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MINI REVIEW

Enteric glial cells: new players in gastrointestinal motility?

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The enteric glial cells, in addition to being support structures for the enteric nervous system, have many other additional roles, such as modulators for the homeostasis of enteric neurons, cells involved in enteric neurotransmission and antigen-presenting cells. Moreover, in the last years, data have been accumulating that demonstrate a possible active role of these cells in the pathophysiology of gastrointestinal motor activity. Thus, as also shown by recent evidence in both experimental animal models, and in some human diseases, alterations of enteric glial cells might have some role in the development of intestinal motor abnormalities.

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The enteric nervous system (ENS) is organized in a complex structure that controls motility, blood flow, uptake of nutrients, secretion, immunological and inflammatory processes in the gut.[1] Two main cell populations are represented in the ENS, neurons and enteric glial cells (EGC), the latter being much more abundant (up to fourfold) than neurons.[2]

The old simplistic view of EGC, basically as support cells for the ganglia and/or nutritive elements for enteric neurons, has changed with the increase in knowledge, and it is now evident that these cells may have an important role in the economy of the digestive system. In fact, EGC display mechanical support, neurotransmitter, immune and homeostatic functions in the gut (Figure 1).[3,4] Even more intriguing is the putative role of EGC as players involved in gastrointestinal motility, as it will be discussed in this review.

EGC AND ABNORMAL GASTROINTESTINAL MOTILITY: EVIDENCE FROM HUMAN STUDIES

It has been pointed out that there is no gastrointestinal disorder for which an underlying glial defect has been established.[3] However, it is possible that abnormalities relative to this cell population may have been overlooked.

EGC and Intestinal Inflammation

The concept that gastrointestinal motility is altered in mucosal inflammatory conditions of the gut is now well accepted, and studies in animal models clearly indicate a causal relationship between the presence of mucosal inflammation and altered motor function.[5] Some intriguing experimental evidences have demonstrated that EGC may have a role in intestinal inflammatory processes,[3,6,7] and that immune-mediated damage to enteric glia might participate in the initiation and/or the progression of inflammatory bowel disease.[8] In fact, EGC functionally interact with lymphocytes,[9,10] respond actively to inflammation and become activated as antigen-presenting cells[11] attracting immune cells to the ENS.[7] Thus, it has been hypothesized that the EGC network disruption might represent an important cause for the development of inflammatory bowel diseases, especially Crohn's disease, even though human data are still lacking.[7]

On the other hand, looking at the above EGC functions and properties, it is not difficult to image an active role of these cells also in the pathogenesis of 'functional' gastrointestinal disorders. The latter are traditionally thought to occur in the absence of anatomical or biochemical abnormalities.[12] However, studies in patients with irritable bowel syndrome demonstrated mild to moderate inflammatory infiltrates closely associated to the enteric plexuses and mucosal activation of the immune system,[13,14] and we have previously shown that some patients with severe intestinal dysmotility and megacolon may have an underlying myenteric ganglionitis (due to a prominent lymphoplasmacellular infiltrate within the myenteric plexus) responsible for their symptoms.[15] Due to their properties and function, it is

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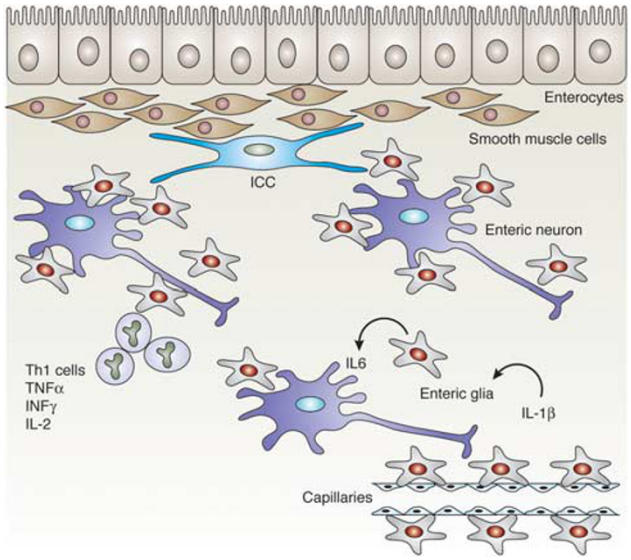

Figure 1 Schematic representation of the anatomic–functional interactions of the EGC with the other elements of the ENS. Neurons are colored in green and the EGC in gray. ICC, interstitial cells of Cajal.

conceivable that EGC could play a role in these instances, by attracting immune cells to the ENS.[3] However, such a hypothesis was not formally tested in these former studies.

