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"History of the stromal cells: from interstitial Cajal cells to telocytes - a brief overview of the human telocytes and their possible functions"

"*Stromal hücrelerin tarihçesi: interstisyel Cajal hücrelerinden telositlere - insan telositlerine ve olası işlevlerine kısa bir bakış"*

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ABSTRACT

In the organ microenvironment, stromal cells make up an essential population, however research on them has been very limited. The stroma mainly consists of fibroblasts that reside together with mesenchymal cells, endothelial cells, pericytes, neurons, adipocytes, immune and other cell types. The different morphologies and functional properties of stromal cells have led to subclassification of different cell types in connective tissue. Among them are the interstitial cells of Cajal and telocytes. Telocytes are one of the newer cells known for their small cell bodies and long telopods and have been recently identified in the connective tissue of many organs. Telocytes are strategically positioned near nerve endings, around blood vessels and in close relation with particular cells. The network of telocytes is engaged in integrating information from multiple sources and coordinating tissue homeostasis in response to the tissues local functional requirements. Extracellular vesicles provide a means of bidirectional communication, and their secretome appears to control the mechanisms of stem cell differentiation. Telocytes have been identified in various organs, specifically in human heart, lungs, brain, eye, thyroid, skeletal muscles, skin, salivary glands, gastrointestinal tract, pancreas, gallbladder, liver, and organs of the male and female urogenital system. Additionally, given the heterogeneity of the organs in which telocytes are found, and their capability to play a role in the etiopathogenesis of various diseases, the concept of "telocytopathies" has emerged. In conclusion, telocytes are increasingly becoming a focal point for the understanding of idiopathic diseases that affect humans. The development of new diagnostic and therapeutic approaches, should set forth they have the potential to contribute to regenerative medicine.

Keywords: Stromal cells, connective tissue, interstitial cells of Cajal, telocytes.

ÖZ

Stromal hücreler, birçok organda özelleşmiş mikro ortamların yaratılmasında önemli bir rol oynamasına rağmen bunlarla ilgili yapılan araştırmalar oldukça kısıtlı olmuştur. Stroma esas olarak fibroblastlar, mezenkimal hücreler, endotel hücreleri, perisitler, nöronlar, adipositler immün ve diğer tip hücrelerden oluşur. Stromal hücrelerin değişik morfolojiler ve işlevsel özelliklere sahip olmaları, bağ dokusunda farklı hücre türlerinin alt sınıflanmasına sebep olmuştur. Bunların arasında Cajal'ın interstisyel hücreleri ve telositler de yer alır. Telositler, küçük hücre gövdeleri ve uzun telopodları ile bilinen ve yakın zamanda birçok organın bağ dokusunda tanımlanmış olan yeni hücrelerden biridir. Telositler, sinir uçlarının ve kan damarların yakınında olarak, belirli hedef hücreler arasında, oldukça stratejik bir konumdadırlar.

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Telositlerin görevi, birden fazla kaynaktan gelen farklı bilgileri entegre etme ve dokuların yerel fonksiyonel gereksinimlerine yanıt olarak doku homeostazını koordine etmektir. Hücre dışı vezikülleri, çift yönlü bir iletişim sağlarken, sekretomlarının, kök hücrelerin farklılaşma mekanizmalarını düzenlediği görülmektedir. Telositler aynı zamanda, insan kalbi, akciğer, beyin, göz, tiroid, iskelet kasları, deri, tükürük bezleri, gastrointestinal kanal, pankreas, safra kesesi, karaciğer, ve erkek ve dişi ürogenital sistemlerinde olduğu gibi birçok organda tanımlanmıştır. Buna ek olarak, telositlerin bulunduğu organların heterojenliği göz önüne alındığında, ve çeşitli hastalıkların etiyopatogenezinde rol oynayabilme kabiliyetleri, "telositopatiler" tanımını ortaya çıkarmıştır. Sonuç olarak, telositler, özellikle insanları etkileyen idiyopatik hastalıkların anlaşılmasında, yeni teşhis ve tedavi yaklaşımlarının geliştirilmesinde giderek odak noktası olmaktadırlar ve rejeneratif tıbba katkı sağlayabilme potansiyeline de sahiptirler.

