Interstitial Cells of Cajal
Pathology, injury and repair

“Dhuha Al-Sajee¹ and Jan D. Huizinga²

ABSTRACT: Interstitial cells of cajal (ICC) are specialised cells located within the musculature of the gastrointestinal tract (GIT). Although they form only 5% of the cells in the musculature of the GIT, they play a critical role in regulating smooth muscle function and GIT motility in coordination with the enteric nervous system. C-kit is a transmembrane glycoprotein that plays a critical role in ICC development and maturation. Physiological conditions such as ageing, as well as pathological conditions that have different disease processes, negatively affect ICC networks and function. Absent or disordered ICC networks can be associated with disorders in GIT motility. This review highlights the mechanism of ICC recovery from various types of injury which entails understanding the development of ICC and the factors affecting it. ICC transformation into malignant tumours (gastrointestinal stromal tumours) and their potential as contributors to therapeutic resistance is also discussed.

Keywords: Cajal interstitial cells; Gastrointestinal tract; Diabetes mellitus; C-kit; Ageing; Gastrointestinal stromal tumors.

INTERSTITIAL CELLS OF CAJAL (ICC) are specialised mesenchymal cells that were first described in the tunica muscularis of the gastrointestinal tract (GIT) by Ramon y Cajal in the 19th century.¹ They form networks in the muscular layers of the alimentary tract, with their location in the GIT being organ and species specific.² ICC originate slow wave intestinal pacemaker activity and mediate input from the enteric nervous system.¹³ Studies on these cells have lead to the discovery of c-kit expression by ICC, a protein that is as important as insulin and insulin-like growth factor-1 for ICC development and maintenance.⁴⁻⁹ Similar to other cells in the body, ICC are affected by various insults to the GIT such as inflammation, obstruction, diabetes mellitus (DM), and ageing.¹⁰,¹¹,¹² This can cause a decrease in their number and/or disruption in structural or functional abnormalities which ultimately affect gastrointestinal (GI) motility.⁶,⁷ On the other hand, harbouring a c-kit mutation causes ICC to grow into hyperplastic sheets and even transform into malignant gastrointestinal stromal tumours (GIST).¹² However, ICC have the ability to recover and repopulate after removal of injury.¹⁰,¹¹,¹⁴ This review will discuss ICC development; the effect of DM, diabetic gastropathy, and ageing on ICC as examples of an ICC injury; the possible mechanisms

¹Department of Pathology & Molecular Medicine and ²Farncombe Family Digestive Health Research Institute, McMaster University, Hamilton, Ontario, Canada

*Corresponding Author e-mail: d.alasaj@yahoo.co.uk
of recovery, and finally ICC transformation into GIST.

ICC Classes and Localisation in the GIT

ICC are found in the GIT, from the oesophagus to the internal anal sphincter. This distribution varies in different organs within the GIT and in different species. ICC associated with the myenteric plexus (ICC-MP), also called ICC in the myenteric region (ICC-MY), or ICC associated with Auerbach's plexus (ICC-AP), ICC-intramural, is an ICC network within the circular muscle (CM) and longitudinal muscle (LM) layers. ICC-submucosal plexus (ICC-SMP) indicates ICC at the submucosal border of the CM layer in the colon. ICC-deep muscular plexus (ICC-DMP) is the presence of ICC in the deep muscular plexus in the inner surface of the CM in the small intestine. ICC-septa (ICC-SEP) are found in the septa separating the CM bundles and are described in humans and larger animals. ICC-SEP are considered a part of the ICC-IM by some while others recognise them as a separate entity. In general, ICC-MP are present at all levels of the GIT except in the oesophagus, where only ICC-IM are present. ICC-MP and ICC-SMP are described as existing in the stomach, while ICC-MP, ICC-IM, and ICC-DMP are present in the small intestine. ICC-MP, ICC-IM and ICC-SMP are generally identified in the colon. Stellate subserosal ICC have been found outside the LM layer in the subserosa in mouse colons.

