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Interstitial cells of Cajal — systematic review

A. Pasternak[1, 2], M. Szura[2], K. Gil[3], A. Matyja[4]

[1]*Department of Anatomy, Jagiellonian University, Medical College, Krakow, Poland*
[2]*Department of Experimental and Clinical Surgery, Jagiellonian University, Medical College, Krakow, Poland*
[3]*Department of Pathophysiology, Jagiellonian University, Medical College, Krakow, Poland*
[4]*1st Department of General Surgery, Jagiellonian University, Medical College, Krakow, Poland*

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This paper reviews the distribution of interstitial cells of Cajal (ICC) in the human gastrointestinal (GI) tract, based on ultrastructural and immunohistochemical evidence. The distribution and morphology of ICC at each level of the normal GI tracts is addressed from the perspective of their functional significance. Alterations of ICC reported in as well as in GI stromal tumours are reviewed, with emphasis on the place of ICC in the pathophysiology of disease. (Folia Morphol 2016, 75, 3: 281–286)

Key words: gallbladder, gallstone disease, anatomy, interstitial cells of Cajal, telocytes

INTRODUCTION

Interstitial cells of Cajal (ICC) have been described for the first time by Spanish neuroanatomist Santiago Ramon y Cajal (1852–1934) in 1889 [2, 3]. In his paper "On the ganglia and nerve plexuses of intestines" Cajal found in the tissue of mammal's gastrointestinal (GI) tract single small ganglionic cells which he named interstitial ganglia. In his opinion they were separate nervous cells, richly dispersed within internal circular layer of intestinal smooth muscle, where they created unions with numerous nerve bundles, which paralleled smooth muscle fibres, extremely dense plexus (deep muscular plexus). The cells were different according to shape: fusiform, triangular, and sometimes multipolar (star-like). According to Cajal these "primitive neurons" or "interstitial neurons" could play modulatory role in contraction of smooth myocytes of alimentary tract. Nervous cells which created Auerbach and Meissner's plexuses different from interstitial cells were referred by Cajal to as proper celiac (splanchnic) ganglia [3].

Since that time ICC were detected in many other tissues, always in the vicinity of smooth muscle cells. ICC were identified in alimentary tract of many species, i.e. mice [37], rats [23], guinea pigs [26]. In humans ICC were found in the wall of alimentary tract [25], pancreas [50], in the muscle of atria and ventricles [18, 19, 49], vagina [55], mammary gland [13, 51], oviduct [48], ductus deferens [40], urinary tract [28, 54, 62], uterus [7], and in the blood vessels [15, 16].

Initially ICC have not been found in the wall of the guinea pig gallbladder [43]. However it was Sun et al. [57], who found in 2006 ICC in the mice gallbladder, and Lavoie et al. [30] in 2007 of the guinea pig. Ortiz-Hidalgo et al. [42] described for the first time ICC in the human gallbladder based on the study of benign stromal tumour of the gallbladder consisted of cells of ICC phenotype. They confirmed it using immunostaining. They found ICC in the healthy fragment of the gallbladder wall, what may suggest that they are regular component of its wall. The finding of the authors from Mexico was confirmed in 2007 by researchers from Romania, who identified ICC in the gallbladder resected during cholecystectomy, not associated with neoplasms [42].

Address for correspondence: A. Pasternak, MD, PhD, Department of Anatomy, Jagiellonian University, Medical College, ul. Kopernika 12, 31–034 Kraków, Poland, e-mail: artpast@tlen.pl

EMBRYOGENESIS OF ICC

Interstitial cells of Cajal show some ultrastructural features common with cells which originate from neural crest cells (i.e. neurons and cells of neuroglia), as well as with cells of mesenchymal origin (i.e. fibroblasts, smooth muscle cells). This is why their developmental origin remained obscure for many years. Studies of Lecoin et al. [31] and Young et al. [72] carried out on birds and mammals respectively, proved definitely that ICC are derivatives of mesenchymal cells which show expression of kit (receptor of tyrosine kinase). However some of kit-positive mesenchymal cells differentiate into smooth muscle cells. In such case within precursor mesenchymal cells one can see down-regulation, what means that kit receptor expression in decreased while expression of myofilament proteins is increased. ICC contrary to smooth myocytes preserve in adult form expression of kit-receptor [71]. Cell signalling through kit receptor is necessary for development and phenotype maintenance of ICC. Cells which require kit signalling must remain in a close contact with cells presenting kit-ligand. Mesenchymal cells reveal expression of kit receptor beginning with 12th day of gestation. Neuroblasts and mature smooth myocytes which are located in the vicinity of cells of mesenchyme that differentiate, have kit-ligand (SCF) on their surface, so they take part in a stimulation of mesenchyme differentiation toward ICC.