Anahtar Sözcükler: *Stroma hücreleri, bağ dokusu, Cajal'ın intertisyel hücreleri, telositler.*

INTRODUCTION

Over the years, parenchymal cells in a specific organ have been the focus of research in tissue biology. However, more recently, the stroma has emerged as an exciting new field of study, holding important insights to understanding complex tissue dynamics. The stroma consists of fibroblasts, immune cells, endothelial cells, pericytes, neurons and these are considered as the key cell types. Nevertheless, the stroma may also contain other cell types, like adipocytes and mesenchymal stromal cells, depending on the tissue (1). The many facets of the distinct stromal cell populations are only now starting to be acknowledged since the stromal cells in the various tissues have significantly different morphologies and functional features (2). Around 411 cell types, together with 145 various sets of neurons, have been proposed by Vickaryous and Hall for adult *Homo sapiens* (3). Morphological properties observed under light and transmission electron microscopy (TEM) were used historically to identify and characterize different cell types in this field, however topographical and functional criteria are equally crucial and have to be further investigated (4).

The predominant mesenchymal cell type in the connective tissue is fibroblast. Fibroblasts were identified in anatomically diverse connective tissues after Rudolf Virchow discovered them in 1858 and Ernst Ziegler described them as such in 1895. They have a distinctive fusiform morphology that demarcates them from other stromal cells (5). Additionally, subpopulations and heterogeneity are present in fibroblasts. Although the cause of fibroblast heterogeneity is unknown, there is evidence that it is at least partially a consequence of the mesenchymal stem cell differentiation and migration from multiple tissues (6). Despite their role in creating specialized microenvironments in numerous organs, stromal cells are still relatively understudied, mostly due to their insufficiently recognized cell types and subtypes.

Over one hundred years ago, Ramon y Cajal discovered the "interstitial neurons" in the gut which were recognized for their distinctive features. Moreover, since the 1970s these cells were investigated using TEM, when it was found out that they are certainly not neurons due to the fact that their ultrastructure was totally different and they were introduced as Cajal's Interstitial Cells (ICC). After ICC discovery, several studies on different organs have been performed to clarify their possible roles. During this time, researchers identified an other morphologically distinct cell type from ICC and described it as Interstitial Cajal-Like Cells (ICLC) for the reason that they exhibited different immunophenotypes and were functionally distinct from one another (7). In respect to this, researchers gradually came to understand the possibility of a 'novel' as-yet-undisclosed cell type. Therefore, giving them a unique name that applies only to them seemed appropriate. Given this, the Interstitial Cajal-Like Cells started to be referred to as "telocytes", by carrying the Greek designation 'Telos'. In terms of philosophy Aristotle aimed to convey the maximum potential of an entity—either a thing or a person—by using this phrase. Additionally the word telopodes (Tps) was used to describe their exceptionally long, extentions in order to discern them from the other interstitial cells (8).

Telocytes (TCs), are distinguished by their small cellular bodies, oval-shaped nuclei, minimal cytoplasm, and extraordinarily long prolongations known as Tps. According to TEM, TCs body has average dimensions that differ fom 6.31 μm to maximally around 16.42 μm. Clusters of heterochromatin found in the nucleus, make up

