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Notes about telocytes and immunity

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Abstract: The interstitial cells known as telocytes have been described in various organs. Their role in the normal physiology and pathogenesis of numerous diseases is well known. They have been described in the context of various diseases (gallstone disease, endometriosis, uterine myoma, hydronephrosis, myocardial infraction, psoriasis, etc.), while their impact on inflammation, involvement in angiogenesis, and repair highlights their part in local homeostasis. What is known about their relationship with the immune system? Their secretomes, genome, immune profiles, contacts with surrounding cells, and specific localization allow us to give a possible explanation for their involvement in pathological pathways. This review aims to present the roles and features of telocytes in the context of intestinal immunity (the largest in our body), in the spleen, their interactions with immunocytes, and their place in stem cell niches.

Keywords: immune response, telocytes, interleukins, cytokines, macrophages.

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Introduction

The immune microenvironment is essential for life and all physiological processes in both humans and animal organisms. Aging, tissue regeneration, the tumor microenvironment, allergic and inflammatory reactions, alloimmunization, immune reconstruction and immunosuppression, oncogenesis, immune invasion, autoimmune diseases — these are just some examples of the role that immunocytes play in physiology and pathophysiology. The crosstalk between different types of cells is crucial, forming the background of diseases as well as for the maintenance of homeostasis. Each population of cells should be considered as a piece of a puzzle, and which constitute

an axis of specific physiological action. For instance, platelet-derived mediators (integrins, α-granule proteins, δ-granule molecules, and others) may initiate the immune response. Further, platelet-neutrophil interactions mediate the formation of a specific axis to effect NETosis (the formation of neutrophil extracellular traps), while platelet-dendritic cells interactions stimulate antigen presentation to T-cells by dendritic cells [1]. We also have multiple components of immunity, while different cells are characterized by diverse properties and their multifaceted nature. Due to their ability to form homo- and heterocellular contacts with smooth muscle cells, nerves, immunocytes (macrophages, mast cells, and lymphocytes), stem cells, melanocytes in the eye, erythrocytes, and Schwann cells, as well as their secretion of signaling molecules (ectosomes, exosomes, apoptotic bodies), and receptors for growth factors, telocytes (TCs) attract great attention and provoke robust discussion as to their nature and role [2–5]. They are of mesenchymal origin and make numerous contacts with immunocytes. Chi *et al.* conclude that these cells "might be active players in local immunoregulation and immunosurveillance, acting as important 'local data suppliers' for the immune response" [6]. Morphological characteristics of TCs have been extensively described in reviews [2–4]. The development and activity of the immune system are coordinated by cytokines, short-lived small proteins essential for paracrine, autocrine, and endocrine signaling. TCs have their own cytokine profiles and may impact macrophage and B cell secretion. Multiple hypotheses and speculations, facts and myths, data and conclusions all refer to a single pool of cells with described by several synonyms: "telocytes", "interstitial Cajal-like cells", "fibroblast-like cells", "PDGFRα+" (platelet-derived growth factor receptor alpha), "interstitial pacemaker cells". In this brief summary, we intend to collect the available data about the role of telocytes in the immune microenvironment by conducting a thorough search on PubMed for all available studies containing the above-mentioned synonymous terms. In particular, we want to place emphasis on the network of telocytes and surrounding cells in different parts of the immune system, as well as their possible roles.

Telocytes in the intestinal surface microenvironment

Intestinal immune regulation has heterogeneous mechanisms, and the working of the mucosal immune system is fundamental to the human body. One of the regulatory mechanisms involved is the release of acetylcholine from the nonneuronal cholinergic system, involving the epithelial cells, crypt-villus organoids, immune cells, and intestinal stem cells [7]. Crypt fission occurs mostly under the action of stem cells [8]. Special secretory epithelial cells, Paneth cells, are located at the base of epithelial invaginations in the small intestine known as the crypts of Lieberkuhn [9, 10]. They may initiate an immune response and maintain local homeostasis [11]. TCs are present in the intestinal villus-crypt axis [12]. There are different subpopulations of TCs

in the human gut with possible region-specific roles, differentiated based on their immunohistochemical profile. Their functions include the formation of a 3D network in the myenteric plexus, a mechanical role in the submucosal border of the circular muscle layer [13, 14], and they constitute a component of stem cells niches [15]. TCs are positive for platelet-derived growth factor α (PDGFRα), which is why in some studies they have been known as "PDGFRα+" cells. Even during the embryonic period, the circular and longitudinal muscle layers express PDGFRα+, which is essential for further differentiation of longitudinal muscles [14]. Both types of muscle in the intestine are innervated by enteric motor neurons for the realization of contractile and motor functions. Nitric oxide synthase (NOS) immunopositive neurons are involved in muscular contractility and vascular tone [16], while nitric oxide (NO) is a powerful agent in the immune system. NO is produced in neurons after stimulation by pro-inflammatory cytokines (interferon γ, interleukin 1, and tumor necrosis factor α) due to NOS [17, 18]. Of note, TCs may stimulate peritoneal macrophages to produce NOS and interleukin-6 through the paracrine pathway [6]. Due to the toxic and protective effects of NO, its balance is important for tissue homeostasis (especially for contractility, angiogenic, and immunological effects). TCs often have been observed close to nerve fibers, including NOS-positive.

