Review

Maria Giuliana Vannucchi* and Chiara Traini

Interstitial cells of Cajal and telocytes in the gut: twins, related or simply neighbor cells?

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Abstract: In the interstitium of the connective tissue several types of cells occur. The fibroblasts, responsible for matrix formation, the mast cells, involved in local response to inflammatory stimuli, resident macrophages, plasma cells, lymphocytes, granulocytes and monocytes, all engaged in immunity responses. Recently, another type of interstitial cell, found in all organs so far examined, has been added to the previous ones, the telocytes (TC). In the gut, in addition to the cells listed above, there are also the interstitial cells of Cajal (ICC), a peculiar type of cell exclusively detected in the alimentary tract with multiple functions including pace-maker activity. The possibility that TC and ICC could correspond to a unique cell type, where the former would represent an ICC variant outside the gut, was initially considered, however, further studies have clearly shown that ICC and TC are two distinct types of cells. In the gut, while the features and the roles of the ICC are established, part of the scientific community is still disputing these 'new' interstitial cells to which several names such as fibroblast-like cells (FLCs), interstitial Cajal-like cells or, most recently, PDGFRα$^+$ cells have been attributed. This review will detail the main features and roles of the TC and ICC with the aim to establish their relationships and hopefully define the identity of the TC in the gut.

Keywords: CD34; *c*-Kit; connective tissue; differentiation; fibroblast-like cells (FLC); interstitial Cajal-like cells (ICLC), neurotransmission; PDGFRα$^+$ cells; scaffold.

***Corresponding author: Maria Giuliana Vannucchi,** Department of Experimental and Clinical Medicine, Histology and Embryology Research Unit, University of Florence, Viale Pieraccini, 6, I-50139 Florence, Italy, e-mail: mariagiuliana.vannucchi@unifi.it
Chiara Traini: Department of Experimental and Clinical Medicine, Histology and Embryology Research Unit, University of Florence, Viale Pieraccini, 6, I-50139 Florence, Italy

Introduction

The term telocyte (TC) was introduced for the first time in the scientific literature in 2010 (1). Since these cells were described, an increasing number of papers have been published on this issue and cells with TC features have been found in almost all mammalian organs (2–7). These cells reside in the interstitium of the connective tissue and are characterized by peculiar features seen using transmission electron microscopes (TEM).

More than a century ago, Santiago Ramon y Cajal described a particular cell type in the gastrointestinal tract (GI) that appeared to function as an 'endostructure' of the intrinsic nervous system; he named these cells 'interstitial neurons' because they were identifiable through staining techniques which specifically labeled neurons (e.g. methylene blue or silver impregnation) and were located in the interstitium between nerve endings and smooth muscle cells (SMCs) (8). Subsequent work established their structural and functional characteristics and these cells were finally named interstitial cells of Cajal (ICC) (9–14).

Thanks to the research group of Prof. Popescu, the possibility that TC and ICC could correspond to a unique cell type where the TC represented an ICC variant distributed in other organs outside the gut was considered. The controversial results obtained by different research groups testing this possibility, caused the TC cells to be initially named as interstitial Cajal-like cells (ICLC) (2). In 2010 the ambiguous term of ICLC was abandoned and TC was finally proposed (1).

To date, part of the scientific community is still questioning in regard to the existence of the TC as a unique type of cell with proper morphological peculiarities and roles. In the gut, while the morphology, the topography and the roles of the ICC are established, this 'new' cell type, also named fibroblast-like cell (FLC), or ICLC or, most recently, PDGFRα$^+$ cell, is still looking for a proper identity and it is matter of debate whether TC and ICC are somehow related.

The present review will discuss the morphological and functional properties of TC and ICC in the mammalian gastrointestinal tract.

Interstitial cells of Cajal (ICC)

After Cajal described the 'interstitial neurons' many morphologists investigated these cells, establishing their embryological origin (mesenchyme), common to the SMC and different from that of the neuronal cells (15), confirming their location in the interstitium and demonstrating their ability to form networks. Contemporarily, physiologists were able to attribute to them the role of pacemakers for gut peristalsis, being able to generate slow waves (13, 16–18). Indeed, a combination of morphological and functional investigations was also able to demonstrate that the ICC play a role of intermediate in neurotransmission (12, 17–19). Another function attributed to some ICC populations is that of being part of the 'stretch receptor'. In particular, in the small intestine this role would be played by the ICC-DMP (11, 12, 20, 21), in the stomach, by the ICC-IM (22).

