enable TCs to modulate intercellular communication and tissue function across diverse anatomical sites (Banciu et al. 2016).

Mechanosensory Capabilities

TCs have emerged as a distinct interstitial cell population with specialized mechanosensory capabilities, distinguishing them from other stromal cells such as fibroblasts. The unique morphology of TCs is thought to be integral to their ability to sense and respond to mechanical cues within the tissue microenvironment. Their TPs facilitate extensive physical interactions with neighboring cells and ECM components, positioning TCs as a potential mediator of mechanochemical signaling. Proteomic analyses have revealed that TCs exhibit a dynamic protein expression profile in response to culture conditions, with significant alterations in proteins associated with structural, catalytic, and binding functions. Notably, myosin-14 remains consistently overexpressed in TCs during extended culture periods. Myosin-14 is involved in sensory perception processes, indicating that TCs are capable of mechanical sensing and converting mechanical stimuli into biochemical signals. This molecular machinery supports the hypothesis that TCs actively detect changes in tissue tension or deformation and respond by modulating local cellular activities. Additionally, gene ontology analyses show that TC differentially express genes related to development, morphogenesis, and tissue organization compared to fibroblasts and mesenchymal stem cells. The upregulation of genes like Col4a4, Col4a5, and Col4a6, which are key components of the ECM, suggests that TCs may contribute not only to ECM production but also to its remodeling in response to mechanical stress (Zheng et al. 2013). Such gene expression patterns strengthen the concept that TCs are responsive to their biomechanical environment and can coordinate adaptive responses at both the cellular and tissue levels. In addition to their

intrinsic molecular features, the anatomical distribution of TCs highlights their mechanosensory capacity. In various organs, including the urinary bladder and oviduct, TCs have been shown to share functional similarities with myofibroblasts, cells known for their roles in sensing mechanical forces and aiding tissue repair. In these situations, TCs can differentiate into organ-resident myofibroblasts as needed. This plasticity suggests that TCs might act as a reservoir for mechanically responsive cells that can be recruited during tissue remodeling or regeneration (Vannucchi and Faussone-Pellegrini 2016). The spatial arrangement of TCs within oral tissues also indicates their role in mechanoreception. For example, in the oral mucosa and periodontium, areas exposed to constant mechanical forces from chewing, TCs are strategically located among collagen fibers and near blood vessels, nerve endings, and stem cell niches (Kondo and Kaestner 2019). Their proximity to these structures allows them to directly convert mechanical signals into coordinated cellular actions that are vital for maintaining tissue homeostasis. Taken together, these findings emphasize the diverse mechanosensory abilities of telocytes. Through a combination of specialized morphology, dynamic protein expression profiles including persistent myosin-14 upregulation, distinctive gene expression patterns related to ECM interaction and morphogenesis, and strategic placement within mechanically active tissues, TCs are uniquely suited to detect mechanical cues. This enables them to preserve structural integrity and also to influence regenerative processes in response to changing biomechanical conditions.

Telocytes in Tissue Microenvironment Regulation

TCs represent a distinct interstitial cell population characterized by their strategic positioning within the tissue microenvironment, where they exert significant influence on the regulation of local homeostasis and cellular dynamics. The spatial arrangement of TCs in close proximity to other cell types enables them to participate actively in the maintenance and modulation of the tissue microenvironment (Nicolescu 2016b). A defining feature of TCs is their ability to form intricate three-dimensional networks through their TPs, which facilitate direct physical interactions with neighboring cells, such as stem cells, immune cells, nerve endings, and vascular elements. This network architecture supports both structural integrity and functional communication within tissues. The presence of gap junctions between TCs and adjacent cells has been demonstrated in vivo, suggesting that TCs can modulate calcium signaling dynamics in response to stimuli from neighboring muscle or epithelial cells. Such