Evidence for Involvement of ECG in Abnormal Gastrointestinal Motility

Only a few studies have been published in which the role of EGC has specifically investigated in human gastrointestinal motor disorders. For instance, we found a significant decrease of EGC (together with a decreased number of interstitial cells of Cajal (ICC)) in both the submucosal and myenteric plexuses in patients with colonic diverticular disease.[16] Since in this condition the hypertrophied colonic smooth muscle may represent a partially obstructive mechanism, we hypothesized that the function and the population of EGC might be loss due, at least in part, to this mechanism, in analogy to what happens to ICC in similar experimental animal models.[17]

We have subsequently reported that the EGC (together with enteric neurons and ICC) are significantly reduced in patients with idiopathic severe slow-transit constipation requiring surgery for symptoms' relief[18] (Figure 2a–d). The EGC decrease (but not that of ICC and enteric neurons) was also present in the small bowel (terminal ileum) of the same patients,[19] suggesting that ECG might have some role in the abnormal motor activity described in these patients. Findings similar to those described above in the colons of patients with slow-transit constipation have recently been reported by our group in patients with chagasic and idiopathic megacolon.[20]

Moreover, we have found a significant decrease of EGC, but not ICC, in both the myenteric and submucosal plexuses of patients with severe constipation due to obstructed defecation refractory to treatment.[21]

PUTATIVE MECHANISMS FOR EGC INFLUENCE ON GASTROINTESTINAL MOTILITY: EVIDENCE FROM ANIMAL STUDIES

Only a few studies are available on this topic, mostly originating or being inferred from experimental animal models, and in which the motility data have frequently been reported as adjunct findings.

The development of both EGC and enteric neurons is strictly regulated by microenvironmental factors[3,22,23] such as glial cell line-derived neurotrophic factor (GDNF), neurotrophin-3 (NT-3), ciliary neurotrophic factor (CNTF) and leukemia inhibitory factor (LIF).[3] Among these, GDNF has a prominent role in promoting the development and survival of enteric neurons, as suggested by the fact that the ENS almost completely fails to develop in GDNF knockout mice.[24] The trophic function of GDNF is also supported by *in vitro* studies, demonstrating that this factor promotes the development of glia in unselected cell populations from fetal murine bowel.[25] Moreover, it has been shown that mature EGC produce GDNF.[26]

So far, it has not been demonstrated that glial expression of trophic factors contributes to the maintenance of enteric neurons in man. However, several such lines of evidence are available for animal models. For instance, GDNF can modulate enteric neuronal survival and proliferation in postnatal mice through a neuropeptide Y-mediated mechanism,[27] and GDNF overexpression prevents hyperglycemia-induced delayed gastric emptying in diabetic animals.[28] Conversely, the absence of GDNF receptor alfa2 in mice causes the loss of substance P (an excitatory transmitter)-containing myenteric neurons, with subsequent decrease of small bowel transit.[29]

In addition, the selective ablation of EGC by a gliotoxin causes a decrease of small intestinal motility and transit in rats and, more importantly, this enteric glial dysfunction is not accompanied by intestinal inflammation.[30] Overall, these data suggest that EGC are involved in the modulation of enteric neural pathways responsible for the control of the motor activity of the gut.

Glial cells are well recognized sources of neurotrophic factors and neurotrophins (both chief regulators of ontogenetic differentiation and adult function[31,32]) in the central nervous system, and the latter control gene expression and neuronal phenotypes.[33] Expression of neurotrophins (NT-3, -4, -5 and -6) and of their thyrosine receptor kinases has been described in the adult ENS,[34–36] and there is evidence that these factors may be secreted by glial cells.[37] Thus, it has been suggested that neurotrophins may be produced by EGC to modulate neuronal gene expression and in turn the phenotypes of enteric neurons.[38] Interestingly, it has been reported recently that EGC may influence the neurochemical coding of enteric neurons. In fact, in a mouse model, enteric glial ablation caused a marked reduction in the vasoactive intestinal