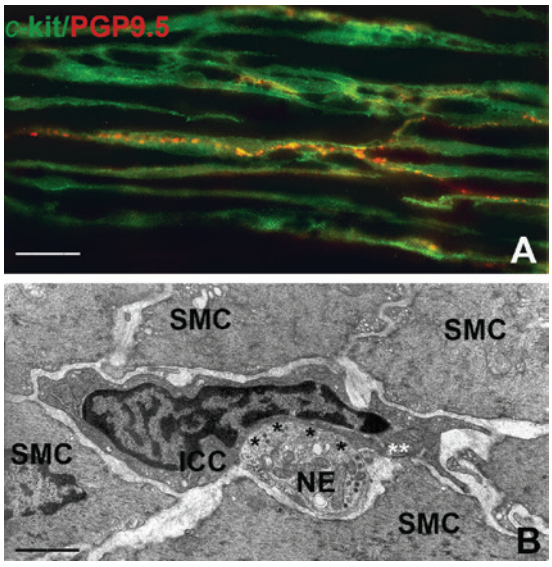

Figure 1: ICC. Fluorescence microscope. Transmission electron microscope.
(A) *c*-Kit/PGP9.5 double labeling in guinea pig small intestine. Numerous PGP9.5 (red) varicosities are closely apposed to the ICC (green). Transmission electron microscope (TEM). (B) A nerve ending (NE) take a strict contact (black asterisks) with an ICC which, in turn, make a gap junction (white asterisks) with a smooth muscle cells (SMC). Bar: A=28 μm; B=0.5 μm.

c-Kit receptor

A fundamental contribution to the ICC studies came from the discovery that these cells express the *c*-Kit receptor, a type III tyrosine kinase receptor (23). By using the *c*-Kit labeling, the ICC were found throughout the entire gut wall and showed similar, but not identical, locations. Moreover, it was verified that the ICC form networks, are closely apposed to nerve endings and connected to the SMC by gap-junctions (Figure 1).

In regard to their location the ICC can be divided in two main groups. One group, corresponding to the ICC located at the myenteric ganglionated plexus level, is identified with the acronym ICC-MP (myenteric plexus) or ICC-AP (Auerbach plexus), and corresponds to a homogenous population of ICC forming a 3-D network around the ganglia and the nerve strands of the myenteric plexus in the entire GI tract. A second group, corresponding to the ICC located intramuscularly (11), form 3-D and/or 2-D nets independently of the gut tract and on the muscle wall portion where they are located. Accordingly, in the esophagus and stomach, these ICC reside almost exclusively endowed in the thickness of the muscle layers (ICC-IM) forming a 3-D net. In the small intestine two distinct subpopulations are present, one located in the thickness of the muscle layers (ICC-IM) forming a 3-D web, and the other, peculiar to this tract of the intestine, located in a thin and intricate aganglionated nerve plexus named deep muscular plexus (DMP; ICC-DMP) forming a 2-D web. Finally, in the large intestine there are still two subpopulations: one intramuscular (ICC-IM) and the other one, once again peculiar to this region, located at the border between the circular muscle layer and the submucosa, in strict relation with the submucous plexus (SMP), and named ICC-SMP. The manipulation of the *c*-Kit receptor (24) has allowed to ascertain which ICC populations are mainly responsible for the slow waves generation in the different regions of the GI tract (25). In fact, although the ICC are commonly referred to as the pacemaker of gut peristalsis, this role is not played by the same ICC populations. In the small intestine this role is played by the ICC-MP while in the large intestine the ICC-SMP are the dominant pacemakers. In the stomach, the ICC-MP are considered the pacemakers; however, in mutant mice lacking the ICC-MP, slow waves are generated by the ICC-IM (24–27). The *c*-Kit receptor expression has been related to ICC differentiation. Briefly, it has been demonstrated that this receptor is necessary for the ICC-MP differentiation and the maintenance of their phenotype; while it is fundamental for the maintenance of the differentiated state of the ICC-IM (28).