around one fourth of the volume of the cell. They also consist of abundant mitochondria, rough and smooth endoplasmic reticulum, a small Golgi apparatus and cytoskeletal components in the perinuclear cytoplasm. The TCs configuration can be determined by the number of Tps; for a single Tp, it can be piriform; for two, it can be spindle or fusiform; for three, it can be triangular; and last but not least they can have a stellate form (8). A Tp is made up of several enlarged, cistern-like podoms, which incorporate caveolae, mitochondria, and endoplasmic reticulum, alternated with thin, fibrillar-like segments called podomeres. Tps have a moniliform appearance because of their podomere/podom structure (9). These individual characteristics, segregate TCs and Tps from other cell types such as axons, fibroblasts, myofibroblasts, antigen-presenting dendritic cells, and neuronal dendrites and axons. At present, TCs are detected in the surrounding stroma of numerous organs such as: the heart, the vasculature, lungs, the meninges and choroid plexus, skeletal muscle, gastrointestinal system (GIS), the pancreas, salivary glands, liver, gallbladder, urinary and the male and female reproductive system organs in several species, including those of reptiles, fish, birds, mammals and notably humans (10). TCs in tissue stroma are positioned in a "tactical" manner, between blood capillaries and their particular target cells, and in close proximity to nerve fibers (8). Its location is a factor that facilitates its histomorphological identification in the tissue. The TCs interstitial system is made up of cells that combine information from the vascular, neuronal, immunological, interstitium, and stem cells by means of homocellular or heterocellular connections (11). Moreover, direct intercellular channels of communication can be provided by extracellular vesicles (ECVs) or intercellular junctions that are important for intercellular signaling. The ECV can potentially add to the change the recipient cells' post-transcriptional activity and control stem cell differentiation and proliferation (10).

TEM is considered as a "gold standard" for identification of TCs (8). Other methods for TC examination are immunohistochemistry (IHC) and/or immunofluorescence (IF). However when utilized in conjunction with one another, these two techniques, IHC and TEM can provide the most useful detection of TCs. Although a unique marker for TCs has not yet been discovered, researchers typically use CD34 for initial identification (11). In addition, other markers, such as CD117/c-kit, PDGFR α and β (plated-derived growth factor receptor alpha and beta), vimentin, nestin, desmin, caveolin-1, iNOS, VEGF, cadherin-11, connexin 43, MMPs, CD44, estrogen and progesterone receptors are potentially considered as accurate for TC detection (12, 13). As a matter of fact, these markers differ in expression from organ to organ, which makes the simple detection of TCs much more difficult in spite of the absence of a TC-specific marker. For this reason, the most suitable method is the use of double IHC with combined markers. Based on the physical characteristics of TCs, researchers have hypothesized a number of putative physiological roles for them, including intercellular communication, paracrine modulation of their environment, pacemaking, and neurotransmission mediation. It is interesting to note that scientists also took into account the possibility that they might function as cells that can switch phenotypes or act as progenitor cells, that might undergo further differentiation (13).

Furthermore, the term 'telocytopathies' is proposed to describe a variety of diseases due to the heterogeneity of the organs in which they arise and the role of TCs in their etiopathogenesis. However, the key conundrum that has to be resolved is the correlation vs. causality issue. This is relevant since functional aberrations or quantitative TC decrease are mentioned in majority of studies that explore the role of TCs in disease development (14).

A Brief Overview of The Human TCs

The presence of TCs and telocyte-like cells has been highlighted in numerous tissues with human origin during the past two decades, but official evidence of their presence was only made public in 2010. Studies suggest that TCs may be at the root of a number of pathologies linked to various diseases, and as a result of disruption of TCs-cell communication with the tissue's resident cells, diseases may result with a poor prognosis. Researches on TCs, related to tissue regeneration, have also been widely reported. This review provides a brief summary of original studies related to only human TCs, in the organs where they have been identified thus far, during these last thirteen years.