Inflammatory bowel disease (IBD), including Crohn's disease (CD) and ulcerative colitis (UC), are widespread autoimmune disorders characterized by an inflammatory process with elevated T helper type 1 and type 2 response, while T helpers 17 cells (maintained by interleukin 23) are also involved in both diseases [19]. Cytokines and chemokines play a role in pathogenesis, depending on the affected region of the gastrointestinal tract. T helper (Th) 1-related cytokines (tumor necrosis factor, interferon-γ, interleukin 12) and Th-17-related (interleukin 17A, 21 and 23) are elevated in Crohn's disease, while ulcerative colitis is associated with overexpression of Th2-related cytokines (interleukin 4 and 13) [20]. Paneth cells have a central place in the pathogenesis of CD. Their decline leads to CD development and could be considered a risk factor. Interestingly, tumor necrosis factor α (TNF α) can also promote Paneth cell death [21]. The possible role of TCs in dysmotility and disturbance of tissue organization in patients with CD was previously described. In patients with CD, TCs have decreased and even disappeared in some observed tissue specimens [22], while other pathology specimens demonstrate TC damage and reduction in number [23]. In addition, they can have morphological modifications and lose CD34 expression as a reaction to chronic inflammation. The rapid proliferation of TCs might be a source of tissue regeneration [24]. Interleukin 33 (a member of the IL-1 family), produced by fibroblast-like cells, is also involved in the pathogenesis of IBD and stimulates the production of NO [25]. Intestinal immunity depends not only on gut microbiota and mucosa immunity. Cells such as telocytes arrive via contacts with neighbor cells, signaling and increasing/decreasing in number.

Telocytes in the spleen

Our spleen is the largest secondary lymphoid organ of the immune system and of the human body. At least two populations of TCs have been identified in the interstitial spaces of the spleen. They primarily form homocellular contacts (making a network with other telocytes) or heterocellular contacts (with macrophages, neutrophilic granulocytes, natural killer cells) [26, 27]. A study on the animal model of Niemann-Pick disease type C, that is on Npc1 mutant mice (Npc1-/-) with enlarged spleens, showed an increase in the number of splenic TCs. This might be explained by attempted regeneration or the involvement of nursing or recruiting stem cells [28]. In Npc1-/- mice, the increase in the number of TCs correlates with an increase in the macrophage population. Splenic TCs most likely stimulate macrophage growing and secretion of cytokines/chemokines. This tendency is common for other organs and tissues. For instance, based on the data, fibrosis is accompanied by reduction in the number of telocytes (however, it is still under discussion whether this is due to a primary or secondary process), while TCs are elevated in the spleen during Niemann-Pick disease type C (often associated with neurodegeneration), and in the oviduct in patients with uterine myoma (the data has not yet published). Furthermore, it has been reported that elevated TCs in the human oviduct could correlate with a risk of ectopic pregnancy (tubal) development [29]. An increase in the number of TCs might be considered a compensatory trigger for regeneration, assuming the fact of their close contacts with stem cells (niche stem cells). Special close contacts between telocytes and mast cells in trachea and in the trigeminal ganglion are known as stromal synapses. [3, 30, 31].

Previously, fibroblast-like cells have been described in the spleen: they form close contacts with B cell blasts and enhance interleukin 6 (IL-6) secretion [32]. Peritoneal macrophages, treated with a medium containing cultured telocytes in vitro, secreted more cytokines/chemokines, especially IL-6 [6]. Interleukin 6 belongs to the IL-6 family cytokines with IL-11 and IL-27, cardiotrophin and cardiotrophin-like cytokine, oncostatin M, leukemia inhibitory factor, and ciliary neurotrophic factor [33]. IL-6 is secreted by B cells and macrophages, and in both situations TCs indirectly regulate IL-6 secretion via interplay with these cells. Of note, IL-6 plays a role in early embryo implantation, the renewal of endometrial blood vessels, stimulation of the production of human chorionic gonadotropin by syncytiotrophoblast cells, and proliferative disorders of the endometrium (including endometriosis) [33–35]. The importance of IL-6 in female reproductive health cannot be overstated. We also know the impact of pregnancy on the TC population: pregnant and non-pregnant uteri have different amounts of TCs in the myometrium. Telocytes constitute about 7% of the total cell number in non-pregnant myometrial cell culture and about 3% of the entire cell population in the myometrium of adult non-pregnant humans [4, 36]. Chi *et al.*

concluded that elevated IL-6 levels might cause an improper endometrial state and implantation failure [6]. We are not sure that can fully explain the intracellular communications induced by pregnancy, but the involvement of TCs via stimulation of IL-6 production in the physiology of female reproductive health is beyond question. Of note, neutralization of IL-6 activity in patients with rheumatoid arthritis (a chronic inflammatory process) does not have less efficiency than neutralization of TNFα [33]. Telocytes have an impact on both cytokine secretion and have been well described as a component of connective tissue and the interstitial space.