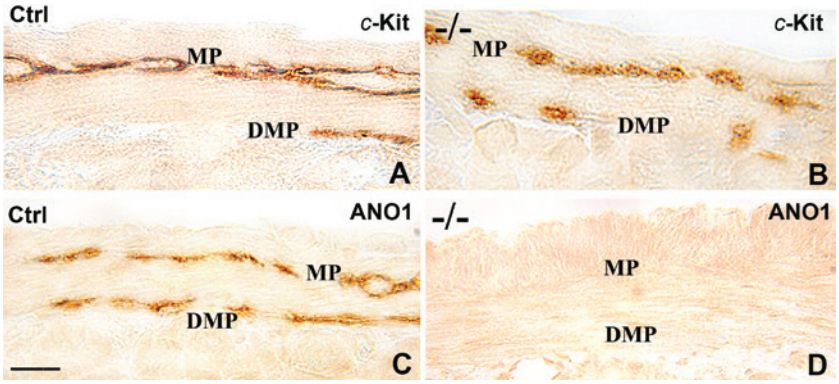

Figure 2: ICC Light microscope.
(A-B) *c*-Kit-immunoreactivity (IR). In the control (A) the ICC at the myenteric plexus (MP) and at the deep muscular plexus (DMP) are *c*-Kit-IR; in the Cav-$1^{-/-}$ mice (B), the *c*-Kit-IR is maintained. (C-D) Ano1-IR. In the control (C), the ICC show the Ano1-IR at both regions whereas in the Cav-$1^{-/-}$ mice (D) no Ano1-IR is detected. Bar: 40 μm. (With permission from ref. 31.)

ANO-1 receptor

Another marker, considered by some authors even better than the *c*-Kit for the ICC identification (29), was recently found; the anoctamin 1 (ANO1). It is a Ca^{2+}-activated chloride channel necessary for slow wave generation and devoid of any effect on ICC differentiation (30). In knock-out mice for *caveolin-1* gene, an integral membrane protein of the caveolae highly expressed in the ICC, the ANO1 expression disappeared in the ileal ICC while the *c*-Kit labeling was maintained. This datum suggested that ANO1, but not the *c*-Kit receptor, is strictly related to the caveolae integrity and functionality (Figure 2) (31).

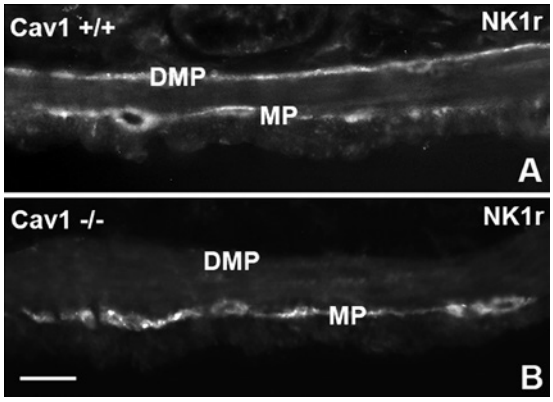

Figure 3: ICC Fluorescence microscope.
NK1r-IR. In Cav$1^{+/+}$ mouse ileum (A) intensely NK1r-IR spindle-shaped cells are present at the deep muscular plexus (DMP) and NK1r-IR neurons are present within the myenteric plexus (MP). In Cav$1^{-/-}$ mouse ileum (B) NK1r-IR cells are completely absent at the DMP. Bar: 40 μm.