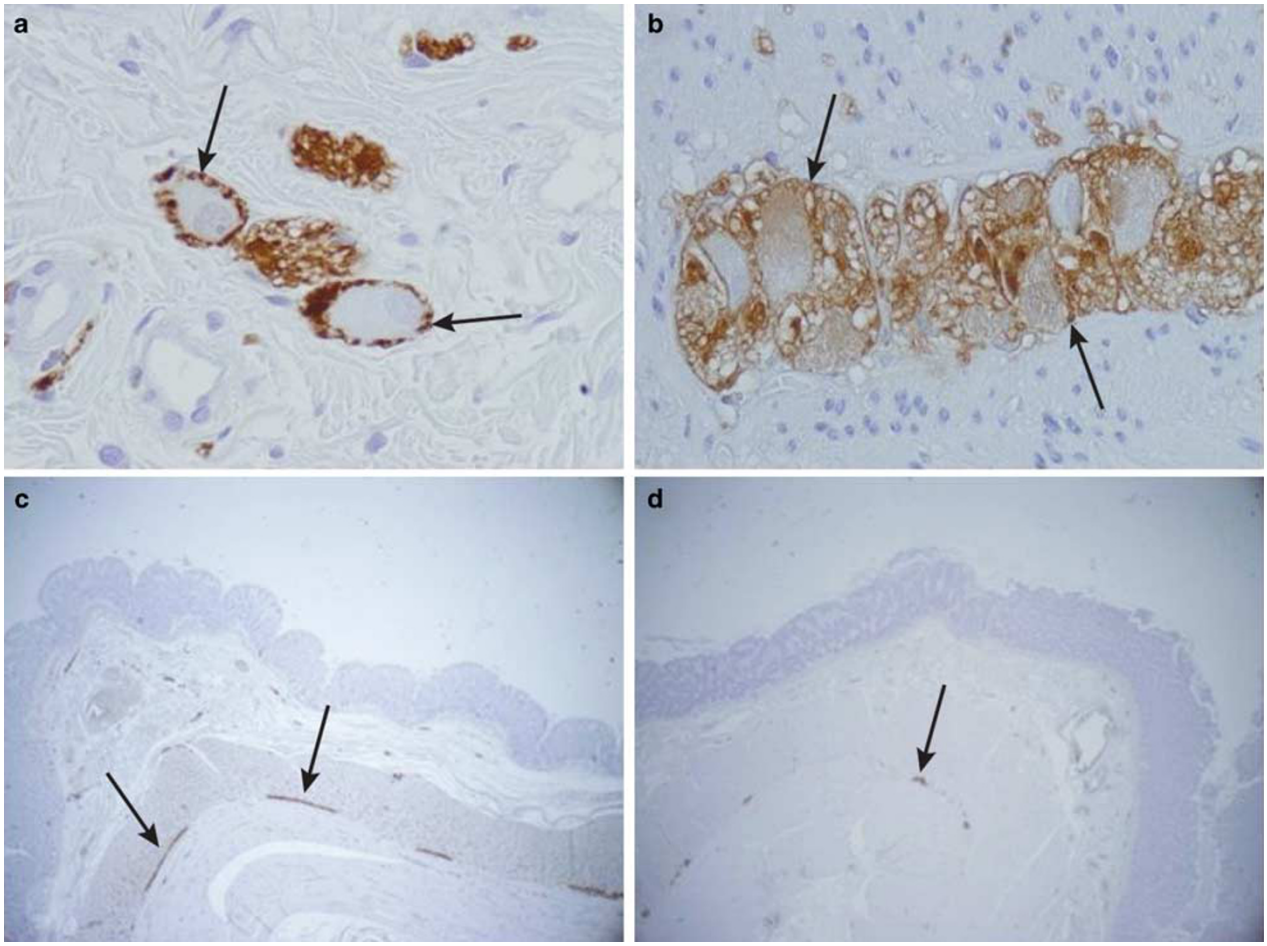

Figure 2 EGC (arrows) tightly packed around enteric neurons in a submucosal (**a**) and in a myenteric ganglion (**b**). S100 immunostaining, original magnifications $\times 40$ (**a**) and $\times 100$ (**b**). Full thickness specimen of human colon of a control subject (**c**) and of a patient with intractable slow-transit constipation (**d**). The arrows indicate EGC in the myenteric plexus. Note the rarefaction of these cells in (**d**). S100 immunostaining, original magnification $\times 10$.

