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Interstitial cells of Cajal and telocytes in the urinary system: facts and distribution

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Abstract: Current knowledge confirms the existence of interstitial cells of Cajal (ICCs) and telocytes in the urinary system (kidneys, ureter and urinary bladder). Therefore, summarizing of available data can be helpful in understanding of pathophysiology of urological disorders. Telocytes (TCs) are a newly discovered type of cell with numerous functions, described in vertebrates (fish, reptiles, birds, mammals, including human). Despite unique characteristics, they have own differences in morphology and properties in urinary bladder and other organs of the urinary system. This review summarizes particular features of ICCs and TCs in the urinary system, emphasizing their involvement in physiological and pathophysiological processes of the urinary bladder.

Key words: telocytes; interstitial Cajal-like cells (ICLC); interstitial cells of Cajal (ICC); CD34: detrusor; urinary tract, ureter, urinary bladder, an overactive urinary bladder; PDGFRα.

Interstitial cells of Cajal (ICCs) were first described by Ramon y Cajal over 100 years ago as a specific gut neuron. Formerly called "interstitial neurons", these cells were re-discovered approximately 20 years ago and have been successfully identified using contemporary methods, including electron microscopy and immunohistochemistry [1–3]. ICCs are found along the entire gastrointestinal tract and are localized mainly

in the smooth muscle layers of the gut. ICCs are known to play an important role in the control of gastrointestinal tract motility by providing electrical impulses for slow wave generation and regulating smooth muscle activity and neurotransmission [4–7]. A characteristic feature of ICCs is the expression of transmembrane tyrosine kinase receptor proteins, including the c-Kit receptor (CD117), which enables the identification of ICCs using immunohistochemical and molecular methods [8]. Disturbances in gastrointestinal motility after the loss of or damage to ICCs have been widely reported in several clinical states, including gastroparesis, constipation, achalasia, Chagas disease, Hirschprung's disease, congenital hypertrophic pyloric stenosis, intestinal pseudo-obstructions, and diverticular disease of the colon [6, 7].

Multiple research teams have investigated cells located in various tissues outside of the gut, including the pancreas, ureter, urethra, bladder, blood vessels, male and female reproductive organs, mammary glands, placenta, heart, and lungs, that are similar to ICCs [9–11]. These cells are known as interstitial Cajal-like cells (ICLCs), a term that was proposed by Popescu and Faussone-Pellegrini in 2010 to be replaced by "telocytes" [10, 11].

We want to summarize current knowledge and emphasis that at least five classes of cells in the urinary system has been discussed in literature: interstitial cells (IC), interstitial cells of Cajal (ICCs), interstitial cell-like Cajal (ICLCs), telocytes (TCs) and fibroblast-like cells (FLC). Several subgroups of IC are located within the bladder wall and make structural interactions with nerves and smooth muscle [12], while Vannucchi *et al.* noted that term "IC" is quite vague [13]. ICCs were firstly discovered in gastrointestinal tract but later were detected in tissues of the urogenital tract [14]. Rasmussen *et al.* reported that two main types of interstitial cells were identified by transmission electron microscopy (TEM) in the human detrusor: ICLCs and FLC [15]. Interstitial cells of Cajal-like cells in the human urinary bladder do not appear to be directly involved in pacemaker activity. They might act as neuromodulators (in the lamina propria) [15]. Nowadays, TCs is the matter of considerable scientific interest, which required more investigations and proved results.

Interstitial cells of Cajal in the urinary system

In recent years, novel type of cells was found in different organs of the urinary system, named as interstitial cells of Cajal. Most of the scientists noted these cells act as pacemakers, driving peristaltic activity throughout the gut and have a key role acting as intermediaries in the transmission of signals from nerves to smooth muscle [16, 17].

In 2000 Sergeant *et al.* described specialized pacemaking cells (ICCs) in the rabbit urethra that may be responsible for initiating the slow waves recorded from smooth muscle cells in the intact syncytium. They were cells, which were morphologically

distinct from normal smooth muscle cells and have varying numbers of branches [18]. In two years, McCloskey *et al.*, using anti-c-kit labeling, showed that ICCs are located on the boundary of smooth muscle bundles in the guinea pig bladder [19]. Solari *et al.* in 2003 firstly proposed that the altered density of c-Kit positive cells in ureteropelvic junction (UPJ) obstruction may have a role in the failure of transmission of peristaltic waves across the UPJ [20]. Huizinga *et al.* in 2005 in their paper emphasized on the criteria that should be used to identify ICCs outside the musculature of the gut [9].