interactions may underlie the observed changes in TC calcium dynamics in response to mechanical or chemical cues in their environment. Furthermore, these gap junctions are essential for synchronizing cellular responses across the tissue, contributing to coordinated physiological processes. The regulatory capacity of TCs extends beyond mere structural support. They are sensitive to various stimuli that alter membrane fluidity and can respond to mechanical forces, as evidenced by studies showing that mechanical manipulation of TC modulates uterine motility. This mechanosensory feature implies that TCs play an active role in sensing and transducing environmental signals into biochemical responses that affect tissue behavior (Banciu et al. 2016). Additionally, TCs have been implicated in paracrine signaling via the release of extracellular vesicles, which can carry bioactive molecules influencing the activity and fate of surrounding cells (Ahmed and Hussein 2023). Within specialized niches such as those in oral tissues, including salivary glands, mucosa, periodontium, and dental pulp, TCs contribute to maintaining stem cell quiescence and survival. Their proximity to stem cells enables them to preserve an undifferentiated state by providing both physical support and molecular cues required for niche function. The niche concept is universal across species but exhibits distinct cellular compositions by tissue type; nonetheless, a commonality is the presence of TCs, which regulate local homeostasis. The ECM forms another critical component of the microenvironment regulated by TCs. Through their interactions with ECM components and stromal elements such as vascular and neural supplies, TCs help orchestrate tissue remodeling processes during development, repair, or pathological conditions (Nicolescu 2016b; Kondo and Kaestner 2019). In inflammatory or fibrotic diseases affecting oral tissues or other organs, damage or loss of TCs correlates with impaired tissue regeneration. Experimental evidence suggests that transplantation or pharmacological enhancement of TCs' survival can promote tissue repair by restoring microenvironmental balance (Ahmed and Hussein 2023). Diagnostic identification of TCs relies on a combination of morphological criteria observed under light microscopy after specific staining protocols (e.g., methylene blue), transmission electron microscopy for ultrastructural confirmation, and immunohistochemical detection using markers such as c-kit (CD117) and CD34 (Cretoiu et al. 2017). These approaches underscore the importance of recognizing TCs as a distinct entity from other interstitial cells, such as fibroblasts or pericytes. In summary, TCs serve as dynamic regulators within the tissue microenvironment by integrating structural support with functional communication networks. Their ability to interact with diverse cell types through direct contact or

paracrine mechanisms positions them at the center of homeostatic regulation in oral tissues. The multifaceted roles of TCs highlight their significance not only in maintaining normal physiology but also in mediating responses to injury and disease.

Telocytes Across Organ Systems: Comparative Perspectives

TCs are a unique population of interstitial cells characterized by their extremely thin, elongated processes called TPs, which allow them to form complex networks within the stromal areas of different organs. Their identification across multiple tissues has prompted comparative analyses to elucidate both conserved and tissue-specific features and their functional implications across organ systems. In the gastrointestinal tract, subepithelial TCs are positioned at the basement membrane of the epithelium, where they interlock to create a thin sheath layer that envelops the epithelial basal membrane. This spatial arrangement is critical for supporting the stem cell niche within intestinal crypts, suggesting a role in maintaining epithelial homeostasis and facilitating regenerative processes. Similar subepithelial distributions have been observed in other organs, such as the prostate and bovine uterine tube, where telocytes form intertwining contacts through their TPs. Although their precise function in epithelial stem cell regulation remains under investigation in these tissues, their consistent localization beneath epithelia suggests a conserved supportive or regulatory role. The heart provides another example of TC diversity and specialization. Here, TCs are distributed throughout the epicardium, myocardium, and endocardium. Their long TPs interact with surrounding blood vessels and other stromal elements, implicating them in structural maintenance and possibly paracrine signaling within cardiac tissue. The presence of TCs in interstitial regions of organs such as the heart underscores their potential contribution to organ-wide structural integrity (Kondo and Kaestner 2019). In cutaneous tissues, particularly within the dermis, telocytes display unique morphological adaptations. They exhibit alternating thin fibrillar segments (podomeres) and dilated cisternal segments (podoms), which house mitochondria, endoplasmic reticulum, and caveolae. This moniliform configuration is readily visualized using advanced imaging modalities such as focused ion beam-scanning electron microscopy (FIB-SEM), revealing three-dimensional arrangements that facilitate extensive cellular interactions (Ahmed and Hussein 2023; Cretoiu 2016). Immunohistochemical profiling further distinguishes dermal TC subsets: some express vimentin and CD117,