Characterisation of ICC

MORPHOLOGY

ICC are variable in their morphology in accordance to their location and function. ICC-IM are spindle-shaped cells with bipolar processes that run parallel to the longitudinal axis of smooth muscle cells. ICC-IM and ICC-SMP show a resemblance to the smooth muscle cells, while ICC-MP are more multipolar and have more cytoplasmic processes. This variation in shape has been explained by the effect of the surrounding microenvironment, such as the type of nerve supply and the relation to the smooth muscle cells, in addition to the type of food passing through that part of the GIT.

ULTRASTRUCTURE

According to electron microscopy results, all ICC classes probably share the following features: the presence of numerous mitochondria, abundant intermediate filaments, the presence of surface caveolae, and partially (variably) developed basal lamina. ICC also have well-developed smooth and rough endoplasmic reticulum, and gap junctions connecting them to smooth muscles and other adjacent ICC. The lack of thick myofilaments is an important differentiating point from smooth muscle cells. ICC are also thought to be non-contractile. Another cell that may have similar ultrastructural features to ICC is the fibroblast; however, fibroblasts do not show caveolae, and rarely have smooth cisternae, intermediate filaments, or a partial basal lamina.

ICC MARKERS

ICC were identified by their morphology until the discovery of c-kit, which is considered its defining marker. C-kit is a tyrosine kinase that is a 145 kD transmembrane glycoprotein. It is a member of the type III tyrosine kinase receptors. C-kit acts as a receptor for stem cell factor (SCF), which serves as its ligand. In its normal state, c-kit is present as a monomer in the cell membrane. Upon binding to its SCF ligand, a dimerisation of the protein takes place thus activating itself through autophosphorylation of the tyrosine residues. This will activate intracellular signaling pathways that are important for normal cellular growth and development. A negative regulatory effect is mediated by SH2 domain-containing protein tyrosine phosphatase that inhibits the excessive signalling and cellular transformation, as occurs in malignancy. Thus, certain mutations in c-kit can lead to oncogenic transformation and SCF-independent activation causing kinase activity and cancer development, or GIST. The other cell that expresses c-kit in the GIT is the mast cell. This led to the need to search for other specific markers to detect ICC. One recently discovered marker is the transmembrane protein 16a (tmem16a) which encodes anoctamin-1 (ANO1), a calcium-activated chloride channel. Antibodies against ANO1 identified it as a selective biomarker for all classes of ICC at all levels of the GIT in humans and animals.
as well as primates. ANO1 is more specific for ICC and, unlike c-kit it does not stain mast cells. A recent study found that ANO1 plays an important role in pacemaking activity by affecting the conductance of ICC and slow wave generation; however, it was found that ANO1 played no role in ICC development.

Another much less specific marker of ICC is CD34, an 11 Kd transmembrane glycoprotein. CD34 is a marker for endothelial cells and haematopoietic cells, as well as fibroblasts. Its expression within the ICC has been debated. A study by Robinson et al. using a single-cell reverse transcription and polymerase chain reaction (RT-PCR) on cultured murine intestinal cells and immunohistochemistry on the human small intestine could identify a small subset of ICC expressing c-kit and CD34. CD34 is also a marker for ICC progenitor cells, which have been found to lose their CD34 expression and acquire more of c-kit expression as they mature into ICC. CD34’s role in ICC function is of little significance.

CD44 is another marker for ICC. It is also a transmembrane glycoprotein that is expressed by mesenchymal stem cells and tumours. It has been found to be expressed in ICC progenitor cells, and in immature as well as mature ICC. The role of CD44 in ICC development has been studied but does not show any significant impact. Other markers include vimentin gamma enteric actin, alpha-type platelet-derived growth factor receptor (PDGFRα), and others.

