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Telocyte-Based Angiogenesis Potential in Tissue-Engineered Transplantation and Reconstructive Medicine Structures

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Abstract

Telocytes (TCs) are interstitial cells that were first identified in 2005 and formally named in 2010. Telocytes are cells that have a small cell body and long, thin appendages called telopods. TCs have been identified as critical interstitial cells for nursing or guiding stem cells and progenitor cells at niches. For this reason, researchers pay attention to them as new targets for regenerative medicine. The network of these cells provides the possibility of intercellular communication in the tissue and thus the organs. Telocytes not only provide mechanical backrest for stem cells and progenitor cells but also cause the increasing, differentiation, and movement of stem cells. It is shown that these cells are involved in the formation of blood vessels. Since one of the challenges of connective tissue engineering is the angiogenic potential of engineered products, we will review the results of studies on the potential of telocytes in angiogenesis in different organs.

Keywords: *Telocyte, Angiogenesis, Vascularization, Reconstructive medicine*

1. Introduction

Tissue engineering is a field that focuses on replacing living organs and tissues, as well as reconstructing damaged ones. There is promising potential in the field of reconstructing various body parts. However, contrary to popular belief, the clinicalization of these techniques and products could be faster. Several factors have been reported that can cause a slowdown in the process. One reason is the insufficient blood vessel supply to meet the metabolic demands of dense connective tissues.

Numerous approaches have been suggested to address this challenge. Two methods have been developed to improve islet transplantation. The first method involves using an immunoisolation device made of electrospun nylon (1). The device has an inner component that acts as a cellular barrier while allowing diffusion. The outer component can be optimized for tissue integration and faster vascularization. This method is shown in (Fig.1.A). The second approach, shown in (Fig1.B), involves implanting angiogenic agents on scaffolds; this increases the chances of tissue transplantation by promoting the growth of new blood vessels and angiogenin throughout the scaffold. The study by Shi et al. tested this method (2).; This study showed that structures containing this factor increased neovascularization.

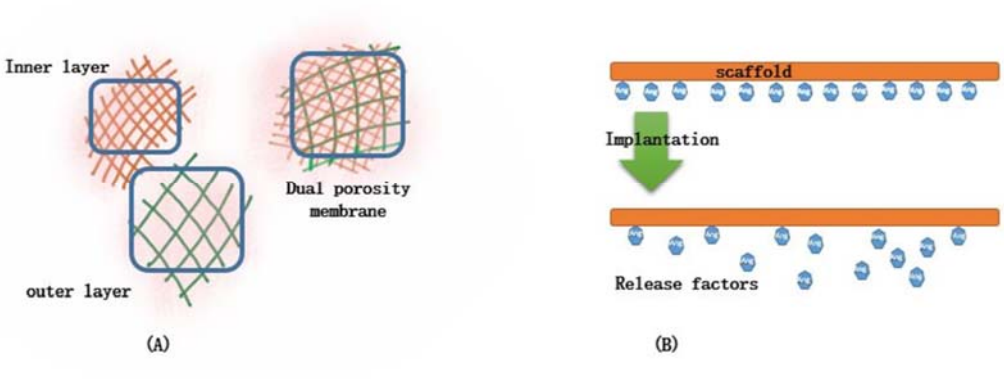

Figure 1. Schematic methods have been proposed to overcome.

angiogenesis; (A): The use of an immunoisolation device based on electrospun nylon; (B): angiogenesis factor implanted throughout the scaffold.

A proposed technique in liver tissue engineering (3) involves using nanocidal chambers for microstamping. Another approach that has been proposed is to create a spatial slope in the scaffold in order to provide growth factors. Graded signals are created by mimicking the distribution of common morphogens through connected or imprinted factors. These agents release angiogenic substances based on cellular activity and are regulated, and the formation of a new vascular network is regulated (4).

The formation of tissues and organs before transplantation is rapidly expanding. This approach depends on the proliferation of cell populations or natural and artificial scaffolding. However, some tissues developed under these conditions cannot provide the biomechanical properties necessary for tissue function in the body. Blood vessels, for example, are made using a variety of biomaterials and cell populations and perfusion cultures that are histologically very similar to body blood vessels; however, when transplanted, these structures could not withstand pressure changes and failed (5).

Another method is the use of cell or cell therapy. Stem cells have been suggested to induce regression and vascular network formation, and the use of these cells is associated with either pre-transplant differentiation or post-transplant differentiation induction. These cells may also be a source of pro-angiogenic factors. It is a well-established fact that these cells have the ability to fuse with host vessels, employ perivascular cells, and inaugurate flow, as demonstrated by studies (6).Peripheral organ structures are more likely to be formed by angiogenic factors such as VEGF[1] or its producing cells (endothelial cells) and their precursors, which are more likely to be located in primary tubular structures (7).