peptide and substance P immunoreactive neurons of the submucous plexus, with an increase of choline acetyltransferase and a decrease of nitric oxide synthase immunoreactive neurons in the myenteric plexus.[39]

Overall, the above and other evidences suggest a close functional link between EGC and enteric neurons.[40]

HYPOTHETICAL MECHANISMS OF GUT MOTOR ABNORMALITY RELATED TO EGC DYSFUNCTION IN HUMANS

How can we reconcile the clinicopathological observations in patients with the evidence obtained in experimental animal models? Although we are still unable to identify a human pathological process entirely due to abnormalities of EGC, it is likely that the significant decrease of this cell population described in several conditions (noteworthy, all characterized by constipation) may have pathophysiological implications. For instance, it could be hypothesized that the reduction of EGC, coupled to that of other cell types involved in the control of enteric motility, might have some pathogenetic role in the motor disturbances of these patients through several mechanisms. In fact, the decrease or loss of EGC might cause degeneration of enteric neurons due to the dysregulation of neurotrophic factors, in a manner similar to that observed in the animal models described above. With this respect, it is worth noting that patients with 'idiopathic' constipation and loss of EGC often have a concomitant loss of enteric neurons through increased apoptotic phenomena,[18,41] whereas in constipated patients with Alzheimer's disease (a degenerative condition of the central nervous system), EGC are preserved and the loss of enteric neurons is not due to apoptotic phenomena.[42]

Moreover, the loss of EGC in constipated patients is likely to aggravate the impaired pacemaker signals due to the decrease of ICC observed in these patients, since it has been postulated that ATP released from EGC provides a feedback system for ICC to modulate slow wave activity[43] (Figure 3).

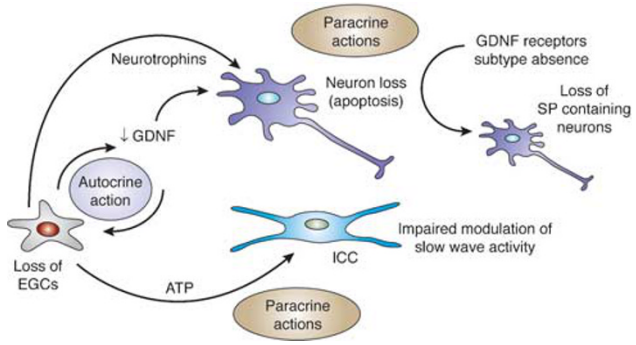

Figure 3 A novel working hypothesis on how the decrease/loss of EGC can contribute to abnormal gastrointestinal motor activity in humans.

Unfortunately, we have yet no idea on why EGC (and ICC, and enteric neurons) are decreased in such patients; to date, the only evidence in an experimental animal model is that the number of EGC decreases with age.[44] However, this influence has not been evaluated in human beings so far,[45] and it was not confirmed in our age-matched controls.[18] Moreover, we want to stress that the hypothesized damaging effect of anthraquinone laxatives on the ENS has not been confirmed with modern immunohistochemical techniques.[46] Recently, we found chromosomal abnormalities of enteric neurons and EGC in severely constipated patients undergoing surgery and hypothesized that a genetic basis might be present to explain the decrease of these elements in the ENS in a subgroup of these subjects.[47]

CONCLUSIONS

It is probably safe to state that people interested in gastrointestinal motility should look in a different perspective at EGC. In fact, from a traditional, old-fashioned view of these cells as elements having a simple mechanical support function, hence no more than mere spectators of events, it can be hypothesized that the EGC might have a more active role than previously thought in the complex organization of the motor activity of the gastrointestinal tract. Further studies are obviously needed to confirm these preliminary observations (and speculations), to establish a more precise role for EGC (which interface between the neural and the immune systems) in the motor functions of the gut and, perhaps, to take the 'idiopathic' or the 'functional' out from the label of some disorders (ie, slow transit constipation).[48] Moreover, in view of the new and exciting perspectives, such as the promises of neural stem cells transplantation[49–51] for the treatment of disorders of the peripheral and central nervous system, these studies could possibly be helpful in establishing a more targeted therapeutic approach to some motor disorders of the gastrointestinal tract.[52]

CONFLICT OF INTEREST

None.

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