TCs in Human Heart, Vasculature and Lymphatics

Detailed ultrastructural investigations of the human epicardial and myocardial TCs show that these cells are in close contact with each other and that the epicardial TCs can create a three-dimensional (3D) cellular web that is associated with the 3D network of myocardial TCs and provide intercellular signaling (15). TCs have also been identified in the subepicardium, subepicardial arteries and in the subepicardial fat as well as in the endocardium and subendocardium near the endocardial stem/progenitor niche (16, 17). Moreover, it is reported that the sinoatrial node (SAN) of the human heart also consists of these cells (18). In addition, TCs have been discovered in the the base of the heart valves where they potentially contribute for the flexibleness of the valves and mechanical support (19). TCs in the human heart have been studied in a variety of diseases, such as isolated atrial amyloidosis, atrial fibrillation, tetralogy of Fallot, myocardial infarcts and heart failure, and they have been attributed with few roles related to these conditions (20–24). Regarding the human vasculature, TCs in the human thoracic aorta have been identified in several levels of the aorta and it has been found that they produce exosomes containing vasculogenesis-related proteins. Evidence of TCs in the human aorta is thought to be important for cell homeostasis, tissue remodeling, and regeneration (25). Furthermore, it has been detected that TCs are implicated in the formation of thoracic aortic aneurysms (TAA) and via the production of ECV they may contribute for the phenotype switch in smooth muscle cells (SMC) (26). Moreover, it is reported that tiny blood vessels of the intestinal villus type contain perivascular villus type TCs (VTTCs) which take part in ensuring sufficient endothelial fenestrae, and prevent leaking in the villus tip epithelial structures. At present, heart TCs appear to have the potential to create cell-based strategies for heart regeneration, repair, and protection (27). TCs in the human lymphatic system have also been identified. Lymphatic endothelial cells (LECs) and TCs may exhibit similar morphological traits. A morphological study aiming to distinguish their immunophenotypes revealed that TCs are *PDGFRα+/ CD34+* while *LYVE-1−* and *PDPN−* and LECs are also *PDGFRα+/PDPN+* and *LYVE-1+* but *CD34−* thus, this makes it clear that they are definitely two different cell types however, physically adjacent to one another. Considering the location of the TCs near the LECs, suggests a possible role of TCs in controlling the work of the lymphatic capillaries (28).

TCs in Human Lung and Pleura

Human lungs contain TCs and Tps along the airway tree, the vascular system and the mesothelium. Their flexible and resistant 3D networks might help keep intralobular bronchioles' lumens open and prevent blood vessels from closing. Additionally, they have been found in the under-epithelial stroma in close proximity to clusters of stem cells (SCs), where they seem to form SC-TC niches (4). Moreover, it has been reported that, a lack of TCs has been observed in a fibrotic lung affected by systemic sclerosis (SSc). This loss may have important implications for the pathophysiology of the fibrotic lung (29). The significance of TCs in lung diseases and their possible therapeutic value require more investigation.

TCs in the Human Gastrointestinal Tract

In the gastrointestinal tract (GI) in humans, TCs form 3D networks in the underlying mucosa and inside the muscular layers. Moreover, TCs encircle intestinal crypts, gastric glands, blood vessels and nerves. In addition, it is interesting to note that a number of TCs are found to be running parallely and share the same location such as the ICC (30) and presumably work in tandem while aiding to each others functions, especially in regards of motility. The presence and distribution of TCs has been investigated in several GI tract diseases, specifically in Crohn's disease, (31) ulcerative colitis (32) and in the aganglionic area of the Hirschsprung gut (33) where the number of TCs was found to be dramatically reduced or even absent. This loss of TCs may contribute to colonic dysmotility. However, further analyses need to be carried out in order to understand what is the role of TCs in gut motility and their relation with different GI tract pathologies.

TCs in Human Liver

TCs have been additionally discovered in human liver, moreover in the portal area and in the periphery of the hepatic lobule where their relationship with idiopathic portal hypertension has been emphasized (34). Hepatic TCs are reduced in human liver fibrosis, leading to altered extracellular matrix architecture and lack of control over fibroblast/myofibroblast activity (35).

Furthermore, TCs may promote metastasis of hepatocellular carcinoma, but the mechanism is unknown. In the liver, the formation of extra-gastrointestinal stromal tumors (EGISTs) appears to be clearly linked with the TCs, offering hope for the development of targeted treatments (36). Eventually, the probable involvement of TCs in cancer, liver fibrosis, and, accordingly, hepatic regeneration, creates a new field for research.

