

DIABETIC ALTERATIONS OF INTERSTITIAL CELLS OF CAJAL

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Interstitial cells of Cajal (ICC) are the cells originating from mesenchyma that represent only 5% of the cells in the musculature of the gastrointestinal tract (GIT), but they play an important and critical role in smooth muscle function and GIT motility regulation. Absence, reduction or structural alteration of ICC subpopulations are observed in several human gut disorders. This review aims to briefly summarize the current data on morphological and pathophysiological features of ICC subpopulations in the diabetic animal models and in patients. Diabetes mellitus (DM) is a well-known cause of gastroenteropathy and gastrointestinal dysmotilities which occur in up to 30–50% of patients after 10 years of type I or II diabetes. A loss or dysfunction of ICC has been shown to lead to higher basal tone of the lower esophageal sphincter with spontaneous contractile activity and impaired relaxation, gastric dysrhythmias, gastroparesis, slow intestinal transit, impaired neuroeffector mechanisms with altered visceral afferent signaling in various human dysmotilities and in animal models. The importance of ICC is becoming more evident in diabetic gastrointestinal dysmotility. ICC alterations were associated with gastrointestinal motility disorders in diabetes, such as reduced and arrhythmic slow wave pacing activity and decreased muscle response to the activation of enteric motor neurons. The mechanism of ICC disturbances is multifactorial and the interaction between these factors is a complex one. The pathogenesis of ICC loss includes increased oxidative stress, reduction in growth factors, change in intracellular signaling pathways and regulatory factors. Each of these factors could provide a potential therapy for diabetic gastrointestinal neuropathy.

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Diabetic alteration on interstitial cells of cajal

Interstitial cells of Cajal (ICC) were first described at the end of the last century by the Nobel prize laureate Santiago Ramón y Cajal (1). Since then, ICC have been in the focus of many research dealing with their origin and role in the digestive tract, and nowadays considerable attention is paid to the ICC role in gut motility disorders,

especially to the ICC changes in diabetic gastroenteropathy. This review aims to briefly summarize the current data on morphological and pathophysiological features of ICC subpopulations in diabetic animal models and in patients. We also review the possible underlying mechanisms of these alterations, with the focus on oxidative stress and growth factors.

Origin of interstitial cells of cajal

When ICC were first discovered by Cajal, he thought that they were nerve cells (2). However, after the discovery that CD117 (c-kit; a proto-oncogene encoding for the tyrosine kinase receptor) was expressed in ICC (3, 4), and that they depended on signaling via Kit receptors for the development and phenotype maintenance (5-7), these cells could be identified at the light microscope level as the cells of mesenchymal origin. The appearance of ICC in the gastrointestinal tract (GIT) occurs about 3 weeks after the appearance of the enteric nervous system, immediately following circular muscle layer differentiation (7-12).

ICC develop independently of the neural

crest-derived enteric neurons or glia and originate mainly from the Kit-positive mesenchymal mesodermal precursors (2, 13, 14). As suggested by developmental studies, smooth muscle cells and ICC have a common precursor which expresses c-kit (15, 16). Afterwards, Kit is indispensable in mesenchymal precursor division during the differentiation towards ICC, and for normal postnatal development, maturation, networking, function, and maintenance of the ICC phenotype in the GIT (6, 13).

Classification of interstitial cells of cajal

ICC are classified into several subtypes based on different distribution patterns, anatomical locations, morphological and functional features. Functional ICC subtypes that exist within the tunica muscularis of the GIT are ICC of the myenteric plexus (ICC-MP) that form a cellular network around the myenteric plexus in the space between the circular and longitudinal muscle layers; intramuscular ICC (ICC-IM), including ICC of the circular (ICC-CM) and longitudinal muscle (ICC-LM); ICC of the submucosa (ICC-SM), at the interface between submucosal connective tissue and the inner muscle layer; ICC of the submucosal plexus (ICC-SMP); ICC of the septa (ICC-SEP), in the connective tissue septa that separate lamellae of the muscle; and ICC of the deep muscular plexus (ICC-DMP), located within the deep muscular plexus region of the small intestine (17-19). The cellular network of ICC-MP is relatively looser in the colon and gastric corpus than in the small intestine, ICC-DMP are present exclusively in the small intestine, and ICC-SM are present only in the colon and pyloric region of the stomach (18, 20, 21).