Embryological Origin of ICC

When ICC were first discovered by Cajal, he thought that they were nerve cells. Later, it was believed that ICC were specialised smooth muscle cells based on previously mentioned ultrastructural features between them. With the discovery of c-kit expression in these cells, a neural crest origin for the ICC was suggested. However, ultrastructural features such as basal laminae, scarcity of rough endoplasmic reticulum, the presence of gap junction contacts between ICC and smooth muscle, and close contacts with the nerve endings made a neural origin less likely. In addition, studies on the embryological development of ICC in the murine small intestine and colon have revealed that animals deficient in c-kit and kit-ligand (KL) have shown a marked reduction in the ICC network despite the normal density of the associated enteric nerves. A neural crest origin was excluded by Young b (1996). Thus far, studies have provided evidence that ICC originated from a common mesenchymal precursor cell instead of a neural crest-derived cell.

Development of ICC

THE IMPORTANCE OF C-KIT AND STEM CELL FACTOR IN ICC DEVELOPMENT

The stimulation of c-kit by KL or stem cell factor (SCF) is an important step in the development of ICC; hence, mice lacking c-kit (W/Wv) or kit ligand (Sl/Sld) have disrupted ICC networks. Since the common progenitor of ICC and smooth muscles express c-kit, it has been postulated that a subset of these precursors will respond to KL and differentiate into ICC, while the rest of the precursor cells will develop into smooth muscle cells. Sources of KL in the gut are either neuronal or non-neuronal. SCF is found in soluble and membrane bound forms (sol-SCF and mb-SCF, respectively). The sol-SCF is needed for the maintenance of ICC progenitors. Mb-SCF is required later on for ICC progenitors to be fully differentiated into mature ICC.

Whether neuronal membrane-bound KL has a role in ICC maintenance has been precluded by the ability of ICC to develop in cultures of a murine bowel that is devoid of extrinsic nerves, Schwann cells, or neurons. However, it has been suggested that neuronal KL is important for the development of ICC-MP, while non-neuronal KL, which is provided by the smooth muscle cells, is required for the development of ICC-IM. This could explain the loss of ICC-MP from the aganglionic segment of sl/sl deficient mice. Another observation is that in Crohn’s disease the diffuse injury to the nerves is associated with a remarkable loss of ICC-MP, more so than ICC-IM. Although this contradicts previously stated evidence in the literature, and that there is the possibility that ICC loss in Crohn’s can
be due to the effect of inflammation, it is important to investigate further the possible role of neuronally derived KL in ICC maintenance.  

The importance of c-kit in the development of ICC has been studied using c-kit deficient mice, the so-called W/Wv mutant mice. At five days postnatal, these mice showed normal c-kit positive ICC networks; however, the network density starts to decrease thereafter, suggesting that c-kit is important only in the later postnatal development of ICC in the small intestine, and that determination of the ICC lineage in embryos does not require c-kit. Interestingly, in these mice the only classes of ICC which were lost were ICC-MP in the small intestine, and ICC-IM in the stomach, lower oesophageal sphincter, and pyloric sphincter. There was a mixed loss in the colon. In the small intestine, loss of ICC-MP correlated with the loss of electrical slow waves, which indicates that these classes are more important for the characteristic pacemaking activity than other classes of ICC that were preserved. Thus, ICC may differ in their sensitivity to the reduced levels of c-kit, and ICC dependence on c-kit is age-related. ICG PRECURSORS AND ICC STEM CELLS  