ICC and nerve contacts

All the ICC populations receive nerve terminals; however, great differences in the number and vicinity of these contacts have been described (11) suggesting that there are ICC such as the ICC-DMP almost exclusively engaged in the neurotransmission (12). Moreover, it has been shown that ICC express molecules indicative of their role either in excitatory (NK1 receptor) (32) or inhibitory (nitric oxide synthase) (12, 33, 34) neurotransmission. These data point out that ICC are under direct neural control and that, by their contact, they transmit information to each other and to SMCs, according to the Cajal hypothesis. Interestingly, by using one of the *c-kit* mutant mouse strains, the W/W^e, it was reported that the ICC-DMP, commonly considered spared by the gene mutations (24, 28, 35, 36), lost the NK1 receptor and received a significant reduced number of SP nerve endings (Figure 3). This result was considered responsible for an anomalous tachykinergic control of the small intestinal motility (37). Moreover, using WW^v mice that lack intramuscular ICC (ICC-IM), electrical stimulation of nitrergic nerves was not followed by a significant muscle relaxation, and stimulation of cholinergic nerves did not cause the appearance of excitatory junction potentials in SMCs, leading to the conclusion that innervation did not occur via direct communication between nerves and smooth muscle but that ICC was an essential intermediary (see 38 for review).

ICC plasticity

ICC are commonly affected in several motility disorders. Experimentally, however, the resolution of these

disorders resulted in the recovery of ICC networks suggesting the existence of ICC plasticity (18). In healthy, ICC numbers are dynamic (39) indicating that the integrity of the ICC networks has to be tightly controlled with processes that regulate both ICC loss and ICC replacement. ICC loss might be due to apoptosis (39) and trans/de-differentiation (40, 41) whereas ICC replacement includes cell repair, proliferation from adult ICC and ICC stem cell precursors proliferation (42). As reported above, the *c*-Kit signaling pathway is responsible for ICC development and maintenance of the phenotype. Nevertheless, several other signaling pathways contribute to ICC survival and network organization (see 18 for review). Interestingly, although in adults the ICC number could recover, mitotic ICC were never observed. Therefore, the possibility that local ICC precursors are present in the gut wall has taken hold. Studies in postnatal murine gastric muscle revealed rare cells that expressed very low level of *c*-Kit and normal level of CD44, CD34, Ano-1, and receptors for insulin and IGF-1 (42, 43). In adult mouse colon, 14 days after BAC treatment, the damaged areas re-innervated and together with the nerve structures, cells with FLC features were detected. These FLC contacted both nerve endings and SMCs and later, acquired some typical ICC features (41). A morphological study in developing ICC of mouse small intestine showed that these cells acquired their mature features by day 17 after birth whereas the slow wave activity was already present, thus suggesting that the functional properties of ICC precedes their complete morphological maturation (44). In the human small intestine, the appearance and differentiation of all the ICC types occurred in concomitance with those of the related nerve and muscle structures. Therefore, the ICC-MP appeared first during the fetal life, ICC-IM and ICC-DMP later and their differentiation was still incomplete at birth (45).

Telocytes (TC)

The possibility that the TC could be a variant of the ICC outside the gut was taken into consideration since these cells were described and for this reason these cells were initially named interstitial ICLC (46). This name, however, soon showed its ambiguity and vagueness and the term TC, considered more identifiably, was proposed (1). The choice was accompanied by an accurate explanation of the name's meaning, underlining how the term better described the morphological features appreciable under TEM (1, 5). Indeed, the TEM identification was and still is, the best, easiest and certain way to recognize the TC wherever observed (1, 5).

The relatively recent identification of the TC has raised the question of what these cells were previously known as. Keeping in mind their shape and location, it is very likely that, under the light microscopy, by H&E staining, these cells were confused with the fibroblasts/fibrocytes. The very long and extremely thin prolongations are undetectable in these conditions. Under electron microscopy, they could be and, likely, they are still confused with fibroblasts/fibrocytes and, in the gut, also with ICCs. Expert microscopists might have been suspect of these peculiar cells and classified them as 'unknown' cells. This was true until Prof. Popescu and his group recognized and accurately described this new, 'unknown' cell type under TEM. Since then, the same research group and many others have identified cells like the TC either under TEM or under light/fluorescent microscopy.