while others are positive for CD34; papillary dermis telocytes also express platelet-derived growth factor receptor alpha (PDGFRα). The co-expression of CD34 and PDGFRα currently serves as a robust marker combination for identifying skin TCs (Manole et al. 2022). In reptilian models such as the Greek tortoise, CD34+ TCs with rod-shaped morphology contribute to skin resilience under harsh environmental conditions by preserving structural and functional integrity (Ez Elarab et al. 2025). Comparative studies extend to adipose tissue, where cells commonly referred to as adipose-derived stromal cells or adipose stromal/stem/progenitor cells (ASCs) share phenotypic overlap with telocytes. These ASCs are primarily CD34+ and possess multilineage differentiation potential, suggesting that specific stromal populations may encompass or be closely related to TC-like cells. Such findings highlight the heterogeneity of interstitial cell populations across tissues. TCs also participate dynamically in tissue repair processes. For instance, during wound healing stages, spanning inflammation, proliferation, and remodeling, CD34-positive stromal/telocyte (SC/TC) populations can be tracked to monitor their behavior over time. Their involvement in angiogenesis, granulation tissue formation, and immune response modulation positions them as key players in orchestrating complex repair mechanisms (Díaz-Flores et al. 2016). In addition to their supportive roles in homeostasis and regeneration across diverse organs, including the lung, liver, digestive tract, and reproductive system, recent evidence suggests that aberrant activation of TC functions may contribute to pathological states such as tumorigenesis by promoting proliferation or inhibiting apoptosis of cancer cells (Ratajczak et al. 2016). The distribution patterns of TCs across organ systems reveal both shared morphological hallmarks, such as long moniliform processes, and context-dependent functional specializations. Their ability to form extensive networks via direct contacts with neighboring cells enables them to modulate local microenvironments effectively. Furthermore, immunophenotypic diversity among TC populations reflects adaptation to specific tissue requirements while maintaining core features essential for intercellular communication and structural support.

CHAPTER TWO

TELOCYTES IN ORAL TISSUES: STRUCTURAL NETWORKS AND DISTRIBUTION

Anatomy and Histology of the Oral Cavity

The oral cavity is a complex anatomical region characterized by a diverse array of tissues, each contributing to its multifaceted functions in mastication, speech, and defense. Histologically, the oral cavity comprises several distinct layers and specialized structures. The mucosa forms the primary lining, consisting of a stratified squamous epithelium supported by an underlying connective tissue layer known as the lamina propria. This lamina propria is densely packed with collagen fibers and houses numerous blood vessels, immune cells, and interstitial cell populations that are integral to tissue homeostasis (Kondo and Kaestner 2019; Rosa et al. 2019). Within the oral mucosa, accessory salivary glands are distributed throughout both the lamina propria and deeper muscle layers. These glands include mucous and serous types, which help maintain oral moisture and facilitate digestion through their secretions. The connective tissue stroma not only anchors these glands but also provides a supportive environment for various cellular elements, including fibroblasts, immune cells, and recently identified TCs. The tongue exemplifies the intricate organization of oral tissues. It is composed of interlacing skeletal muscle bundles that are firmly attached to the overlying mucosa via dense connective tissue. Embedded within this matrix are numerous minor salivary glands scattered throughout both the lamina propria and muscle interstitium. The presence of TCs, particularly those expressing CD34, has been documented in both the lamina propria and within the interstitial spaces of striated muscle. These TCs form part of a stromal network that interfaces with other cell types such as nerve fibers, blood vessels, and glandular elements (Rosa et al. 2019). Beyond the tongue, TCs have been observed in various regions of the oral cavity. In salivary glands, they are found surrounding acini and ducts as well as in close proximity to capillaries and nerve fibers (Kondo and Kaestner 2019). Their elongated processes (TPs) extend through the connective tissue stroma, establishing