Recently, Lornicz et al. examined a postnatal murine stomach (aged 7–14 days) for the presence of ICC precursors. Using flow cytometry and immunohistochemistry, they could identify a small subset of cells that expressed a very small amount of c-kit along with CD44 and CD34. These cells were oval to round in shape and had few or no cytoplasmic processes. They were detected as small clusters in the myenteric region, in between the muscle fibres as well as in the subserosa outside the LM. Culturing these cells in unsupplemented serum-free basal media resulted in a complete loss of ICC, as well as their presumed progenitors. However, small networks of c-kit-negative CD44+ cells showing a similar morphology to ICC were recognised. These were described as senescent ICC only in this study. Thus, a well-defined phenotype for an ICC progenitor was concluded as follows: kitlowCD34+CD44 insulin receptor and insulin-like growth factor receptor (InsrIgfr+) positive cells. The mature phenotype expressed only kit+CD44+ and was negative for CD34. These progenitor cells may have been stimulated directly by sol-SCF and insulin-like growth factor-1 (IGF-1) where they acquired more expression of kit positivity with electrophysiological detection of low-amplitude slow waves. Thus, another phenotype expressing more c-kit than progenitor cells, in addition to expressing CD34+ CD44+ Ins+ Ingfr+, was defined as committed progenitor cells in this study. Interestingly, these cells were able to differentiate into a mature ICC phenotype in terms of acquiring more intense expression of c-kit, and losing CD34, Insr and Igfr expressions in response to mb-SCF produced under the control of insulin and IGF-1. The cells grew in networks similar to ICC networks, and normal slow waves could be detected at that time.  

It is interesting to compare this recent study with a study by Faussone-Pellegrini et al. who studied the morphogenesis of developing ICC in different areas of mice small intestines. They described the presence of ICC-blasts at birth. These ICC-blasts had an oval shape with small processes. They were present in the myenteric plexus and in between the CM and LM layers. These cells acquired the ultrastructure of mature ICC by day 17. However, electrical slow wave activity developed before day 17. This suggests that the functional maturity of ICC preceded their morphological development. Interestingly, these observations were similar to the observations of Lornicz et al. in 2008. A further study by Bardsley et al. considered kitlowCD34+CD44+InsrIgfr+ cells to be ICC stem cells (ICC-SC). This is because the derived ICC progenitor cell lines from two mouse strains, the transgenic immortomice and the wild type C57BL/6J mice, had the ability to preserve their phenotype and develop into mature ICC. In addition, the ability of these cells to differentiate in vitro as well as in vivo into mature ICC could be due to endogenous production of IGF-1 and SCF acting in an autocrine loop manner. Although kit signalling is important for the proliferation of ICC stem cells, c-kit was not important to their survival since in mice hypomorphic for kit and KL, ICC-SC were not reduced compared to an obvious reduction in mature ICC networks. Neither antibodies to kit, nor SCF, nor tyrosine kinase inhibitors could inhibit the proliferation of these cells, while mature ICC were greatly affected.
Response of ICC to Injury

ICC are affected in several diseases that directly or indirectly involve the bowel, such as inflammation, obstruction, and DM. In these conditions, there is either a disruption in ultrastructure only, which is an early event, or a decrease in ICC networks leading, in severe cases, to loss of function. In the following sections, ICC in the diseases such as DM, idiopathic gastropathy, and ageing will be discussed.

ICC IN DIABETES MELLITUS

One of the most important complications of DM is gastrointestinal dysfunction, in particular diabetic gastropathy. It occurs in 30–50% of individuals with type I or II DM. Since GI motility requires the interaction between enteric nerves, smooth muscles, and ICC, GI dysfunction generally involves changes in all of these factors. Many DM studies which use animal models as well as human samples are found in the literature. Ordög et al. and Wang et al. studied ICC densities in two types of diabetic animals: non-obese diabetic (NOD) mice and streptozotocin-(STZ) induced diabetic rats respectively. In both studies, ICC loss was patchy and not uniform throughout the stomach. Ordög demonstrated that ICC density loss started midcorpus 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. The remaining ICC displayed changes in ultrastructure such as increased cell processes and loss of contact with adjacent enteric ganglia. The fundus did not show loss of ICC-IM but there was excess extracellular space separating the ICC from the adjacent enteric nerves. In contrast, Wang et al. showed that the loss of ICC density in the stomach of STZ-diabetic rats mainly involved ICC-IM and ICC-SM. Also notable was an associated ultrastructural change in nerves and the loss of enteric nerves. An interesting finding was the presence of fibroblast-like cells in the ICC-IM surrounding the enteric ganglia. They were described by the authors as representing immature or recovering ICC which might be involved in tissue healing and repair. Other investigators have considered these fibroblast-like cells to be a distinct subset of cells in the alimentary tract that might participate in alimentary tract motility. Similar ICC loss has been observed in the small intestines and the colons of diabetic animals.