TCs in the Human Gallbladder

TCs in the human gallbladder are found to be predominantly located in the muscularis mucosae and they have been suggested to be engaged in signaling mechanisms. It is also suggested that modified bile composition in cholelithiasis patients, might be the cause for the reduction of TC density in the gallbladder (37). Likewise in the liver and pancreas, stromal tumors, like EGISTs, can affect the gallbladder and be directly or indirectly associated with TCs (36). Targeted treatment may be an option given that TCs have been linked to the formation of EGISTs and the pathogenesis of gallstones.

TCs in Human Pancreas

TCs have been also identified by TEM in the exocrine pancreatic stroma of human pancreatic tissue, where they were present between acini, ducts, nerves, and blood vessels. It has been proposed that pancreatic TCs possibly compromise with acinar cells and small blood vessels and also establish reciprocal connections with satellite cells that have a receptor function. TCs are thought to be crucial for pancreatic development, function, and take part in the carcinogenic microenvironment (38). TCs may be helpful for detecting alterations in the stromal milieu, delivering biological molecules, and facilitate the identification of the etiology of chronic pancreatitis and other pancreatic diseases on a cellular level.

TCs in Human Salivary Glands

TCs have been identified in the parotid stroma in close contact with acini, ducts, blood vessels and nerves, as well as in the subductal and interacinar stroma. TCs could modulate neurological and vascular processes in the parotid gland (39). The regulation of local tissue homeostasis by TCs is assumed to be impaired in organs affected by autoimmune diseases. In the minor salivary glands in conditions like Sjögren's syndrome and non-specific chronic sialadenitis, TCs presence has been seriously affected (40). The findings suggest that TC degradation in the small salivary glands may have important clinical repercussions.

TCs in Human Thyroid

Although stromal CD34+ dendritic and fibroblastic cells have been noticed in the thyroid stroma for a long time, it has now been established that these stromal cells are, in fact, TCs. TCs with their Tps, encircle the side of the thyroid follicles' which is opposite to the lumen, separating them from the surrounding capillaries. In addition, the network of Tps may have a role in controlling the release of thyroid hormone due to the fact that they are specifically positioned between the blood capillaries and the thyroid follicles. Moreover, it is tempting to hypothesize that TCs, following thyrotropin receptor activation, can contribute to the etiology of thyroid autoimmunity and thus offer novel potential therapeutic targets (28).

TCs in Human Skeletal Muscles

TEM imaging and IHC investigations revealed human TCs in fetal and adult skeletal muscle interstitium. In addition to being adjacent to nerve terminals and capillaries, TCs were also observed to be in close relation with myocytes and satellite cells, indicating their involvement in intercellular signaling (41). According to (42) in a cell culture study, they are seen to represent a distinct cell type inside the muscle stem cells niche. Furthermore, it has been suggested that TCs have a role in a number of physiological functions in the skeletal muscle, including angiogenesis, tissue regeneration, and homeostasis maintenance (43). Ultimately, it would be crucial to look into how TCs could contribute to the onset of various myopathies and how they might be used in the treatment of skeletal muscle regeneration.

TCs in Human Brain

TCs in the human brain are among the least studied. Thus, there are only two studies related to Glioblastoma (GBM). GBM for its growth and invasion, uses ion channels and transporters, such as Na - K-ATPase. Few of the β-subunit isoforms in Na - K-ATPase which may play a role in regulating cellular dynamics, especially during the development of cancer, are reported to be expressed by TCs (44). Mitrofanova et al. studied the presence and roles of TCs in human GBM specimens where it has been observed that the TCs are found in the walls of tumor vessels, in glial scarring as well as in GBM/ astrocytoma primary cultures. As a result, the possibility that

TCs contribute to GBM neovascularization has been brought up. Interestingly, TC counts in GBM specimens were found to be ten times greater than those in astrocytomas. Improved targeted therapy and the creation of novel anti-neoplastic medications are anticipated to result from research into the GBM cell types (including TCs) and their involvement in the formation of brain tumors (45).