TC identification by immunohistochemistry (see Table 1)

Although the TC identification by immunohistochemistry is still uncertain, it is commonly accepted that the CD34 is a good marker to identify these cells, in the gut and outside it (3, 7, 47). CD34 is a sialylated transmembrane glycoprotein detected in hematopoietic stem cells (48). Its expression decreases as these cells differentiate. Interestingly, CD34 labeling was found also in cells outside the hematopoietic system such as the endothelial cells (49) and the so-called ICLC in several organs [see ref. (1) for review]. In the gut these CD34 positive cells were located in the connective tissue of the submucosa (Figure 4), among the muscle bundles (Figure 4) and around the myenteric plexus ganglia and nerve bundles, and showed an elongated and ramified body resembling ICC. However, several reports demonstrated that ICC never showed CD34 positivity (3, 50) (Figure 4).

Recently, by using the PDGFRα antibody, cells sharing the same distribution of the CD34 positive cells were identified (51–55). The PDGF/PDGF receptor signaling pathway plays critical roles in mammalian organogenesis and murine GI villous morphogenesis, and it has been demonstrated that selective inhibition of the PDGFR suppresses longitudinal smooth muscle differentiation (53). The presence of cells PDGFRα$^+$ in the same areas where the TC were described, raised the question whether they were or not the same cell type. The question was solved by Vannucchi et al. (51). These authors clearly showed, in the human gut, that all of

Table 1: Ultrastructural features characterizing telocytes and ICC.

	Telocyte	ICC
Nucleus	Small and ovoid. Contains clusters of heterochromatin associated to the nuclear envelope. Maximum one and small nucleolus	Large, ovoid, 1-2 nucleoli. Peripheral condensed chromatin
Cell body	Small, oval containing scarce cytoplasm Nucleus/cytoplasm ratio 1:3	Large, spindle-shaped, containing a great amount of cytoplasm. Nucleus/cytoplasm ratio 1:5
Processes	Called telopodes. From two to ≥five. Very long (100 microns) and thin, with a moniliform profile due to the alternation of podomers (thin portions) and podoms (large portions)	Long, large starting from the cell body and then progressively thinner, with a smooth profile
Smooth endoplasmic reticulum	Scarce cisternae and only in the cell body	Numerous cisternae in the cell body and processes
Rough endoplasmic reticulum	Some cisternae in the cell body and in the podoms	Scarce cisternae, mainly in the cell body
Mitochondria	Small, oval or rounded, accumulated in the podoms	Numerous, elongated, accumulated in the body and at the process emergency from the body
Thin filaments	Scarce, small bundles under the plasmalemma	Several small bundles under the plasmalemma
Intermediate filaments	Scarce, gathered in small bundles in the cell body	Abundant, gathered in bundles in the cell body and along the processes
Caveolae and intracytoplasmatic vesicles	Scarce caveolae, numerous coated vesicles	Numerous caveolae all along the plasmalemma of both body and processes, scarce coated vesicles
Basal lamina	Absent	Always present although discontinuous
Cell-to-Cell contacts	TC-TC: Numerous, mainly of the mechanical type TC-ICC: Sporadic TC-SMC: Very rare	ICC-ICC: Numerous, mainly gap junctions. ICC-TC: Sporadic ICC-SMC: very frequent, mainly gap junctions
NE contacts	Sporadic, with a gap >40 nm	Very frequent, with a gap ≤20 nm
Gut wall distribution	In the mucosa, submucosa and muscle wall	In the muscle wall only
Networks	2-D and 3-D nets whose meshes are extensible	2-D and 3-D nets whose meshes are not extensible