These cells also act through regression factors. Angiogenic factors are summarized in Table 1.

Table 1. Angiogenic factors

Factors	Description
VEGF	VEGF, known as VPF[2],[1] is a signal protein made by cells that promotes the formation of new vessels
FGF-1	Acidic FGF[3] act as a modulator of endothelial cell movement and proliferation, as well as an angiogenic factor
FGF-2	Basic fibroblast growth factor mediating angiogenesis
Ang-1	Angiopoietin-1 has important roles in vascular development and angiogenesis
Ang-2	Angiopoietin-2 has important roles in vascular development and angiogenesis
PIGF	A placental growth factor is a key molecule in angiogenesis and vasculogenesis, in particular during embryogenesis
FGF-4	Fibroblast growth factor-4
HGF	Hepatocyte growth factor (HGF) has a major role in embryonic organ development
Ephrin-B2	Ephrin-B2 is mediating developmental events, mainly in the in erythropoiesis and nervous system

[1] Vascular Endothelial Growth Factor
[2] Vascular Permeability Factor
[3] Fibroblast Growth Factor

Factors	Description
PDGF-BB	PDGF[4] has role in blood vessel formation. The process of forming new blood vessels from pre-existing blood vessel tissue is known as angiogenesis.

Excessive protein expression may have a significant effect on neovascularization (8).

Recently, a group of cells called telocytes have been proposed as candidates for regression induction. These cells were previously referred to as ICLC,, are widely distributed in connective tissue. These cells have been recognized in different organs of different species, such as the cardiac system (epicardium), endocrine glands, myocardium or heart valves, reproductive system, urinary system, gastrointestinal tract, respiratory tract (lungs and trachea, pleura), arteries (mesenteric arteries, aorta, coronary arteries, internal arteries of the chest, carotid arteries, portal vein, pulmonary artery, or Lymphatic), glands (parotid glands, mammary glands, partial salivary glands), skin. Meanwhile, the species involved in the research include humans, pigs, chickens, rabbits, sheep, cows, cats, dogs, and Chinese soft turtles. These identified telocytes can form a three-dimensional network and communicate with surrounding cells (e.g., fibroblasts, muscle cells, immune cells, fat cells, or nerve cells) (9).

2. Telocytes:

These are special types of intercellular cells in various organs. One of the main characteristics of these cells is intermittent telopods and podomeres, which were named in 2010.

Morphology: These cells are small in size and have long and thin processes. These processes are called telopods. Electron microscopic images are now the gold standard for identifying these cells. Depending on the number of telopods, the cell body can have different shapes. For example, if a cell has two telopods, it can be seen as a spindle, and if it has three telopods, it can be seen as a triangle and more than three telopods. The infrastructure of telocytes shows many intermediate filaments that participate in the formation of the cytoskeleton. The longitude of telopods varies from 10 to hundreds of micrometers (Fig.2).

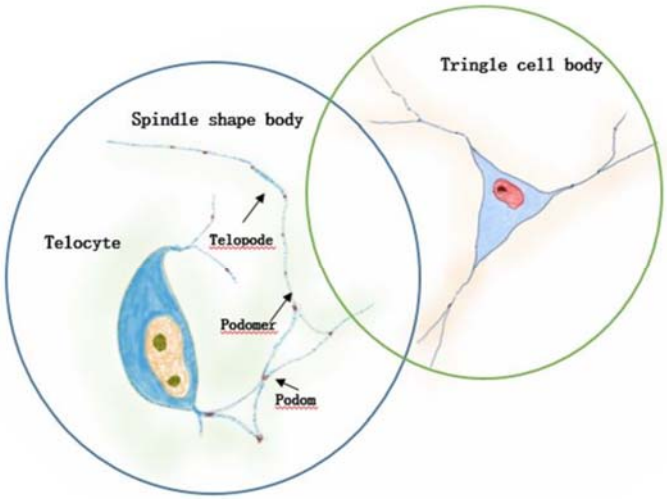

Figure 2. Schematic of Telocyte's structure.

2.1 Telocytes' Connections:

These cells have several homocellular and heterocellular connections. Homocellular connections form an extensive network in the tissue. A variety of heterocellular connections greater than any other cell in the body also exists. The heterocellular connections of telocytes could provide mechanical performance or be used for intercellular exchanges and signaling. The connections have different names depending on their function. The heterocellular connections between these cells with myocardiocytes, stem cells, ICC cells,

[4] Platelet-Derived Growth Factor

smooth muscle cells, macrophages, and Schwann cells have been reported (10).