TCs in Human Eye

It has been reported that a stromal network of TCs surrounds the conjunctival lymphatic lacunae in the human eye and that stromal CD34-expressing cells/TCs are constructing a consistent pan-stromal network (46). The stroma of the human sclera contains a progenitor cell niche that is accomodating TC-like cells (47). Furthermore, TCs are distributed throughout the normal corneal stroma, with different TCs subtypes being distinguished by the expression of c-kit, the stem cell marker. Keratoconic corneas have been observed to be very degradated with a nearly total extinction of the TC subpopulation. It has been suggested that TCs may aid in the preservation of corneal stroma and may function as stem cells during the repair and regeneration of the cornea (48,49).

TCs in Human Skin

The majority of TCs in human skin have been shown to reside in the dermis, where they have been observed to be closely related to other stromal cells as the fibroblasts, adipocytes, mast cells, as well as collagen and elastin fibers (50)**.** TCs discovered in the reticular dermis have been surrounding the sebum glands, the eccrine sweat glands, arrector pili muscles, the perifollicular sheath, and blood vessels (51). Additionally, TCs have been found in the hair follicles close to stem cells (9). Due to the frequent observation of intimate, planar connections between mast cells and TCs, it is possible to explain why allergic skin disorders are so prevalent in clinical practice (9). Moreover, conditions like systemic scleroderma and psoriasis vulgaris are also known to influence the TCs, causing changes in their shape, distribution, and quantity (29,52). TCs have been identified in both basal and squamous cell carcinomas, where they establish homocellular connections and a 3D network inside the peritumoral stroma (53). In summary, TCs may be involved in regulating skin homeostasis and remodeling, and their many intercellular connections and possible vital roles may have implications for skin regeneration.

TCs in Organs of the Human Urinary System

TCs have been observed in the human kidney, pelvis, ureter, and bladder. Studies in the human kidney cortex have confirmed the presence of TCs in the interstitium and divided them such as: capsular stromal cells SC/TCs, subcapsular and interstitial SC/TCs, mostly centered near blood vessels and renal tubules (54). However, TEM images showed no typical TCs observed in the human kidney medulla, and no positive expression of CD117 indicating that the amount of TCs in the medulla samples were inadequate for TEM and IHC detection (55). Human ureter-specific TCs continue to divide into three distinct subgroups, some of which are considered to make up the ureter's stem cell niche (56). They exhibit a comparable ultrastructural phenotype, which is distinct from bladder interstitial cells, with thinner and longer cytoplasmic processes (57). In terms of pathology it has been postulated that the presence of TCs may contribute, or be indirectly related to the pathomechanisms of hydronephrosis (58), and congenital primary obstructive megaureter (POM) (59). Moreover, TCs found in the human bladder build networks that are able to follow the wall relaxation and distension of the bladder. In order to prevent aberrant wall deformation TCs are expected to modify their shape in response to organ activity (60). It has also been revealed that c-kit positive TCs have been more extensively distributed in the submucosa and muscularis layers of the bladder, in bladder cancer (BC). Finally, TCs can have a role in tissue regeneration, disease etiology, and cancer in urinary system organs (61). Nevertheless, the functional significance of TCs in the urinary system has to be clarified and may be a fruitful study topic for therapeutic purposes.

TCs in Organs of the Human Female Reproductive System

Human Uterine TCs

TCs are found in the human myometrium and contribute to its contractibility. According to certain theories, c-kit positive interstitial cells (TCs) may send out a signal that causes myometrial SMC to contract (62). TCs presence has also been reported in the human endometrium, where they may participate in endometrial regeneration, and communication between cells inside the endometrium (63). Additionally, TCs have been observed in the corpus uteri, cervix, and leiomyoma specimens.

Furthermore, a comparison of the density of TCs in myometrium with fibroid foci and healthy myometrium revealed that the density of TCs in fibroid foci was much more lower (64, 65). It is furthermore reported that dysmotility and irregular contractility of the human oviducts may result in ectopic pregnancy (EP) (66). Increased TC numbers, have been found in the tubal tissues of ectopic pregnancies, which may impact the blastocyst's translocation to the uterus by reducing tubal motility. (67). However, further research is required to fully comprehend their function and role in EP and other fallopian tube pathologies. Recognizing the molecular mechanisms and the function of TCs both in human pregnant and non-pregnant uterus is of an extreme value for understanding their putative role in pregnancy maintenance and implantation.