Secretome features of telocytes

The secretory profile of TCs includes macrophage inflammatory protein 1α (MIP-1α), macrophage inflammatory protein 2 (MIP-2), and monocyte chemoattractant protein-1 (MCP-1), also known as chemokine (CC-motif) ligand 2 (CCL2). MCP-1 participates in the pathogenesis of such diseases as rheumatoid arthritis, cardiovascular diseases, neuroinflammatory diseases, and different types of oncological diseases. Lately it has been reported that MCP-1 might be considered a biomarker in patients with COVID-19 [37–39]. MIP-2 is involved in chemotaxis and cell migration. MCP-1 might be a molecular target in the therapy of patients with many diseases, especially given its importance in the tumor microenvironment. The role of telocytes in the tumor microenvironment has been described previously [40]. TCs secrete interleukin 2, 6, 10, and 13. Some cell culture experiments demonstrated that sometimes TCs secrete more interleukins than fibroblasts [37].

Vascular endothelial growth factor (VEGF) and epidermal growth factor (EGF) are secreted by TCs, and this process can be discussed beyond just the context of angiogenesis and tumorigenesis. VEGF signaling insufficiency speeds up aging and leads to “inflammaging” (age-related multiorgan chronic inflammation) [41]. EGF impacts intestinal stem cell proliferation and intestinal homeostasis by promoting organoid formation for further regeneration [42]. This growth factor is produced at the base of intestinal crypts in Paneth cells, where TCs are also found. Moreover, two additional substances are secreted by Paneth cells: neuregulin 1 (NRG1) and Wingless Family member 3 (WNT3) during intestinal homeostasis. Neuregulin 1 is detected in telocytes and could compensate for NOS deficiency in endothelial cells (in the kidney and heart) [43]. The WNT 3 pathway is important for human malignancies, and its upregulation is common for patients with uterine myoma [44], which is characterized by a decline in the number of telocytes [18].

Stem cell niche and telocytes

Stem cells (immune and tissue) have an epigenetic memory of inflammation that increases sensitivity to next interactions. Inflammatory memory is typical for long-lived stem cells with the ability to repair tissue in health and disease [44–46]. It is still unknown how they cope with and process recurrent inflammatory-provoking signals, but this mechanism might be more important in the context of autoimmune states. Tissue homeostasis is maintained through balanced self-renovation, while additional stem cells can be activated in particular situations, requiring regeneration or repairing. Usually, this process is controlled within "niches" (restricted tissue microenvironments) [47]. TCs have been found in the stem cell niche microenvironments of the heart, lung, skeletal muscle, skin, liver, aorta, eye, meninges, and choroid plexus [40, 48–50]. In addition, they also express stem cell markers on the surface (c-kit, Sca-1, Oct-4), that mediate their regenerative role and involvement in antitumor immunity. Oct-4 (octamer-binding transcription factor 4) is essential for oocyte development and is important in carcinogenesis, because of its effect on the tumor cell's differentiation. In the majority of cases, cells with Oct-4 expression could be considered cancer stem cells [51]. Additionally, telocytes have been found in bone marrow [52, 53]. Hematopoietic stem cells in bone marrow respond to epigenetic and metabolic alteration and participate in innate immune memory [54]. We hypothesize that telocytes might also be involved in this process, because of their action in the prenatal and postnatal periods of life. As an essential component of cell stem niche microenvironment, TCs may regulate the activity of tissue-resident stem cells [48] and be involved in tissue repair and regeneration.

Final remarks

To the authors' knowledge, telocytes are dissimilar to any known cell type due to their plasticity and versatility. They have direct and indirect impacts on structure, secretion, and expression that in turn affect tissue differentiation, regeneration, repair and immunity. Instead of a typical conclusion, we want to bring your attention to five remarkable facts about telocytes that merit additional study:

1. Telocytes have the longest cellular prolongations in the human body.
2. Telocytes are more sensitive to hypoxia than fibroblasts.
3. Telocytes have been detected in all human organ systems.
4. Telocytes react to damage via reduction in number, morphological changes, or the loss the expression of certain markers.
5. Telocytes "officially" exist in the literature for only 22 years, but as of today, their important role in the pathogenesis of multiple "classical" diseases has been identified.

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Conflict of interest

None declared.

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