ICCs were detected in in the lamina propria region (ICC-LP) between the urothelial layer and the muscularis of the detrusor, while Sui *et al.* depicted ICCs in the sub-urothelial layer [21]. They were located close to nerves and make contacts between ICC-LP and nerves [16, 22]. Although, ICCs in the detrusor muscularis of the guinea-pig and mouse are distinctively different from the ICC-LP, both in distribution and morphology [16, 17, 23]. Piaseczna-Piotrowska *et al.* demonstrated the distribution of ICCs is different in the trigonum and the corpus of the urinary bladder [24].

ICCs have potential plasticity and have own spontaneous activity. They are responsible for Ca^{2+} waves generation and neuromuscular transmission. ICCs are also involved in the conjugation, propagation and modulation of peristaltic waves in the upper urinary tract. Bladder ICCs acting as a conduit for the relay of information from the urothelium to the underlying detrusor. These pacemakers play a significant role in bladder dysfunction [23, 25–28].

We cannot omit in the contest of article's subject the polemic has occurred in the scientific world during a year. Senol *et al.* demonstrated that in cases of the ureteropelvic junction (UPJ) obstruction the numbers of interstitial Cajal cells were decreased, being either absent or significantly reduced [29]. In the response Cisek wrote in his commentary to the article, that "*The association of change in ICC density and obstruction is correlative, and the pathophysiologic inferences remain speculative (cum hoc ergo propter hoc fallacy, or correlation is not causation)*" [30].

Era of Telocytes in the urinary system

In the same time, in 2005 L.M. Popescu's group from Bucharest, Romania, described a new type of cell that resides in the stroma of several organs, which became known as interstitial Cajal-like cells. These cells have been shown to differ from fibroblasts and mesenchymal stem cells. A few years later, in 2008, M.S. Faussone-Pellegrini and her team from Florence, Italy, described ICLCs in the muscle coat of the human gut and noticed they consistently differed from the ICCs in both ultrastructure and immunophenotype. Finally, in 2010, after confirming the presence of this particular cell type in the stroma of many organs and characterized it by immunohistochemistry and electron microscopy, the two groups agreed they were describing a 'novel' cell type

and that the name ICLCs should be changed to a more appropriate one — Telocytes (TCs). Transmission electron microscopy is considered the most accurate method for identifying TCs, often combined with a double immunolabeling [10, 11, 31–33].

TCs have been found in a large variety of organs: heart (endo-, myo-, epi- and pericardium, myocardial sleeves, heart valves), digestive tract and annex glands (esophagus, stomach, duodenum, jejunum, liver, gallbladder, salivary gland, exocrine pancreas), respiratory system (trachea and lungs), urinary system (kidney, renal pelvis, ureters, bladder, urethra), female reproductive system (uterus, Fallopian tube, placenta, mammary gland), vasculature (blood vessels, thoracic duct), serous membranes (mesentery and pleura), and other organs (skeletal muscle, meninges and choroid plexus, neuromuscular spindles, fascia lata, skin, eye, prostate, bone marrow). They have unique morphology, own immunohistochemical and gene profiles, secretomes, electrophysiological properties, and make homo- and heterocellular contacts, involved in a variety of physiological and pathological processes [10, 34, 35].

Telocytes have very long cellular extensions — telopodes (Tps), which are probably the longest cellular prolongations in the human body. Tps are made by an alternation of dilated portions, named podoms (250–300 nm), containing mitochondria and endoplasmic reticulum and podomers (~80 nm) with thin segments. Likewise, they make homo- and heterocellular junctions and form three-dimensional networks [34–36]. Despite the fact that have not yet been found a specific marker for TCs, usually for primary identification scientists use CD34 [33]. These cells are usually located in the vicinity of smooth muscle cells, nerves, immunocytes (macrophages, mast cells and lymphocytes), stem cells, melanocytes [37], erythrocytes [38] and with Schwann cells in the heart [39]. They might be involved in the signaling processes, motility, reparation, immunological responses and pathophysiological background of diseases [10, 31, 32, 35].

Telocytes are present in the upper lamina propria of the human renal pelvis, ureter and urethra, as well as in kidney (in sub-capsular space) and urinary bladder [40, 41]. In ureter and urinary bladder, they mainly exist in between smooth muscle bundles [40]. Telocytes have also been identified around renal tubules and vessels in the kidney cortex interstitium, with shed vesicles identified in close vicinity of TCs [41, 42]. In the upper lamina propria of renal pelvis, ureter and urethra these cells have similar ultrastructural features which were different from those of bladder TCs:

1) thinner and longer cytoplasmic prolongations;
2) presence of dense core granules and microtubules;
3) no peripheral actin filaments.

Both steroid hormone receptors (estrogen and progesterone) are expressed in male and female the upper lamina propria TCs [43–45]. Estrogen receptor immunoreactivity has been reported in human urethra, but not in human bladder,

while progesterone receptor immunoreactivity has been described in human bladder mucosa. The expression of one or both of these receptors indicates that the function of ureteropelvic junction (ULP) TCs is at least partially influenced by steroid hormones [40, 45, 46].

