

REVIEWS

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Nature of Interstitial Cells of Cajal of the Upper Urinary Tract

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A – research concept and design; B – collection and/or assembly of data; C – data analysis and interpretation; D – writing the article; E – critical revision of the article; F – final approval of article; G – other

Abstract

Interstitial cells of Cajal (ICCs) were discovered in the gastrointestinal tract over 100 years ago and since then numerous digestive tract pathologies involving ICCs have been described. Many researchers explored ICCs presence and function in the upper urinary tract. Currently, we know that ICCs have potential plasticity, their own spontaneous activity and that they are responsible for Ca²⁺ waves generation and neuromuscular transmission. ICCs are also involved in the conjugation, propagation and modulation of peristaltic waves in the upper urinary tract. Despite everything we know about ICCs, their role in the pathogenesis of the upper urinary tract abnormalities remains still unclear and results of published studies are confusing. The authors' intention was to review the scientific literature regarding ICCs and to summarise the current knowledge about their nature in the upper urinary tract (*Adv Clin Exp Med* 2014, 23, 4, 627–632).

Key words: interstitial cells of Cajal, ICCs, upper urinary tract.

Interstitial cells of Cajal (ICCs) in the gastrointestinal tract were first described by Ramon Y. Cajal in 1893 [1], and recently they have once again become a subject of research. Ramon Y. Cajal, who in 1906 won the Nobel Prize in Physiology, probably would not have predicted that 100 years later interstitial cells of the urinary tract would once again become a subject of research and that their role in the pathogenesis of upper urinary tract pathology would prompt such a lively debate [1–3]. The lack or the limited number of ICCs was extensively described in many gastrointestinal tract pathologies, such as esophageal achalasia, congenital pyloric stenosis, Hirschsprung's disease, lazy bowel syndrome or chronic intestinal pseudo-obstruction [4–17].

ICCs are located between nerve endings and smooth muscle cells, so they can transmit signals from neurotransmitters and take part in neurotransmission [4, 18–20].

Thanks to their spontaneous electrical activity, ICCs may act as pacemakers or they can take part in the neurotransmission between nerves and smooth muscle cells. Similar observations

have been made in other tubular organs with peristalsis [21–28].

It is unquestionable that ICCs are necessary for the creation of slow electrical waves, which condition slow peristalsis in smooth muscles. The absence of slow activity of smooth muscles limits or completely inhibits its peristalsis [29–31].

The expression of tyrosine kinase receptors – c-kit on their surface and the positive reaction with antibodies against proto-oncogene c-kit indicated that interstitial cells are also present in the urinary system, and studies on physiology and pathology provided sufficient data regarding their structure and activity [2, 32, 33] (Fig. 1).

Interstitial cells of the urinary tract were initially called interstitial cells of Cajal-like to differentiate them from cells of the gastrointestinal tract, but with time, they started to be simply called interstitial cells of Cajal [34, 35].

The expression of Gap junction-alpha-1 protein indicates potential linking functions of interstitial cells and their role in propagating peristalsis in the urinary tract. It is believed that ICCs take part in spreading original impulsion of atypical smooth