WHY ARE ICC LOST IN DIABETES?

Loss of ICC results from the imbalance between factors that injure, and factors that regenerate and maintain ICC. The effects of both factors on ICC were investigated by Hovarth et al. In this study, ICC showed better tolerance in terms of maintaining their densities to hyperglycemia than normoglycemia in the absence of insulin or IGF-1 supplements. Thus, absence or relative deficiency of insulin may be the main factor contributing to ICC loss in DM, and leading to abnormal gastric motility and gastroparesis. Since ICC do not have insulin receptors, this points to the indirect effect of insulin on ICC. Smooth muscle atrophy and enteric nerve loss are other factors contributing to ICC loss in DM. SCF, which is produced by the smooth muscle and enteric nerves, mediates the effect of insulin and IGF-1 on ICC. Thus, when the smooth muscle atrophies, the resulting decrease in the SCF results in a loss of ICC. In DM there is a loss of neuronal nitric oxide synthase-(nNOS) derived nitric oxide that maintains ICC proliferation. As ICC can tolerate hyperglycemia, this suggests an endogenous ability to remove reactive oxygen species (ROS). Alternatively, this might be due to the presence of other factors. Carbon monoxide produced by the stress-induced enzyme heme oxygenase-1 (HO-1) is a cytoprotective for ICC. HO-1 is upregulated mainly in macrophages residing in the muscle layer in close contact with ICC and enteric nerves. HO-1 increases the expression of c-kit and nNOS and reverses the delay in gastric emptying.

ICC IN IDIOPATHIC GASTROPATHY

Studies comparing the cellular and ultrastructural changes in diabetic and idiopathic gastropathy found that at the light microscopy level, there were no differentiating features between the two except that in idiopathic gastropathy the damage to the ICC was more diffuse in nature. In general, both conditions share the following features: loss of ICC density, especially in ICC-MP; an inflammatory infiltrate mainly of CD45+ cells in the myenteric plexus and macrophages; loss of nNOS expression, which was more evident in idiopathic gastropathy than in diabetic gastropathy; ultrastructural...
changes in ICC such as swollen mitochondria and intracytoplasmic vacuoles; thickened basal lamina; loss of contact with the nerves, smooth muscle cells and with other ICC, and increased spacing of the smooth muscle by increased fibrous tissue. Nerves also showed more diffuse ultrastructural changes in idiopathic gastroparesis, such as increased filaments and empty nerve endings. 38

As the most constant feature in these two disorders, ICC loss is most likely responsible for the disturbed gastric motility in both diabetic and idiopathic gastropathy and in other conditions that present as GI dysmotility. 3,7,8,14,34–39

**Possible Mechanisms for ICC Recovery and Repair**

**ICC HAVE THE ABILITY TO RECOVER FOLLOWING INJURY**

Studies have found that ICC have the ability to re-differentiate into other cell types upon injury, and that those redifferentiated cells retain their kit-positive phenotype. 10,13,38 In one study where c-kit was blocked, ICC-MP dramatically decreased in number and the ones remaining showed ultrastructural features similar to smooth muscle cells in terms of developing myofilaments, and in expressing desmin (a smooth muscle marker) and c-kit. 13 In another study, fibroblast-like cells or fibroblast-like ICC cells were found in the area of ICC-IM and were associated with the enteric nerves. These cells could represent recovering or immature ICC that would be involved in repair and recovery of ICC. These cells were also found in the areas of ICC following injury to the gut, as in obstruction or inflammation, and their number decreased following recovery of ICC and removal of the insult. 30,41 In contrast, a study by Horiguchi et al. comparing the ultrastructure of the small intestine in wild type and c-kit deficient mice detected fibroblast-like cells in the small intestine of both strains in equal distributions. These cells showed a similar ultrastructure in all regions of the small intestine which contrasts with the diversity expressed by ICC. 33 The fibroblast-like cells described in this study had small gap junctions with smooth muscle cells as well as nerves. Unfortunately, no immunohistochemical studies to identify the immunophenotype of these cells and their relation to ICC were mentioned in this study. Collectively, one may think of ICC as dynamic cells that are adaptable to changes in their microenvironment, thus acquiring a more protective phenotype upon injury so that they can differentiate back to the usual ICC when the insult is removed.