Telocytes in different parts of urinary tract (renal pelvis, ureter, bladder and urethra) demonstrated range of immunoreactivity to caveolin-1, estrogen and progesterone receptors, which indirectly indicates that each region itself might contain subpopulations of TCs [15, 46]. These cells could establish close contacts with macrophages in sub-capsular space of kidney, and with smooth muscle bundles, blood vessels and nerve endings in ureter and urinary bladder [41].

Telocytes in the urinary bladder

Vannucchi *et al.* proposed that in the human urinary bladder there were at least three TCs subtypes, two of which located in the sub-urothelium and one in the submucosa and detrusor. Telocytes form a thick multilayered area parallel to the urothelial surface, while in submucosa they were seen scattered within submucosa thickness. In detrusor TCs were present at its submucosal border and around the muscle bundles [13], which also were described by Ramussen *et al.* as CD34-positive and c-Kit-negative cells (called at that time ICLC) [15, 16, 47].

TCs in submucosa of the human urinary bladder are CD34/calreticulin-positive, but PDGFRα/αSMA/c-kit negative. Important to note, cells located immediately under the urothelium were PDGFRα/ calreticulin-positive and αSMA/CD34/c-Kit-negative, despite located deeper in the sub-urothelium — αSMA-positive. The last one were similarly to myofibroblasts and probably were "fibroblasts with myoid differentiation" as suggested Vannucchi *et al.* In the urinary bladder TCs were calreticulin-positive, independently on their location [13].

Several classes of K^+ channels may participate in the regulation of detrusor excitability and contractility during bladder filling. Three families of Ca^{2+}-activated K^+ conductances have been characterized in detrusor smooth muscle cells (SMCs): large-conductance (BK), intermediate conductance (IK) and small conductance (SK) Ca^{2+}-activated K^+ channels [48, 49]. Lee *et al.* found that TCs in murine detrusor muscle express small-conductance Ca^{2+}-activated K^+ channels, most prominently the SK3 isoform, whereas expression of SK channels was low in smooth muscle cells [48, 50]. As followed from this data, SK channel regulation of bladder excitability is likely mediated through TCs rather than through SMCs.

Platelet-derived growth factor receptor-α^+ (PDGFRα) cells were also found between individual smooth muscle cells in smaller bundles of smooth muscle. A dense population of PDGFR-α^+ cell was also found within the lamina propria of the bladder with the cellular network closely packed in the sub-urothelium region [51]. Li *et al.* showed that

injection of renal TCs can attenuate renal dysfunction and ameliorate renal histological damage following renal ischemia–reperfusion injury [52].

Putative role of telocytes in the urinary system

The function of TCs in kidney might be involved in the reparation of injured tissues and immune responses during disease such as acute kidney injury, renal failure and renal fibrosis [40]. Important to note, that telocytes are involved in pyeloureteric peristalsis [52]. Lang *et al.* described telocytes in UPJ and atypical smooth muscle cells as two populations of pacemaker cells [53]. Koleda *et al.* mentioned that telocytes express vanilloid receptor-like 1 protein (VRL-1/TRPV2) suggests the role they may have in the modulation of pyeloureteric peristalsis as sensors of physical and chemical stimuli [54]. His command also experimentally proved that density of UPJ telocytes was different among normal ureters and obstructed. Increased expression of c-kit-positive telocytes in congenital UPJ obstruction may indicate the development of a compensatory mechanism for the failure of urine to be propelled from the renal pelvis through the ureter [54]. Zheng *et al.* suggested that TCs in urinary bladder might be involved in the reparation of injured tissue during diseases, like in the skeletal muscles [40].

Unfortunately, the quantity of data at hand is insufficient for clear understanding the functions of telocytes in the urinary system. As they have a close cooperation with muscle cells and nerve endings, possess SK channels and receptors of growth factors and hormones, have subtypes in the urinary bladder and detected in detrusor, Vannucchi *et al.* suggested that these cells might be involved in bladder reflexes [13]. One of the main functional hypotheses for bladder the upper lamina propria telocytes (UPL) is a role in signal transduction between the urothelium and the underlying nerve endings during bladder filling and bladder emptying [46]. As Gevaert *et al.* concluded, a signal transduction role might then also be suggested for the ULP telocyte networks in the entire urinary tract, that is, during collection of urine in the renal pelvis, during propulsion of urine in the ureter and during the barrier function of the urethra. These regional differences in function might then be reflected by the different (immunohistochemical) phenotypes between ULP telocytes [46]. Involvement of telocytes in the regulation of detrusor excitability and pathogenesis of overactive urinary bladder is required more detailed investigations and significant data.

Conflict of interest

Authors declare no conflict of interest.

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