contacts with epithelial cells, vascular structures, and immune cells. This spatial arrangement suggests a role for TCs in mediating intercellular communication across different compartments of oral tissues (Kondo and Kaestner 2019; Popescu and Nicolescu 2013). The periodontium further illustrates the complexity of oral histology. It consists of the gingiva, periodontal ligament, cementum, and alveolar bone. Each component contains specialized cellular populations embedded within an extracellular matrix rich in collagen fibers. TCs have also been implicated in forming structural networks within these regions, where they may interact with resident stem cells and contribute to tissue repair mechanisms (Díaz-Flores et al. 2016). In addition to their structural roles, TCs participate in dynamic cellular interactions via heterocellular junctions with stem cells (SCs), immune cells such as mast cells and macrophages, and specific parenchymal cells, such as myocytes and glandular epithelial cells (Popescu and Nicolescu 2013). These junctions often involve direct nanocontacts or gap junctions that facilitate bidirectional signaling essential for maintaining tissue integrity. The distribution pattern of TCs across oral tissues reflects their adaptability to diverse microenvironments. For instance, immunohistochemical studies reveal that TCs exhibit organ- and region-specific phenotypes depending on their location within different layers or structures (Xiao and Bei 2016). In the early stages of inflammation or repair processes within oral tissues, CD34+ TCs rapidly become activated, highlighting their potential involvement in regenerative responses (Díaz-Flores et al. 2016). Collectively, the anatomy and histology of the oral cavity provide a rich context for understanding how TCs integrate into existing cellular frameworks. Their widespread distribution across connective tissue compartments, from lamina propria to glandular stroma, underscores their significance as novel interstitial players in both physiological maintenance and responses to injury or disease.

Telocytes in Salivary Glands

Major Salivary Glands

TCs are a distinct interstitial cell population of the major salivary glands, characterized by their small cell bodies and exceptionally long, slender cytoplasmic extensions known as TPs. These cells are distributed throughout the connective tissue stroma of the salivary glands, where they form intricate three-dimensional networks that interact with various neighboring cell types, including myoepithelial cells, fibroblasts, immune cells, and vascular elements (Sasso-Cerri et al. 2024). The presence of TCs

in the stroma has been confirmed in both human and animal models using ultrastructural analysis and immunohistochemical markers such as CD34 and CD117. In adult submandibular glands, CD117 positivity is observed around ducts and nerves, while CD34 selectively marks both the TC body and its TPs. Notably, vimentin and smooth muscle α-actin also highlight the TPs, supporting their identification in situ (Nicolescu 2016b). The spatial organization of telocytes within major salivary glands suggests a role in maintaining glandular architecture and facilitating intercellular communication. Their proximity to acini, ducts, blood vessels, and nerve fibers positions them as potential mediators of signaling between epithelial and stromal compartments (Sasso-Cerri et al. 2024; Rosa et al. 2019; Nicolescu 2016b). This is further supported by observations that TCs encircle secretory structures within the glandular parenchyma, possibly regulating glandular function in cooperation with adjacent myoepithelial cells (Rosa et al. 2019). The ability of TCs to establish close contacts with other stromal cells via their TPs may enable them to coordinate responses to physiological stimuli or injury. Functionally, TCs are implicated in tissue homeostasis through several mechanisms. They may regulate extracellular matrix composition and remodeling by interacting with fibroblasts and immune cells present in the stroma (Sasso-Cerri et al. 2024). Additionally, their involvement in paracrine signaling pathways could influence epithelial turnover and regeneration. For instance, Wnt signaling has been proposed as a key pathway through which telocytes support tissue integrity during development and repair processes (Rosa et al. 2019). The presence of TCs near stem/progenitor cell niches within the gland further raises the possibility that they participate in maintaining these niches or modulating stem cell behavior. In pathological conditions affecting major salivary glands, such as sialadenosis or Sjögren's syndrome, alterations in the stromal microenvironment, including changes in TC density or function, may contribute to impaired excretory function and glandular atrophy (Sasso-Cerri et al. 2024). Damage to myoepithelial cells or disruption of stromal networks involving TCs can result in hyposalivation or xerostomia due to compromised saliva secretion. From a regenerative medicine perspective, the unique properties of TCs make them attractive candidates for therapeutic strategies aimed at restoring salivary gland structure and function. Their capacity for extensive networking within tissues suggests they could facilitate integration of transplanted cells or scaffolds during tissue engineering approaches. Furthermore, their interactions with stem/progenitor cells highlight a potential role in supporting endogenous repair mechanisms following injury or disease. Overall, current evidence underscores the significance of

TCs as integral components of the stroma of the major salivary glands. Their morphological features enable them to serve as structural organizers and communication hubs within glandular tissues. By influencing cellular dynamics across various compartments – epithelial, stromal, vascular – TCs contribute to both normal maintenance and adaptive responses in disease conditions.