Recent evidence has suggested that ICC subtypes are different in ultra-structural morphology and function, in addition to their different locations (17, 18, 22).

Morphology and ultrastructure of interstitial cells of cajal

ICC-IM and ICC-SM are similar to the smooth muscle cells, having a spindle-shaped form with bipolar processes that run parallel to the longitudinal axis of cells, while ICC-MP are stellate cells, more multipolar, and with more cytoplasmic processes (18, 23). The variations in shape between ICC subtypes are considered to be the effect of the surrounding microenvironment, type of nerve supply, contacts with the smooth muscle cells, and also the type of food passing through that part of the GIT (22).

According to electron microscopy observations, all ICC subtypes share these characteristics: numerous mitochondria, profuse intermediate filaments, presence of surface caveolae, and partially discontinuous basal lamina. ICC also have a well-developed smooth and rough endoplasmic reticulum, and gap junctions connecting them both with each other, forming a network throughout the GIT

wall, and with smooth muscle cells and nerve varicosities (24). ICC share similar electron microscopy features with smooth muscle cells and fibroblasts, but the lack of thick myofilaments is an important difference from smooth muscle cells; ICC are also thought to be non-contractile cells. On the other hand, fibroblasts do not show caveolae, rarely have smooth endoplasmic cisternae, intermediate filaments, or a partial basal lamina as ICC do (18, 22, 24).

Function of icc

Although ICC represent only 5% of the cells in the musculature of the GIT, they play an important and critical role in smooth muscle function and GIT motility regulation. The primary evidence for the ICC role in GIT motility control came from knock out animal models with blocked Kit receptors. These animals developed severe gastrointestinal motility dysfunction, with a lack of slow-wave phase peristaltic movements (25, 26). ICC-MP subtype regulate slow wave propagation in the stomach and small intestine, and in the colon the source of slow-wave pacemaker activity are ICC-SMP (18, 27, 28). These ICC subtypes form the networks responsible for gastrointestinal motor control and contractions of the intestinal musculature (29, 30), while ICC-IM subtype serves as the mediators of enteric motor neurotransmission (31-34). ICC also play a role in afferent neural signaling and act as mechanoreceptors (35-37).

Absence, reduction or structural alteration of the ICC subpopulations are observed in several human gut disorders, such as achalasia, gastroesophageal reflux disease, gastroparesis, infantile hypertrophic pyloric stenosis, chronic intestinal pseudo-obstruction, Hirschsprung's disease, inflammatory bowel diseases, slow colon transit and severe constipation, and some other GI motility disorders, as well as in gastrointestinal stromal tumors (38-46).

Icc changes in diabetes

Diabetes mellitus (DM) is a well-known cause of gastroenteropathy and gastrointestinal dysmotilities, which occur in up to 30-50% of patients after 10 years of type I or II diabetes (47-49). In addition, diabetic gastroenteropathy represents a considerable health care burden and may manifest as dysphagia, heartburn, abdominal pain or discomfort, postprandial fullness, bloating, nausea, vomiting, constipation, diarrhea, and fecal incontinence.

The pathogenesis of diabetic gastroenteropathy is complex and multifactorial. Although it generally has been thought of as a neuropathy, diabetic gastroenteropathy involves not only parasympathetic and sympathetic autonomic nerves, but also enteric glia and neurons, smooth muscle cells, capillary endothelium adjacent to the myenteric ganglia, mucosal endocrine cells and ICC (50, 51). Since GIT motility requires an interaction

between enteric nerves, smooth muscles and ICC, gastrointestinal dysfunction generally involves changes in all of these factors (52). The interaction between these factors is complex, and each of them represents a potential new therapeutic target.

Loss or dysfunction of ICC has been shown to lead to a higher basal tone of the lower esophageal sphincter, with spontaneous contractile activity and impaired relaxation, gastric dysrhythmias, gastroparesis, slow intestinal transit, impaired neuroeffector mechanisms and altered visceral afferent signaling in various human dysmotilities and in animal models (6, 39, 53-57). These gastrointestinal dysmotilities are considered to be the hallmarks of diabetic gastroenteropathy.