2.2 Angiogenic roles:

Regarding the role of telocytes in vascular formation, the evidence suggests a close relationship exists between telocytes, stem cells, and progenitor cells in the niche. The three-dimensional intermediate network created by telocytes provides mechanical support for stem cells and progenitor cells and promotes stem cells' differentiation, maturation, and migration. The progenitor cells act through atypical and myxacrine or paracrine connections (11).

Telocytes secrete VEGF, NO, Interleukin-6, some cytokines, and even miRNAs, which affect and control surrounding cells (12). These cells produce miR126, miR130a, let-7 family, miR-10, miR-155, miR-503 and other proangiogenesis factors. Factors such as miR-21 can activate Hif-1a and VEGF expression and elucidate the AKT & ERK pathways mediating the angiogenesis pathway. Interestingly, telocytes express both stromal-specific miRNAs and vascular smooth muscle; therefore, it has been suggested that telocytes have a strong potential for the treatment of infarction (13,14).

Extracellular vesicles are crucial for maintaining vascular homeostasis, stem cells, monitoring the immune system, repairing tissues, and releasing/transporting fats, proteins, and nucleic acids to target tissues, and various bodily functions rely on their crucial role (15).

VEGF is noticed as a potent promoter of angiogenesis has the ability to stimulate the proliferation of endothelial cells and vascular permeability and is a maintenance agent for blood vessels that have recently formed (16).

In the interstitial skeletal muscle, telocytes communicate closely with blood vessels, nerve fibers, satellite cells, and myocytes and participate in muscle regeneration. Similarly, telocytes are located in the heart near myocardial cells, blood vessels, and nerve endings (17). In addition, cutaneous telocytes are adjacent to fibroblasts, mast cells, and adipocytes (18).

It can be suggested that TCs serve as a pacemaker network, utilizing various components such as gap-junctions, ER[5], and mitochondria. Researchers are thrilled to confirm the presence of gap-junctions between TCs and other cells through immunoreactivity to Cx43 [6]. This vital protein facilitates intercellular communication, regulating differentiation, proliferation, and maintaining homeostasis. This subject emphasizes the significant role played by TCs (19).Angiogenesis is a common phenomenon in physiological and pathological conditions, including the proliferation of vascular endothelial cells, enzymatic destruction of basement membranes, and intermediate matrices by endothelial cells (Vascular endothelial cells migration, and the formation of blood vessel tubes from the germination of vascular endothelial cells). Angiogenesis can be induced by the activation of VEGF and EGF receptors by binding to the relevant factors leading to the induction of tubal arrangement of vascular endothelial cells (20). During recovery and repair of damaged tissues, including angiogenesis, it is believed that telocytes play roles as precursors and nutrient cells in both normal and damaged states through VEGF and EGF secretion (20).

Telocytes are distributed around the vascular space. Two or three layers of these cells form an almost complete sheath with telopods surrounding vascular endothelial cells; by homocellular or heterocellular junctions between telopods or fibrocytes and pericytes. Also, telocytes are dispersed between smooth muscle cells with anisotropic connections between them (21).

A study examining the morphological development of telocytes in rabbit lungs from embryo to birth showed that these cells are involved in angiogenesis, forming, and developing a blood-air barrier in the pulmonary respiratory tract (22).

In the prenatal period, these cells form an extensive network in the lungs through their telopods that contact the alveoli, bronchioles, and stem cells, and the size of the contact components. The number of telocytes also increases around new arteries. Before birth, these cells are star-shaped, have large cell bodies, and short telopods, and have large rough endoplasmic reticulum, mitochondria, and ribosomes. Gradually, these cells become spindle-shaped and the telopods will have large amounts of secretory structure. The number of telocytes decreases after birth, but as the length of the telopods increases, the network expands. The immunohistochemical profile of cells varies during lung growth and cannot be considered a fixed profile (22).

Based on the available evidence, it appears that telocytes exhibit expression of c-kit and CD34, which may suggest their involvement in the process of angiogenesis (23).

Cells located around blood vessels in the pericytic microvasculature, namely pericytes and $CD34^+$ stromal cells/telocytes ($CD34^+$SCs/TCs), in the process of angiogenesis, play an absolutely critical role. A recent study examined the behavior of cells depending on whether the endothelial cells (ECs) from pre-existing microvasculature grow towards the interstitium with vascular bud and neovessel formation (sprouting angiogenesis) or towards the vascular lumen with intravascular pillar development and vessel division (intussusceptive angiogenesis). The study aimed to understand the different mechanisms of angiogenesis and how

[5] Endoplasmic Reticulum

[6] Connexin-43

they affect the growth and development of blood vessels. During sprouting angiogenesis, these cells these cells detach from the vascular wall and undergo mobilization, increasing, employment, and maturation. Pericytes play a vital role in the development, stability, differentiation, and regression during sprouting angiogenesis. Additionally, Pericytes involved in forming the interstitial tissue structure of the pillar core during intussusceptive angiogenesis. During the process of sprouting angiogenesis, perivascular CD34+SCs/TCs multiply and play a crucial role in producing stromal cells for granulation tissue formation during repair, and in tumors they generating cancer-associated fibroblasts (CAFs). On the other hand, in intussusceptive angiogenesis CD34+ stem cells and tissue cells have a lower involvement as precursor cells (24).