the CD34 positive cells were also PDGFRα$^+$ (Figure 5). Moreover, in this study, and in several others, it was demonstrated that none of the CD34 and PDGFRα$^+$ cells were *c*-Kit labeled, definitively excluding that these cells are ICC (50–55) (Figure 4). Notably, while in these reports (54, 55) some cells located in the axes of the villi were PDGFRα$^+$, Vannucchi et al. (51) could not find any CD34 positive cells at this level. Under TEM, cells with the features of TC were described in the axes of the villi and called myoid cells (56–58). These cells, similarly to the ICC, were NK1r-positive, made close contact to each other and nerve fibers (56) and were dystrophin positive (59), but, contrary to ICC, they were *c*-Kit negative and αSMA-positive (59). It is reasonable to hypothesize that these cells are a special variant of TC that might express markers that are species-specific. Moreover, peculiar TC, PDGFRα/αSMA positive and CD34 negative have been described in the human urinary bladder and are called hybrid TC (7). Finally, it cannot be excluded that the discrepancies listed above might be due to different tissue fixation (pre- vs. post-fixation) or to the embedding methodologies employed (freezing vs. paraffin embedding). To note, some authors have considered the PDGFRα$^+$ cells to correspond to the FLC (52, 53, 60). However, because of the vagueness of this indirect definition of the cell identity, also, this name has been gradually abandoned and in the most recent papers these cells are simply called PDGFRα$^+$ cells (54, 55, 61–63). Several groups of researcher have shown that in the gut of rodents and humans the PDGFRα$^+$ cells also express the small conductance Ca^{2+}-activated K^+ channel 3 (SK3) (53, 55, 60–62). It was also ascertained that none of the *c*-Kit positive cells expressed the SK3 and, in ICC deficient mouse strains, the channel expression was preserved (53, 55, 60–62).

TC identification by TEM (see Table 2)

The best method to identify TC is TEM. This is true in all organs and especially in the gut where all the TC, independently of the region they are located, show all the peculiar features already described (1, 5). Under the TEM it was also demonstrated that the TC express the CD34 (Figure 4) (3).

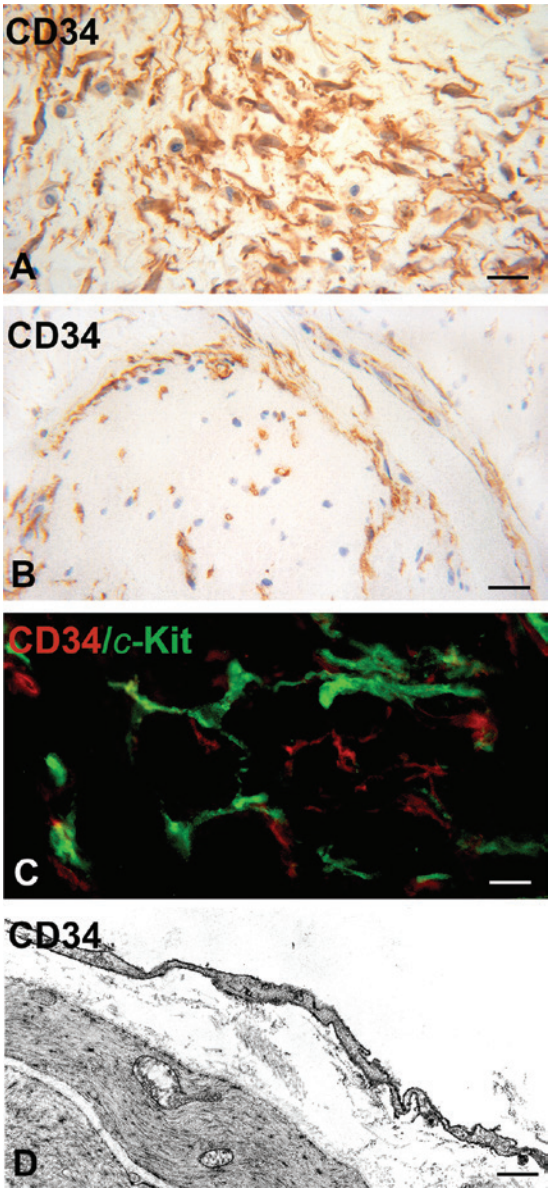

Figure 4: TC Light microscope. Fluorescence microscope. Transmission electron microscope.
(A–B). CD34-IR cells form a 3-D network in the submucosa (A) and a 2-D network around a muscle bundle (B) of human colon. Fluorescence microscope. (C) CD34/*c*-Kit double labeling. The CD34- (red) and c-Kit positive (green) cells are often very close to each other but none of them are double labeled. Human stomach. (D) CD34 immunoelectrolabeling. The labeling appears as electron-dense spherules regularly distributed on the telopode plasma membrane. Mouse stomach. Bar: A–B=30 μm; C=25 μm; D=0.4 μm.