ICC of the stomach are shown to be altered in the studies of DM and gastroparesis in animal models. ICC network reduction has been noted in gastric corpus and antrum in the studies with non-obese diabetic (NOD) mice, a model of human type I diabetes (58, 59). Ordög (58) demonstrated that ICC density loss started at the corpus region of the gaster and worsened towards the antrum, mainly involving ICC-MP. Although slow waves could still be detected in these areas, they were abnormal in amplitude, as well as in frequency, and these slow waves could not propagate throughout the stomach. In the remaining ICC, ultrastructural changes were observed, such as increased cell processes and loss of contact with adjacent enteric ganglia. In the fundus, there was not any loss of ICC-IM, but there was excess extracellular space between ICC and adjacent enteric nerves. In leptin receptor mutant mice (a type II diabetes mice model), a modest ICC count decline appeared in both ICC-MP and ICC-IM throughout the stomach, small intestine and colon (60).

The loss of ICC was also detected in the gastric fundus and corpus of streptozotocin (STZ)-diabetic rats, particularly a depletion of ICC-IM in both circular and longitudinal muscle layers and loss of the ICC-SM (56). Wang also noticed the presence of fibroblast-like cells in the ICC-IM surrounding the enteric ganglia. They were described as immature or recovering ICC which might be involved in tissue healing and repair. Other authors thought these fibroblast-like cells to be a distinct subset of GIT cells that might participate in motility (61).

In a slightly different animal model in which diabetes is induced by the administration of two compounds, STZ and nicotinamide (NA), the resultant diabetes is more similar to human type II diabetes than that in the STZ model; rats manifest moderate hyperglycemia and do not require exogenous insulin to survive (62). Using that model, Veličkov demonstrated a decrease of ICC-IM number, discontinuities and breakdown of contacts between them in the lower esophageal sphincter (63) in STZ-NA induced non-insulin-dependent diabetes rats.

ICC-MP reduction is associated with impaired slow wave peristaltic movements and delayed

gastric emptying, while ICC-IM reduction or alteration, according to suggestions, is associated with impaired relaxation of the gastric cardia, fundus and antrum (56).

Changes in the enteric nervous system, smooth muscle cells and decreased ICC in humans, similar to animal models, were also demonstrated in diabetic patients mainly with accompanying gastroparesis (64-68). Forster et al. reported the results of gastric biopsy from 14 patients with gastroparesis, including nine patients with DM, and showed a reduction in the number of ICC (65). Similar findings (an ICC loss, with the remaining ICC showing injury) were reported in the Grover's study, where full-thickness gastric biopsy specimens from 40 patients with gastroparesis were examined (including 20 patients with diabetes) (67). In 25 patients with DM and gastric cancer who underwent gastrectomy, the study of the gastric tissue did not show any ICC-MP reduction, but only the reduction of ICC-IM in the inner circular muscle layer (66).

Diminishing ICC populations have been reported in other parts of GIT in diabetes animal model, including the colon and small intestine. In contrast to diabetic gastroparesis, about which several papers have been written (56, 58-60, 63), there are very few studies evaluating ICC in intestinal dysfunction in diabetes, partly because of the difficulties in investigation and methods available for diagnosis. Furthermore, the results are conflicting (69, 70), since a loss or disruption of an ICC network is often followed by structural and functional changes in neuronal and smooth muscle elements. Yamamoto et al., using a db/db model of type 2 DM, in addition to stomach, showed a reduced number of ICC in the small intestine and colon (60). Similar ICC losses have been observed in the small intestine and colon of diabetic animals (71, 72). In addition, a loss of c-Kit positive intramuscular ICC has been described in the colon of seven patients suffering both from type 2 diabetes and colon cancer (73). A significant reduction in ICC density in the myenteric region and ICC-IM depletion throughout the entire thickness of the jejunum was shown in the sample obtained from a 38-year-old patient with a 15-year history of poorly controlled diabetes and with evidence of diabetic gastroenteropathy (57).