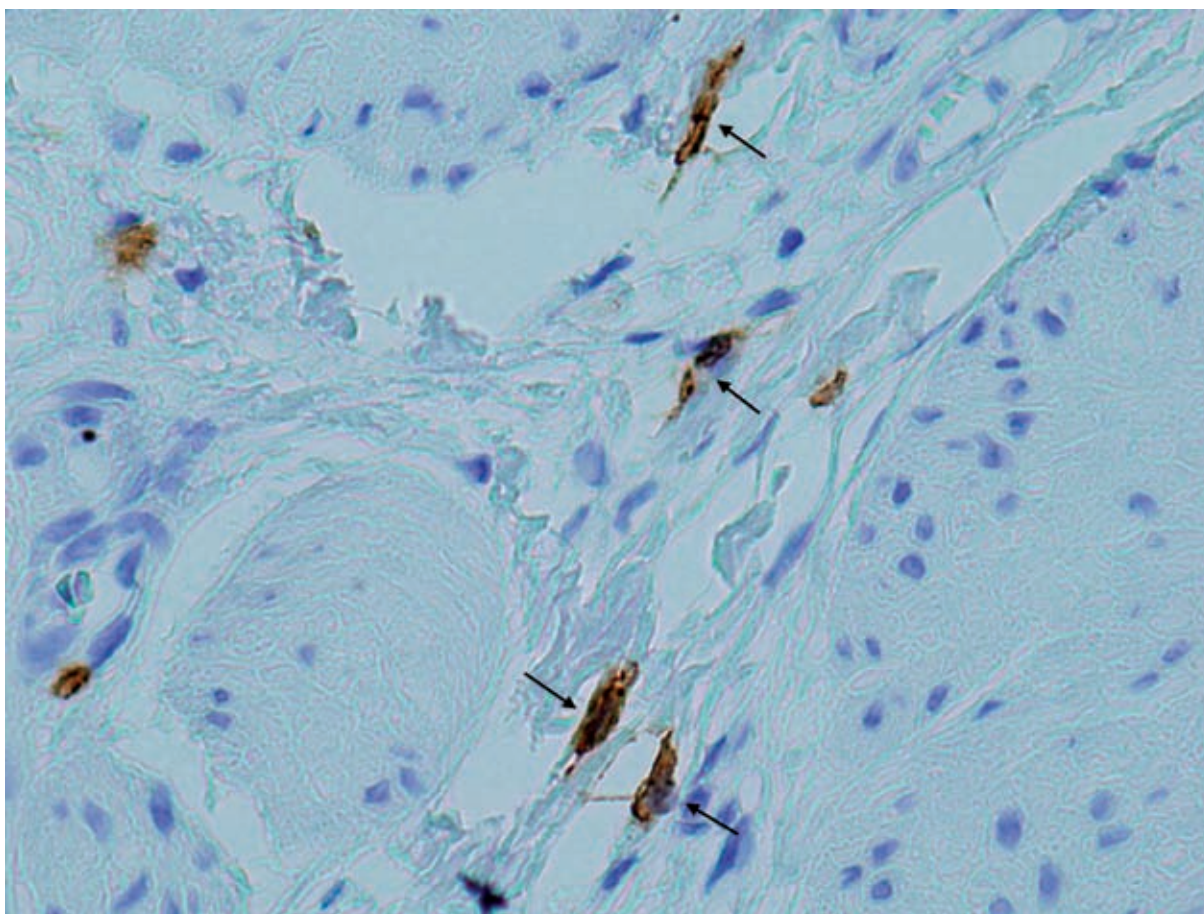


Fig. 1. C-kit-positive ICCs (arrows) in the inner border of the circular muscle layer of ureteropelvic junction. Reduced from $\times 400$

muscle cells into typical smooth muscle cells (t-SMC) that leads to their synchronic contraction and to peristalsis in the urinary tract [36, 37].

The fact that the vanilloid receptor-like 1 protein (VRL-1/TRPV2) is present on the surface of interstitial cells of Cajal may suggest their role in the modulation of pyeloureteric peristalsis based on reported physical and chemical stimuli [32].

In the case of discontinuance of the upper urinary tract, ICCs can, thanks to their automatism, replace originally discontinued a-SMC impulses and maintain electrical and pyeloureteric peristalsis of the lower parts of the ureter [32, 36, 38].

Recent studies show changes in the expression of ICCs in UPJO both in people and in animals [1, 2, 39].

The first report on interstitial cells of Cajal-like in the human urinary tract was published in 2003, when Solari et al. presented results regarding disorders of ICCs expression in patients with UPJO [2].

Morphologically, ICCs of the urinary tract resemble interstitial cells of the gastrointestinal tract thanks to their fusiform cell body with a large, oval nucleus covered with a thin layer of cytoplasm and with two dendrites. The role of ICCs in the human

urinary tract has not been finally defined, but they probably act similarly to the widely known cells of Cajal of the gastrointestinal tract, which is suggested by studies carried out on animal models [21, 40, 41].

In the study on ICCs' role in the guinea pig bladder, McCloskey reported that in response to cholinergic stimulation, these cells are responsible for the development of Ca^{2+} waves [42].

Renal pelvis, ureteropelvic junction (UPJ) and the ureter constitute a functional system which carries urine thanks to the initiated, generalized and transmitted peristaltic wave in the muscle layer of their wall. The appropriate coordination of the pyeloureteric peristalsis influences effective urine outflow and constitutes a significant hydrodynamic factor of the upper urinary tract.

As ICCs are involved in diffusion, modulation and coordination of the peristalsis in ureteropelvic junction (UPJ), some authors claim that the lack or the decreased number of ICCs in the muscle layer of its wall is the original cause of ureteropelvic junction obstruction (UPJO) [2].

Different results of studies carried out on human and animal models in patients' UPJ contribute to a general lack of agreement regarding whether

the changes in the expression of ICCs are original or secondary [1, 2, 39, 43, 44].

Recent studies demonstrate that changes in the expression of ICCs are not surprising. It seems natural that such changes may appear simultaneously with other structural changes of the organ. In 1992 Starr reported a significant growth of the renal pelvis *muscularis externa* in infants with UPJO as compared to healthy ones. Renal pelvis thickens because the number of internal, longitudinal muscle bundles in the renal pelvic wall increases [46].

Density of collagen fibers and elastin in the outer membrane increases between muscle cells [47].

In 1996, Seremetis and Maizels reported an increased expression of the transforming growth factor β (TGF- β) in the renal pelvis in patients with UPJO [47–49].

Ekinici et al. reported an increased amplitude and frequency of basic renal pelvic contractility as a response to UPJO.

The increased amplitude, according to the abovementioned authors, may be secondary to hyperactivity or to the growth of pace-making cells [50].

If we acknowledge the distributory and modulating role of ICCs, it may be construed as a natural occurrence that muscular hypertrophy in UPJO is accompanied by increased ICCs activity and antigen c-kit expression on their surface in UPJO.