It has been observed through research conducted on human cells that CD34+ cells produce exosomes both in vitro and in vivo, which have been found to possess independent angiogenic activity. It has been suggested that Exodus $CD34^+$ plays a crucial role in the paracrine effect of progenitor cell transplantation, which can aid in therapeutic angiogenesis (25). Another study suggests that $CD34^+$ cells have a commitment to the process of angiogenesis after transplantation and that these cells can be used for cell therapy and the development of optimal treatment strategies for myocardial repair (26).

The use of these cells for on-site angiogenesis requires further investigation. First, it should be answered that in cases where the pathology related to these cells has been addressed, these cells have reflected the damage or are involved in the background of the disease.

Many studies have been conducted to explore the possible involvement of telocytes in diverse diseases. Most authors have identified some common quantitative and qualitative characteristics for telocytes in pathological conditions, such as decreased number or destruction of cells (absence of cells) or shortening of telopods.

Kaposi sarcoma (KS) is a type of lesion that involves the growth of blood vessels, and it arises from two main sources of cells:endothelial cells (ECs) and mesenchymal/stromal cells. A research study identified the tissue location, characteristics, and trans-differentiation process of KS cells and studied 49 cases of cutaneous KS by utilizing immunochemistry, confocal microscopy, and electron microscopy to examine the specimens. The findings indicate that CD34+SCs/TCs are present in the outer layer of preexisting blood vessels and surrounding skin appendages. These cells make tiny lumens that converge and are marked with characteristics of both vessels endothelial cells (blood and lymphatic). They share similar traits with ECs at a structural level and contribute to the development of two main types of new blood vessels. It appears that the formation of spindle-cell patterns or lymphangiomatous areas, which can arise from the development of new blood vessels, contribute to the primary variations observed in KS histopathology. Neovessels contain intraluminal folds and papillae, suggesting vessel splitting or intussusceptive angiogenesis may have occurred. This statement highlights that CD34+ stem cells/TCs possess the potential to differentiate into Kaposi's sarcoma endothelial cells, which are known to play a role in the formation of two distinct types of blood vessels. The growth of these vessels involves intussusceptive systems, leading to the creation of multiple Kaposi's sarcoma variants. These discoveries are significant for understanding the origin, diagnosis, and treatment of KS (27).

A different study focused on CD34+SCs/TCs found in unhealthy skin, but also briefly explored their presence in healthy derm and observed that there is a practical absence of these cells in the papillary dermis, but they are present in the bulge as very tiny CD34+ stromal cells (28).

Moreover, researchers conducted further research on TCs/CD34+SCs found in WAT[7] that has been affected by pathology, following a brief examination of these cells in normal fat. Two important issues have come to light. Firstly, the question of whether the lack of CD34 expression in TCs/CD34+SCs has relation with shift in marker expression or the fadeaway of these cells. Based on the findings, it seems that the first option is the more probable one. Secondly, it is being investigated whether in certain invasive and metastatic malignant tumors, TCs/CD34+SCs that surround NCs[8], can act as supportive and/or isolating cells. More investigations are required on WAT's TCs/CD34+SCs, speciallyin lipomatosis and obesity (29).

It has also been shown that a decrease in telocytes can cause a 3D change in the formation of the ECM[9] and the development of fibrosis. A similar decrease in these cells has been reported in various diseases, including myocardial infarction, liver fibrosis, Crohn's disease, and lung disease. However, in the study of leiomyoma, it was shown that these cells are involved in the pathology of the disease through its effect on angiogenesis (30).

3. Conclusion

Telocytes express both stromal-specific miRNAs and vascular smooth muscle. Telocytes are also believed to play a role in normal and damaged states by secreting growth factors as precursors and nutrient cells. These cells are distributed throughout the vascular space. Two or three layers of these

[7] White Adipose Tissue
[8] Neoplastic Cells
[9] Extracellular Matrix

cells form an almost complete sheath with telopods that surround the vascular endothelial cells. Telocytes have markers that are expressed on the surface of stem cells, so it is suggested that these cells are involved in angiogenesis.

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Conflict of Interest:

Authors declare that they have no conflict of interest.

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Ethics statement:

The authors followed COPE.

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