ICC represent an independent source of slow-wave pacemaker movements of GIT, and are also an important factor in neurotransmission between motor neurons, efferent entry from the autonomous nervous system and muscle fibers. It has been proposed that both excitatory and inhibitory neurotransmission between the enteric neurons and smooth muscles are dependent on the presence of ICC-IM. Morphologically, the terminals of enteric motor neurons form tight, synaptic-like contacts with ICC (34, 74, 75). It has

been shown that ICC-IM depolarize smooth muscles through gap junctions, when acetylcholine previously released from the enteric motor neurons

attaches to the Ach receptors of ICC (31). The modulatory role of ICC-IM has also been shown in excitatory neurotransmission, through substance P and neurokinin released from the enteric motor neurons (76). As for inhibitory neurotransmission, IC-IM play an important role in NO-dependent neurotransmission in the lower esophageal sphincter and pyloric sphincters. IC-IM are proposed to be effectors that transduce NO signals into hyperpolarizing responses and in that way modulate and enable sphincters relaxations. A mice model lacking ICC-IM did not show any evidence of nitrenergic transmission (77). Wang et al. observed a loss of nerve fibers due to ICC-IM loss and partial depletion of synapse-like connections with ICC-IM (56). A lack of ICC in diabetes affect GIT motility both by reduced ICC-IM that affect neurotransmission, and by impaired pacemaker activity caused by ICC-MP loss. These findings emphasize the importance of ICC and point out how ICC alterations occurring in diabetes are one of the major factors in the development of GIT neuropathy.

Mechanism of diabetes-induced changes in icc

DM significantly alters the microenvironment of ICC, leading to decreased survival of these cells. Alterations of ICC in diabetes could have potentially arisen from hyperglycemia and associated oxidative damage, reduction of insulin and growth factor signaling, autoimmune attack, or their combinations, resulting from the imbalance between the factors that damage and factors that regenerate and maintain ICC (23, 78).

Increased oxidative stress, associated with hyperglycemia, was an expected result in the study of diabetic NOD mice with gastroparesis. Along with oxidative stress which accompanies DM, a reduced expression of neuronal NO synthase and stress-induced enzyme heme oxygenase-1(HO-1) is reported, and these agents are potentially cytoprotective and a survival factor for ICC (79). HO-1 is upregulated mainly in macrophages located adjacent to the ICC and enteric nerves. In addition, HO-1 increases the expression of c-kit and neuronal NO synthase and reverses the delay in gastric emptying (80).

Some recent studies investigating ICC loss in NOD mice have shown that hyperglycemia alone is not enough to affect ICC, but reduced insulin-like growth factor-1 (IGF-I) and insulin signaling in diabetes plays the major role in reduced survival of ICC (81). In a recent study, ICC changes and ICC loss have been shown in animal diabetic model with moderate hyperglycemia, and as well in diabetic rats treated with antioxidants where glycaemia was even lower or normal (63), demonstrating that hyperglycemia is not the main cause of ICC alterations. Loss of ICC and nerve structures due to absence of growth factors was consistent with metabolic injury in diabetes, and in addition insulin and IGF-I completely prevented the loss of ICC in murine gastric muscle cell cultures (81). ICC showed better tolerance in

terms of maintaining their densities against hyperglycemia than normoglycemia in an absence of insulin or IGF-1 supplements (81). However, ICC do not have insulin receptors; instead, they have receptors for stem cell factor (SCF). SCF is produced by smooth muscle cells and enteric neurons which have the receptors for insulin and IGF-1 and indirectly mediate the effect of insulin and IGF-1 on ICC (58,81). Therefore an interdependence between ICC associated nerve fibers and smooth muscle cells is proposed, as suggested in the studies of ICC-IM and vagal afferent nerves in animal models (82, 83) and in patients (66).