Mesenchymal cells which do not receive kit signalling differentiate into smooth myocytes. After development inhibition of kit, signalling in ICC causes change of their phenotype into smooth myocyte. Pathologic condition may cause change of ICC phenotype which leads to loss of stimulatory function of Cajal cell and its change into hybrid cell. It has not been elicited yet if this process is reversible [53, 66].

ICC — MORPHOLOGICAL FEATURES

Cajal cells are characterised by elongated, fusiform body with few processes. Large, oval nucleus contains one or more nucleoli and peripherally arranged heterochromatin. Cytoplasm in the body of the cell exists as a thin perinuclear margin, which widens at the roots of the processes. Primary processes, 100 μm long give rise to next, secondary or tertiary processes. Cytoplasm of ICC contains numerous mitochondria, which exist in groups mainly in dilated roots of processes and in the processes themselves. It is important to note well developed network of cisterns of smooth endoplasmic reticulum. Within cytoplasm one can find a network of intermediate filaments (vimentin), microtubules, bundles of thin filaments, outstanding caveoli, dense bodies and lysosomes [11].

KIT AS ICC MARKER

Interstitial cells of Cajal reveal membranous expression of c-kit receptor. C-kit protein (CD 117) – 145 kDa is coded by protooncogen c-kit, located in White Spotting, which in humans is placed on the long arm of 4th chromosome in the vicinity of genes coding i.e. growth factors [22]. C-kit belongs to transmembranous receptors and its domains receptor tyrosine kinases (RTK) are activated by growth factors and partake in a transmission of signals from the cell membrane to the interior. Effect of this process is change of gene expression and subsequent biosynthesis of specific proteins. This is how c-kit receptor may participate in control upon survival, proliferation and differentiation of the cell.

Structure of c-kit receptor resembles the composition of platelet derived growth factor receptor (PDGFR) and is as follows:

— extracellular domain which connects ligand is composed of 5 immunoglobulin fragments;
— transmembranous fragment joins the receptor within the cell membrane;
— cytoplasmatic domain — separated by intersection into two subdomains: first connects ATP (TK_1 domain), the second is autophosphorylisation locus and this is it who shows enzymatic activity of tyrosine kinase — mediates transmission of the signal within the cell (TK_2 domain).

Ligand for c-kit receptor is so called Steel factor (Kit ligand — KL or stem cells factor — SCF). The gene coding this factor is located in humans in Steel locus on the long arm of 12th chromosome. The factor itself is a glycoprotein, about 30 kDa, composed of two identical, non-covalently united particles (homodimers) [27]. Connection of ligand to extracellular domain c-kit leads to dimerisation of two neighbouring receptor particles, and rising of the c-kit-ligand complex induces activity of the RTK, which carries out crossing phosphorylation selected tyrosine fragments within contralateral cytoplasmic domain of kit receptor. Autophosphorylation is necessary to recruit enzyme which is activated by receptor kinase — phosphatydyloinositol-3-kinase (PI-3K).

Further transmission and strengthening of the signal occurs through a formation of secondary transmitters and activation of serin-treonin kinases to activate transcription factors, or through influence on DNA synthesis, differentiation, proliferation and stimulation of cell growth.

ROLE OF ICC

Smooth muscles of alimentary tract reveal two types of potentials: slow waves and functional potentials. Basic electrical rhythm (BER) described also as slow waves, originates within longitudinal smooth muscle layer only. Initiators of BER are interstitial cells of Cajal characterised by different membrane potential. Smooth muscle cells do not have special ion mechanisms, necessary to generate and actively propagate slow waves [20]. Cajal cells are characterised by ability to cyclic, spontaneous depolarisation and creation of slow waves. This is how they act as pacemaker in the alimentary tract. Slow waves migrate from these cells toward myocytes of longitudinal layer through gap junctions and nexuses, inducing electrotonic energy within internal circular layer. Most of the studies were carried out on cells of Cajal isolated from canine or mice intestine [24, 29, 32, 33, 60]. Spontaneous and rhythmic electric activity was always observed in these cells, in comparison to smooth myocytes which at the same condition never showed spontaneous activity. Removal of ICC from a fragment of smooth muscle causes complete or almost complete lack of slow waves in the remaining part of smooth muscle [64]. Lack of ICC causes absence of slow waves during electrostimulation [60]. For years the mechanism responsible for rhythmic changes of membrane potential of ICC was a question for scientists. Connor et al. [8] suggested that pacemaker activity is regulated by rhythmic changes in activity of sodium-potassium pump, while Liu et al. [35] proposed release of $Ca^{2+}$from intracellular stores as key process. Experimental studies of Ward et al. (2000) [65] confirmed Liu's hypothesis, that pacemaker ICC activity begins with periodic release of calcium from the spaces of endoplasmic reticulum regulated by concentration of IP_3 (inositol 1, 4, 5 triphosphate). This process activates mitochondria of the cell to subsequent calcium ions intake [65], what generates potential energy, but the mechanism is unknown yet. Sanders [52] suggests that following depolarisation causes opening of type L calcium canals (second source of inflow of calcium to the cell) responsible for transmission of excitation to the neighbouring smooth muscle cells. ICC in the gallbladder are firmly connected to smooth myocytes by gap junctions and are responsible for generation of their rhythmic, spontaneous contraction activity with the frequency of 0.3 Hz [30, 43].