TC subtypes

The TC show immunohistochemical differences depending on the organ where they are located and/or the animal species (64); the gut is no exception to this rule. In humans, although all the CD34 positive cells were found to be also PDGFRα$^+$, in the axes of the villi there were described only as PDGFRα$^+$ cells (51, 54, 55, 63). In the muscle wall of humans and rodents the PDGFRα$^+$ cells also expressed the SK3 channel (see above) but, in the mouse, these PDGFRα/SK3$^+$ cells were CD34 negative (60).

In summary, also in the GI tract, TC show regions and/or species differences. Whether this variability is linked to their role needs to be investigated.

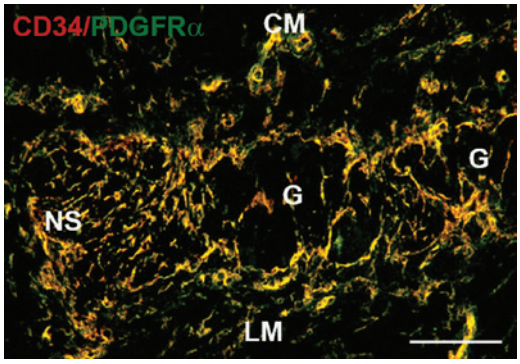

Figure 5: TC Fluorescence microscope.
PDGFRα/CD34 double labeling. Myenteric plexus of human colon. PDGFRα/CD34 double-labeled (yellow) cells surround two myenteric ganglia (G) and form networks along the nerve strand (NS). CM: Circular muscle; LM: longitudinal muscle. Bar: 30 μm.

Table 2: Immunohistochemical labeling of TC and ICC in the gut.

	Telocyte	ICC
CD34	positive	negative
c-Kit	negative	positive
PDGFRα	positive[a]	negative
ANO-1	nd	positive
SK3	positive	negative

[a]Some PDGFRa$^+$ TC described around and along the axes of the villi did not share the CD34$^+$ phenotype. nd: Not determined.

TC roles

The ubiquitous distribution and the organization in 3-D networks of all the TC subtypes testify to a common role, independently of the gut wall portions where they are located. This role consists in being the organizers of the connective tissue. The 3-D scaffolds are likely able to follow the organ distension and relaxation, to avoid anomalous organ deformation, to control blood vessels closure or rheology, to interact with the extracellular matrix determining the orientation of the collagen and elastic fiber (Figure 6) (47).

Interestingly, either TEM or light microscopy revealed that some ICC were intercalated along the TC networks

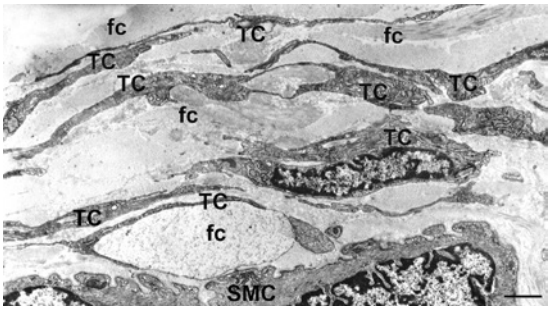

Figure 6: TC Transmission electron microscope.
Numerous TC form an elaborated 3-D network. In the meshes described by the TC long and thin telopodes are contained bundles of collagen fibers. Bar: 1 μm.

or strictly intermingled (3, 64). These spatial interactions suggested two possible roles of the TC: the TC may favor the spreading of neurotransmission signals directed to ICC (3); the TC could, on demand, differentiate in ICC. This last hypothesis was based on the following data: (i) the ICC number did not change significantly with age while these cells underwent apoptosis (3, 39, 41); (ii) no mitotic ICC were ever described (3); (iii) mitotic cells resembling the so-called FLC have been observed in areas were ICC, previously destroyed, re-appeared (41); (iv) it is commonly accepted that the TC might be adult mesenchymal stromal cells located in the connective tissue able to differentiate in different cell types of common embryonic origin (47, 65).