TCs in Human Placenta

TEM has studied the TCs of placental villi during physiological pregnancy (68). According to studies, TCs and their probable involvement in controlling fetal blood flow may potentially be a factor in preeclampsia (PE) patients' oxidative stress, which may not always be linked to malfunction of the endothelium, or trophoblast apoptosis. It has been speculated that the loss of TCs, influences the chorionic villi's relaxation and contraction phases due to the reduction of the potential pacemaker function of these cells. On top of that, it has been discussed that their absence can add to the diminishing of the intervillous area in the villi where they get in touch with the mother's bloodstream. These effects, as a consequence of the reduced TCs number are considered to severely reduce the mother's nutritional contribution to the fetus (69). Further studies on placental TCs can add more knowledge to the pathogenesis of missed abortuses and their potential impact on the fetal health during pregnancy.

TCs in Human Mammary Gland

Resident TCs, in the mammary gland in humans with CD34+ and CD10±/c-kit-/vimentin+ expression have been detected to form regular stromal networks while enclosing excretory compartments and small blood vessels. According to their immunophenotypic characteristics they may take part in the mammary stem cell niche in several stages of differentiation (70). Few other studies have revealed some putative roles of the TCs in the growth of invasive mammary carcinoma (71). Nevertheless, further research in this area in general is required to assess their importance and putative treatment potential.

TCs in Organs of the Human Male Reproductive System

There are surprisingly very few studies on TCs related to the human male reproductive system thus far. Their presence in the human testis has been confirmed by TEM, throughout the testicular stromal compartment. The TCs in the testis stroma seem to be establishing close contacts among themselves, blood vessels and other resident cells in the interstitium such as the myofibroblasts, macrophages and Leydig cells. Consequently, it is believed that TCs and their Tps take part in the movement of substances or hormones, from the stroma to the seminiferous tubules, and are thought to help in the control of the spermatogenesis (72). One study related to a testicular seminoma reported a significant loss of TCs seen along the seminiferous tubule, together with stromal tissue degeneration, and interstitial fibrosis (73). Last but not least, it would be intriguing to look at the TCs in various testicular malignancies, since the examination of pathological tissues might help us understand the potential roles that these particular interstitial cells may play in other diseases.

CONCLUSIONS

In summary, connective tissue stromal cells are still not completely characterized, and due to their various morphologies and functional features, numerous stromal cell subtypes are still awaiting disclosure. The TCs, formerly known as ICLC, are unambiguously one of the stromal cells with the most strategic position and major responsibilities in the stroma. Although most of the studies have been concentrated on demonstrating the presence of TCs in all kinds of organs over the past two decades, it is crucial to understand how TCs differ and coincide in different species, or strains and confirming their evidence and significance in humans is of an utmost importance. Human TCs have been indicated to reside in several organs and systems, including the heart, lungs, pleura, vasculature, lymphatics, brain, eye, skeletal muscles, skin, salivary glands, thyroid, pancreas, liver, gallbladder, gastrointestinal tract, urinary tract, testes, uterus, oviducts, mammary glands and placenta. Many physiological and pathophysiological issues involving the aforementioned organs have been related to these cells. All things considered, it is important to recognize that there is still a large number of under-inverstigated human tissues where TCs can provide more understanding about the

normal and abnormal tissue architecture and function. Finding TCs-specific biomarkers is very important since they can make cell identification simpler and more efficient. The TCs vast potential remains in their capacity to further our comprehension of a number of diseases that are currently categorized as idiopathic and to provide new diagnostic and therapeutic approaches to a broad range of pathological scenarios. All things considered, they definitely seem to be making a growing contribution to tissue engineering and regenerative medicine and deserve maximal attentiveness from the scientific community.

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