**ROLE OF MAST CELLS IN ICC INJURY AND REPAIR**

One of the cells that may play a role in ICC repair is the mast cell. Mast cells have been identified in the inflammatory content of gastrointestinal diseases such as Crohn’s disease, ulcerative colitis, and achalasia. 11,16 Mast cells also express c-kit and in non-pathological conditions they are present in the mucosa and submucosa but rarely within the musculature. 16 In conditions such as Crohn’s disease and achalasia, mast cells were found to be more concentrated in the gut musculature. These immunologically activated cells closely adhere to the injured ICC. Selective degranulation was observed to be towards ICC. These granules, which contain various cytokines, have been described in neighbouring cells including ICC, either through fusion of the cell membranes or transgranulation. 11,16 Mast cells, which have been identified as an additional source of membrane-bound and soluble SCF, are a major source of fibroblast growth factor, and fibroblasts are another source of membrane bound SCF. 11,30 All these data are conclusive of the importance of mast cells in providing factors for survival and maintenance of ICC in disease states.

**ROLE OF MACROPHAGES IN INJURY AND REPAIR**

Macrophages establish close contacts with ICC in normal states as resident macrophages, and during disease states as activated and phagocytic macrophages. This is true for macrophages in the small intestine at the level of the myenteric region, deep muscular plexus, and serosa, but not in mice colons. In human colons, macrophages were also found in close contact to ICC. Resident tissue macrophages provide cytoprotection for ICC through the HO-1 pathway, a mechanism presumed to protect ICC during hyperglycemia. 37 In disease states, such as in infections like *Trichinella spiralis* and in response to injury such as surgery, the macrophages’ influence on ICC depends on the activation pathway. For example,
Effect of Ageing on ICC

Ageing associated disturbance in gastrointestinal function has been attributed to neurodegenerative changes. However, with the knowledge that ICC play a fundamental role in gastrointestinal motility, the effect of ageing on ICC networks had been studied recently on human and animal samples.\(^{36,46}\) To date it appears that only two studies have focused on the effect of ageing on ICC in animal models as well as in human samples. The first study included human stomach and colon samples surgically resected for non-obstructive colon cancer in age ranges of 25–70 and 36–92 years respectively. Although patients did not have any dysmotility problems, there was a significant decrease in ICC network density and ICC cell bodies in stomach samples in relation to age. The colon showed similar results. The decrease in ICC numbers was found to be approximately 13% per 10 years of life after the age of 25 years in the stomach and 12% per 10 years in the colon.\(^{36}\) The ICC cell volume was also decreased. Unfortunately, this study did not demonstrate the ICC senescent phenotype (kit-CD44+)\(^{25}\) that was described in previous studies although these human samples could represent a good model of senescent ICC.

The second study used progeric mice that are deficient in klotho protein, which suppresses the ageing process.\(^{46}\) In this study, it was demonstrated that ICC networks are decreased in the tunica muscularis in the corpus and antrum. ICC-SC were also decreased significantly. In contrast, myenteric neurons and smooth muscle cells showed no changes.\(^{46}\) These prematurely aged mice had additional factors that affected ICC development and maintenance such as low insulin and IGF-1, low mb- and sol-SCF and significantly higher ROS.\(^{46}\) The inability of the senescent ICC-SC to self-renew is one of the causes of ICC-loss in ageing.\(^{36,44,45}\)

**Figure 1:** A small gastrointestinal stromal tumour (GIST) from the subserosal surface, dissected from the first part of the duodenum.