Interstitial cells of Cajal are located between endings of autonomic neurons and muscular cells. They form connections with external neurons, similar to classic synapses. They have receptors for tachykinins (NK1r), i.e. P substance, neurokine K, released from excitatory neurons [67]. They are sensitive to nitric oxide produced by inhibitory neurons, what results in intracellular increase of cGMP. ICC have their own nitric oxide synthase (intraendothelial type), thank to which they can strengthen effect revealed by inhibitory neurons [63].

In experimental studies it was shown that ICC reveal expression of CCK-A receptors for cholecystokinine [9]. As mentioned earlier cholecystokinine is the main hormone causing contraction of the gallbladder. In response to a meal CCK is released from specialised gut endocrine cells (I cells), present in the mucosa of proximal small intestine [34]. So far it was postulated that contraction of gallbladder is caused by direct stimulation of its smooth muscle through cholecystokinine [1, 69]. Studies of Chinese scientists carried out on guinea pigs showed in vitro that contraction of the gallbladder stimulated by CCK-8 is mediated by direct action of CCK-8 on CCK-A receptors of ICC. Besides, complete removal of ICC from tissue fragments depresses a lot contraction reaction of myocytes to CCK-8 [9]. Moreover, studies revealed that damage to interstitial Cajal-like cells (ICLCs) in the gallbladder wall of patients with cholelithiasis could be related to an increased bile lithogenicity index or chronic inflammatory processes involving a gallbladder filled with gallstones [17]. Both mechanisms may participate in gallstone formation by reducing the number of ICLCs in the gallbladder wall. These observations will contribute to further advancements in developing new treatment strategies for gallstones [46].

As it was previously mentioned, ICC are mesenchymal cells acting as the pacemakers for the generation of slow waves in the GI tract. Their electrical activity defines the frequency of the rhythmic contraction. ICC are involved in GI motor activities, as conduits for muscular innervation and are possibly transmitters of sensory innervation in the GI tract. ICC are distributed throughout the GI tract from the oesophagus to the

internal anal sphincter and within different layers specifically submucosal (ICC-SM), myenteric plexus (ICC-MP), intramuscular (ICC-IM), and ICC deep muscular plexus (ICC-DMP) [41]. Loss of ICC, identified by the loss of C-Kit or ANO1 immunostaining, has been recognised in different GI disorders such as slow transit constipation and inflammatory bowel disease, and there is a relatively substantial and growing body of literature on the loss or altered morphology of ICC in gastroparesis.

Studies in animal models of delayed gastric emptying as well as patients with gastroparesis revealed depletion or ultrastructural changes of ICC in the gastric tissue, recently termed ICC-opathy. ICC are the pacemakers of the GI tract and are involved in the transmission of the neuronal signalling to the smooth muscles. Therefore, lack of ICC could be one explanation of delayed gastric emptying in gastroparetic patients [41].

In certain diseases of the GI system the number of interstitial cells is significantly decreased. The direct mechanism of regression of Cajal cells is apoptosis [14], trans/de-differentiation [12, 61], while regeneration of ICC is associated with: proliferation of mature ICC [10], renovation of damaged cells and restoration from stem cells [36]. The newest reports say that mature ICC can still proliferate [10, 36, 39]. Kit signal path activated by kit-ligand is associated with control of survival and proliferation of ICC. We know also, playing similar role, other signal paths with neuronal originated nitric oxide [5], serotonin acting through 5-HT_{2B} receptor [68], interleukine-9 [70], insulin and insulin-like growth factor (IGF-1) [21], heme oxygenase (HO-1) [4]. 5-HT_{2B} receptor is responsible for maintenance of network of ICC [59]. Its activation begins proliferation of ICC. Knock-out mice which did not have that mutation of locus W, coding c-kit protein in mice (W^v/W) and rats (Ws/Ws) leads to decrease in ICC in myenteric plexus of small intestine and stomach, what causes regression of slow waves [58]. Similar phenomenon was achieved by application of antibodies which blocked c-kit receptor in mice. Decrease of number or malfunction of interstitial cells is associated with numerous diseases of GI system, i.e. idiopathic perforation of stomach, Hirschprung disease, gastroparesis, gallstone disease and others [56]. Changes according to number and function of ICC which integrate motor activity of alimentary tract may play role also in gallstone disease [38, 44–47]. Mutation in gene coding kit receptor leads to transformation of ICC and GI stromal tumours development [6].

CONCLUSIONS

Further studies of ICC might lead to a major breakthrough in more understanding of GI physiology which may be considered as a promising target, at least in the long run, for specific pharmacological interventions to restore the normal physiology and motor functions of the GI tract.

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