In regard to the latter point, TC are also considered essential for the survival, proliferation, differentiation, maturation and guidance of several parenchymal stem cells located in the niches of the organs (47). The clearest data have been obtained in the fetal and adult heart. In this organ, the TC seemed to be able, from one side, to build up cellular scaffolds to preserve the stem cells niches, from the other side, to organize 3-D pathways to guide the myocardiogenic stem cells organization and differentiation (66–68). In the gut, a similar role might be played in relation to the glandular stem cells (51, 54) where a strict and privileged spatial interaction between these cells and the TC/PDGFRα$^+$ cells has been described. Of note, the expression by the TC of the PDGFRα receptor is a further element in favor of a such role (see above) (51, 53).

More recently, it has also been suggested that the TC (named PDGFRα$^+$ cells) (54, 55, 63), may be capable of neurotransmission in the gut forming an integrated unit called the SIP syncytium where the SMC (S) are electrically coupled to ICC (I) and PDGFRα$^+$ cells (P)' (63). The existence of the SIP as a sort of circuit able to control and modulate the muscle wall activity is based on several data, some of which clearly demonstrated it, while some other data is still speculative. One fundamental condition to guarantee the circuit functionality is the presence of electrical coupling among the three types of cells. TEM and immunohistochemistry have shown well that there are gap junction between TC (FLC; PDGFRα$^+$ cells) and ICC and between ICC and SMC, less certain is the existence of gap-junctions between TC and SMC. Indeed, these junctions have been described in the small intestine of W/W mutant mice and rats (69) but it is known that in the small intestine some ICC are spared by the mutation. In regard to the nerve contacts, while it has been clearly demonstrated, also functionally, the ICC are deeply innervated and the nerve contacts are often closer than 20 nm, no similar images were reported for the TC. Another condition favorable to the existence of SIP would be the presence of receptors and effectors of neural responses in the cells forming the SIP. Again, the ICC and the SMC possess these requirements. Regarding the TC/PDGFRα$^+$ cells interesting findings are being reported. As mentioned above, the TC express the SK3 channels (55, 57, 62–64); as these channels are involved in the purinergic neurotransmission, TC might be postjunctional cells to mediate this neural pathway (63). Genetic investigations have also demonstrated that the TC/PDGFRα$^+$ cells express key genes involved in purine signaling (62). Currently, the findings regarding a possible role of TC/PDGFRα$^+$ cells in the nitrergic transmission appear less reliable. The possibility that the PDGFRa$^+$ cells could express the soluble guanylate cyclase (sGC) has been deduced by immunoelectron microscopical results showing some interstitial cells labeled with cGC, and by immunohistochemistry (70). However, no double labeling with the PDGFRα marker was done.

Conclusions

In the gut, all CD34$^+$TC correspond to the PDGFRα$^+$ cells. In the villi, the PDGFRα$^+$/CD34 negative cells could correspond to a TC variant similar to the hybrid TC described in the bladder.

The PDGFRα$^+$ definition for these interstitial cells, although correct, is not exclusive, as other cells in the interstitium express this marker (mast cells, endothelial cells); therefore, it is desirable to find a name unique for these cells. The term TC has be used to fulfill this purpose.

It can be definitively excluded that TC and ICC are twins cells. However, these cells are certainly related.

They share the same embryonic origin (mesenchyme); both form networks that run the same regions sometimes in parallel, sometimes some ICC intercalate the TC networks or vice versa. This strict relationship has suggested that TC could spread the ICC signals and TC could represent ICC stem cells.

Very intriguing is the proposed SIP syncytium where the TC and ICC work in sequence to regulate SMC function. In this regard however, the existence of gap junction between TC/PDGFRα$^+$ cells and SMC is still a hypothesis.

TC and ICC can also be considered simply as neighbors. This is the case for the TC present in the thickness of the lamina propria and submucosa, two regions where ICC never reside. Herein the TC play a proper and unique function such as to constitute the scaffold to organize the connective components. Even more, in these regions, it has been hypothesized that the TC might influence the proliferation and differentiation of the stem cells located in the intestinal gland funds. Finally, it has even considered the possibility that in the lamina propria the TC/PDGFRa$^+$ cells might mediate the neurotransmission.

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