Telocytes in Minor Salivary Glands

TCs have emerged as a distinct interstitial cell population within the minor salivary glands, characterized by their unique morphology and strategic localization. These cells are readily identified by their long, slender cytoplasmic extensions known as TPs, which form intricate networks throughout the glandular stroma. The presence of TCs in minor salivary glands has been substantiated through immunohistochemical detection of CD34, a marker that highlights their distribution and network organization. Notably, CD34+ TCs are found enveloping the secretory units of both mucous and serous glands, as well as surrounding excretory ducts. This spatial arrangement suggests a role for TCs in maintaining the structural integrity of glandular architecture and facilitating communication between epithelial and stromal compartments. The proximity of TCs to blood vessels is particularly striking. CD34+ TCs are concentrated around both blood and lymphatic vessels, although CD34 immunoreactivity is absent in lymphatic endothelium, allowing for a clear distinction between these cell types. This perivascular localization suggests that TCs may regulate vascular dynamics or mediate interactions between vascular elements and the glandular parenchyma. Furthermore, the TC network delineates mucosa-associated lymphoid tissue (MALT) aggregates, indicating potential involvement in immune surveillance or modulation within the glandular microenvironment (Rosa et al. 2019). Ultrastructural studies reinforce the concept that telocytes serve as key organizers of the interstitial space. Their TPs establish both homocellular contacts with other TCs and heterocellular junctions with adjacent cell types such as acinar, ductal, and endothelial cells (Manole et al. 2022). These connections likely underpin their proposed roles in intercellular signaling and coordination of tissue responses to physiological or pathological stimuli. In pathological contexts such as viral infection or autoimmune disease, alterations in TC morphology and viability have been observed. For instance, SARS-CoV-2 infection leads to degenerative changes in telocytes within submandibular glands, including chromatin condensation indicative of cell death and cytoplasmic vesiculation containing viral

particles. Such findings raise questions about whether TC loss contributes to glandular dysfunction or results from underlying tissue pathology. The functional repertoire of telocytes in minor salivary glands extends beyond structural support. Their strategic positioning at interfaces between acini, ducts, capillaries, and immune aggregates positions them as potential mediators of homeostasis and repair processes (Sasso-Cerri et al. 2024). Disruption of TC networks has been associated with impaired tissue maintenance in conditions such as Sjögren's syndrome, suggesting that intact TC populations are essential for preserving glandular function. Moreover, the ability of TCs to interact with stem/progenitor cells hints at their participation in regenerative processes following injury or inflammation. Advanced imaging modalities such as transmission electron microscopy have provided detailed insights into the ultrastructure of TPs within minor salivary glands. TPs exhibit alternating thin segments (podomeres) and dilated regions (podoms), which house organelles involved in calcium signaling and metabolic activity (Nicolescu 2016b). This specialized architecture may promote rapid signal transmission across the TC network or allow localized responses to environmental cues. Together, these observations highlight the diverse roles of telocytes in organizing, functioning, and maintaining the resilience of minor salivary glands. Their expansive networks not only serve as structural frameworks but also coordinate signals from vascular, epithelial, and immune compartments. The disruption or loss of TCs seems closely connected to pathological changes in gland structure and function. As research progresses to uncover their molecular signatures and operational mechanisms, TCs offer potential as therapeutic targets for restoring balance or supporting regeneration in diseased oral tissues.

Telocyte Localization in Acini, Ducts, Nerves, and Vasculature

TCs are increasingly recognized as a distinct interstitial cell population within the salivary glands, exhibiting a strategic localization that underpins their multifaceted roles in tissue architecture and function. Their presence in proximity to acini, ducts, nerves, and vasculature suggests an integrative role in maintaining glandular homeostasis and facilitating intercellular communication. Within the parotid gland, the largest of the three main salivary gland pairs and responsible for producing up to 90% of human saliva, the glandular structure is organized into lobules composed of secretory units, acinar or tubular clusters, connected by a hierarchical ductal system. These secretory elements and their associated ducts are embedded within a stromal compartment whose cellular composition