**Figure 2:** A stomach, opened to show a large gastrointestinal stromal tumour (GIST) protruding into the gastric lumen.
A recent study by Asuzu et al. showed that the ICC-SC actually become senile.44 The Wnt signalling pathway is important for SC renewal and regeneration.44 It has been found that elevated Wnt signalling, measured by beta-catenin levels, can lead to hyperproliferation of ICC-SC and eventually to their senescence. Another probable mechanism for ICC loss in ageing is the increase in oxidative stress or an increased apoptosis combined with the inability of ICC-SC to replenish the injured or lost ICC.36,49

TRANSFORMATION OF ICC

GIST are common mesenchymal tumours in the GIT, accounting for 1% of all GI neoplasms. The most common site of these tumours is the stomach (60%), compared to 30% in the small intestine and 10% elsewhere.48 They can occur in other parts of the abdomen and can be small and asymptomatic [Figure 1], or large and produce symptoms ranging from abdominal pain to complete obstruction of the viscus [Figure 2]. They also undergo malignant transformation. Histologically, these tumours are quite variable and this creates a problem for pathologists in providing accurate diagnoses.51 The tumour cells can be spindle [Figure 3] or epithelioid [Figure 4] in shape, or a mixture of both.50–52 With the introduction of immune markers in the diagnosis of these tumours, it was found that they express c-kit, CD34, and CD44, as well as ANO1 discovered on GIST (DOG) 1,1,1.3 and PDGFR.24,50–55 Almost all of these markers present with ICC; thus, ICC is implicated in the development of these tumours. The finding that a c-kit mutation is the most important pathway in the oncogenesis of GIST further linked these tumours to ICC.48–50 Tumours that do not express c-kit were found to express PDGFRa.55 PDGFRa tumours are usually composed of epithelioid cells and they are gastric in location. Of PDGFRa mutant tumours, 30–40% occur in c-kit negative GIST, which suggests that a mutation in PDGFRa can substitute for c-kit mutation in the development of GIST.55 Treatment of these tumours includes surgery followed by the administration of a tyrosine kinase inhibitor such as imatinib. In a percentage of c-kit negative GISTs, imatinib can still be used to target the PDGFRa mutation.53,55 However, a subset of c-kit positive tumours does not respond to imatinib. A recent study found that ICC-SC could be the source of resistance in these tumours.56 In imatinib treatment, antibodies against kit and SCF could not prevent the proliferation of ICC-SC while at the same time inhibiting mature ICC.12,25 This resistance is due to a low expression of c-kit. A recently published abstract by Asuzu et al. showed that there is an epigenetic control leading to low kit expression in ICC-SC and thus resistance to treatment in GIST. This control is mediated by the polycomb group (PcG) of proteins that control gene expression and differentiation of stem cells and, at the same time, repress kit through methylation. Thus, sensitivity to imatinib can be achieved by reversal of this methylation.56

Conclusion

ICC are unique cells that are heterogeneous in their distribution, morphology, structure, and function. Several factors affect ICC development, its response
to injury as well as its repair and healing. ICC loss or reduction in density seems to be a constant factor in different pathological conditions, and in physiological conditions such as ageing. However, a reduced ICC network is not always accompanied by gastrointestinal dysmotility and the number of ICC that need be lost in order to produce functional abnormalities remains to be proven. Repopulation of the injured ICC is proposed to occur from local reserves represented by ICC-SC or progenitor cells. Whether the fibroblast-like cells that appear at ICC locations after injury are actually immature ICC that participate in replenishment of reduced ICC population, or whether they are a distinct cell population, would be an interesting research subject. Although ICC-SC serve in maintaining ICC networks and, hence, GIT function, they start to lose this ability during ageing, and their uncontrolled proliferation causes GI tumours that are treatment-resistant.

References