Another mechanism of ICC alteration could be autoimmunity. The cause of type 1 diabetes is autoimmune destruction of insulocytes and the same autoimmune process may also interfere with gastrointestinal neuromuscular cells, and the development of autonomic neuropathy (84). Anti-Kit autoantibodies and consequently an ICC loss have been found in a patient with intestinal pseudo-obstruction and paraneoplastic gastroparesis (85), but a similar autoantibody has not been reported in diabetes (78). Furthermore, no signs of apoptosis or lymphocyte infiltration have been found in STZ-NA and STZ diabetic rats (56, 63).

Conclusion

The importance of ICC is becoming more evident in diabetic gastrointestinal dysmotility, and autonomic neuropathy is no longer considered a sole cause of diabetic gastroenteropathy in DM. ICC alterations were associated with gastrointestinal motility disorders in diabetes, such as reduced and arrhythmic slow wave pacing activity, decreased muscle response to the activation of enteric motor neurons, delayed gastric emptying, gastroparesis, slow colon transit (58, 80). The mechanism of ICC disturbance is multifactorial and interactions between these factors are complex. The pathogenesis of ICC loss includes increased oxidative stress, reduction in growth factors, change in intracellular signaling pathways and regulatory factors. Each of these factors could provide a potential therapeutic target in diabetic gastrointestinal neuropathy.

However, the questions remain whether neurotransmission can rely solely on ICC and to what degree ICC are involved in neurotransmission, since the number of ICC is considerably lower compared to smooth muscle cells (only 5% of the muscle layer). In contrast to animal models, there are difficulties in investigating the distribution, function, and alterations of ICC networks in human tissue. ICC cannot be assessed after routine sampling, since GIT biopsies are usually restricted to the mucosal and submucosal layer and obtaining control samples from anatomically identical regions is almost impossible.

Moreover, any translation of these findings into clinical treatments has been a challenge. For instance, oxidative stress has been shown to play an important role in DM enteropathy (86), but the

use of antioxidant treatments has not been proven to afford an effective protection of ICC (63, 87).

In conclusion, ICC alterations in diabetes certainly contribute to the gastrointestinal symptoms of neuropathic enteropathy, but their exact contribution to this mechanism is still unclear.

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PROMENE INTERSTICIJALNIH KAHALOVIH ČELIJA KOD DIJABETESA

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Intersticijalne Kahalove ćelije (IČK) su mezenhimalne ćelije koje predstavljaju samo 5% ćelijskih populacija muskularnog sloja gastrointestinalnog trakta (GIT), ali imaju značajnu ulogu u regulaciji GIT motiliteta i funkciji glatko-mišićnih ćelija. Odsustvo, re-dukcija ili strukturalne promene subpopulacija IČK opisane su kod više poremećaja GIT-a. Cilj ovog preglednog članka bio je da rezimira aktuelne podatke o morfološkim i patohistološkim karakteristikama IČK subpopulacija kod bolesnika sa dijabetesom i paralelnim životinjskim modelima. Kod bolesnika sa desetogodišnjim dijabetesom (tip I i II), prevalencija gastroenteropatija i poremećaji motiliteta GIT-a je čak 30-50%. Gubitak ili disfunkcija IČK dovode do povećanog bazalnog tonusa donjeg ezofagealnog sfinktera sa spontanom kontraktilnom aktivnošću i poremećenom relasacijom, disaritmijske želuca, gastropareze, sporog intestinalnog tranzita, izmenjene neuroefektorne mehanizme praćene promenama visceralne aferentne signalizacije i dismotiliteta kod čoveka i životinjskih modela. Značaj IČK postaje sve više evidentan kod dijabetične gastroenteropatije. Poremećaji GIT motiliteta uzrokovani IČK promenama povezani su sa redukovanim i disaritmičnim sporim ritmičkim talasima i smanjenim odgovorom glatkih mišića na aktivaciju enteričkih motornih neurona. Mehanizam poremećaja IČK kod dijabetesa je multifaktorijalan, obuhvata povećan oksidativni stres, redukovane faktore rasta, promene intraćelijske signalizacije i regulatornih faktora, a interakcija ovih faktora je kompleksna. Svaki od ovih činilaca može predstavljati potencijalni terapijski pristup kod dijabetične gastroenteropatije.

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Ključne reči: dijabetes, intersticijalne ćelije Kahala, gastroenteropatija