Yang, in his publication from 2009, similarly to Solari et al., demonstrated changes in the number of ICCs regarding the expression of ICCs in intrinsic UPJO. Yang was, however, much more careful in suggesting that these disorders are the original cause of UPJO. In his discussion, Yang reported that it is possible that changes in the expression of c-kit-positive ICCs may have a secondary character [1].

This conclusion was undoubtedly drawn due to Kuzgunbay's study published several months earlier. Kuzgunbay et al. reported that the expression of c-kit-positive ICCs in the acquired ureteral obstruction in a rat's ureter was time-related. Namely, he reported that after the obstruction developed, the number of c-kit-positive ICCs increased and after 14 days it reached its maximum value. Then, it gradually decreased and after about 60 days it reached a plateau at a statistically significant higher level than in the control group (without UPJO). The placebo surgery did not change the expression of c-kit-positive ICCs [39].

Chang et al. made interesting observations in 2001 in a study on the disappearance of ICCs and disorders of electric activity in the obstruction of a guinea pig's small intestine. The authors reported that the experimentally induced obstruction of a guinea pig's small intestine led to the termination

of ICCs' electrical activity in the small intestine wall proximally from the obstruction, which was accompanied by the atrophy of tyrosine kinase c-kit receptors' expression on their surface. It should be emphasized that the ultra-structural examination of the muscle layer of the guinea pig did not manifest the presence of dead cells in places affected by ICCs. In these areas we observed cells in the form that is transitory between cells of smooth muscle tissue and fibroblasts.

After about 30 days from the restoration of the small intestine patency, ICCs system was rebuilt and the characteristic slow electrical activity returned [43].

Chang's study is significant as it shows that interstitial cells of Cajal lose their activity in the wall of the intestine due to obstruction, which is secondary to the development of pathology. The same conclusions may be drawn if we analyze the results of Kuzgunbay's study, as his observations refer more to the activity (c-kit expression) of ICCs than to their physical number [39, 43].

Der et al. examined the influence of the inflammation in the mouse small intestine on motor function and ICCs activity connected with Auerbach plexus of the intestine muscle. Authors reported that the disintegration of ICCs system and of its connections with smooth muscle cells of the intestine appear immediately in response to the inflammation caused by *Trichinella spiralis*. ICCs disorganization results in slow wave peristalsis obstruction and in the development of disorganized and undirected intestine peristalsis. In this case, after 23–60 days from the development of the infection, previously described structural and functional changes weakened. This is not only another example of secondary changes of ICCs' activity in response to pathology (in this case – inflammation), but also proof that these changes may be reversed [51, 52].

These studies indicate that Cajal cells are considerably plastic in response to the intestine wall disorder in guinea pig, but they also indicate the secondary background of their function disorder, which leads to organ pathology. Chang reported that the lack of active forms of ICCs does not mean that these cells are not there, but it does indicate a lack of antigen expression by which they may be identified. ICCs of the gastrointestinal tract are capable of phenotype changes, so the same can be expected from ICCS of the urinary tract [18, 41, 43, 53].

Still, it has not been explained if interstitial cells of Cajal act in a similar way in the urinary tract. The analysis of the relationship between c-kit-positive and age indicates that c-kit-positive number in UPJ statistically significantly depends on the age

of the patient with UPJO and it decreases with the age of the child with UPJO.

No statistically significant dependency of c-kit-positive ICCs in the normal ureteropelvic junctions has been observed. Statistically significant expression of c-kit-positive ICCs decreases with the age of patients suffering from congenital UPJO, which suggests that their function decreases with the duration of the pathology. Because in the control group there was no expression of c-kit depending on the patient's age, it may be suggested that it is a gradual and regular regression of compensatory changes, if compensatory mechanisms UPJO are used [44, 45].

Based on earlier studies, it may be assumed that one of UPJO pathomechanisms is inflammation or obstruction in the tract that leads to the disorganization of ICCs' system and to the disruption of their activity. The lack of peristalsis in the renal pelvis and in the ureter increases the retention of urine and leads to the further growth of pressure in the upper urinary tract. Consequently, compensation mechanisms are activated: muscle layer grows, the number of collagen fibers and elastin increases. ICCs are responsible for transition between nerve plexus and smooth muscle cells, so their activity increases. The exacerbation

of compensatory processes depends on their effectiveness and is connected with the type of the original urinary tract pathology. In transitory situations compensation processes may either restore the effective drainage of the urinary tract or be insufficient. Then, as time passes, compensatory changes regress, which is manifested, among others things, by the decreased activity of ICCs [44, 45].

Taking the above observations into consideration, it is difficult to unambiguously discuss changes in the number of ICCs in the urinary tract due to the fact that their identification with antibodies directed against receptors of tyrosine kinase c-kit indicates only the expression of such receptors, which, due to their plasticity, makes it possible to assess only their activity.

The fact that ICCs can be identified in an indirect way and that they have considerable plasticity and heterogeneous pathology (UPJO) can explain numerous interpretations of results of studies of c-kit-positive number in UPJO [1, 2, 44].

There is a growing need for further research regarding ICCs in the human upper urinary tract by means of other research tools, such as electron microscopy. ICCs activity and structure in the urinary tract can explain the upper urinary tract pathology, particularly due to its autonomic innervation.

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