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"Cell Players in Gut Motility" Review Series

Interplay among enteric neurons, interstitial cells of Cajal, resident and not resident connective tissue cells

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Guest Editor

It is well known that gut motility is regulated by the neurons of the enteric nervous system (ENS), in particular by those located within the ganglia of the myenteric (Auerbach) plexus. John Furness *et al.* [1] have amply documented that the ENS is composed of a complex network of neurons and in the last decades, utilizing a variety of sophisticated immunohistochemical, electrophysiological, pharmacological and tracing techniques, a variety of subtypes of neurons have been identified differing from each other by a combination of morphology, neurotransmitters, electrophysiology, target tissue and direction and length of axon projection. Importantly, few decades ago it has been demonstrated unequivocally that gut motility is also regulated by the so-called interstitial cells of Cajal (ICC) [2, 3], which in turn are under enteric neuron control [3–5]. The target of both neurons and ICC are the smooth muscle cells (SMC). Briefly, two cell players are the leaders in gut motility, the neurons and the ICC, being the SMC executive cells only.

The first review that will appear in this series is that of Eather Young, one of the most experts in ENS development. This review deals on the birthdating of the different neuron subtypes and the unexpected steps they follow to achieve their final specific chemical coding, underlying on the mechanisms controlling enteric neuron differentiation and development of enteric neuronal microcircuits in animals and human beings. Moreover, Eather Young stresses fascinating and not fully understood clues on the formation of the enteric neural circuits that is dependent on the generation of the specific neuronal subtypes, their specific projections and connections. Among these clues: why some neurotransmitters or their synthesizing enzymes, or combinations of neurotransmitters, which are not expressed in the mature nervous system, are expressed transiently in the developing ENS, and how neuron diversity is generated at the appropriate sites from apparently identical neural crest-derived cells. The latter is a central question in neurogastroenterology, as defects in this process are likely the cause of some paediatric motility disorders.

There is some more evidence in recent years that a co-presence of ICC and neuron defects is often correlated with a clinical outcome poorer than that in the presence of an ICC or a neuronal defect alone. As an example, delay in neuronal development or neuron immaturity that directly cause dysmotility can negatively influence the ICC number or differentiation and, consequently, also ICC functioning. In a forthcoming review, all information on the relationships between neurons defects and ICC imbalance will be reported and it will be stressed that, in the presence of a dysmotility, to elucidate its aetiology researchers must verify whether (*i*) neurons are able to synthesize and release their specific neurotransmitter, (*ii*) possess the receptors for the neurotransmitters and the hormones regulating their function and (*iii*) also express their maturity markers. Another poorly studied aspect of neuronal defects needs to be put in focus: the importance of the presence in the neurons of a perfectly differentiated and organized cytoskeleton, the apparatus that guides the neurotransmitter up to the site of release and allows clustering of the receptors for hormones and neurotransmitters at the synaptic sites.

The ICC, once negligible players in gut motility, are now blazing protagonists [3]. These cells were discovered by Cajal more than one century ago, at the end of the 1800 [2] but underwent to a booming interest in the last years only. At present, morphological, physiological and combined morpho-functional studies mainly conducted in laboratory mammals (normal and mutants) and in human beings (in health individuals and patients affected by specific gastrointestinal diseases) have proved that there are several ICC populations distributed throughout the entire gut, some playing a pacemaker role and some others being involved in neurotransmission, and probably also in a stretch receptorial function [3–5]. Recently, there has been a rapidly evolving knowledge of specific molecules that are expressed on ICC, some of which useful for ICC identification, others functionally implicated in neurotransmission, and some acting as receptors for specific molecules, such as neurotransmitters and hormones. The second

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review of this series will consider some of the molecules released by resident and not resident connective tissue cells (macrophages, mast cells and other immune cells), which may exert a beneficial or noxious influence on ICC. Morphological relationships among ICC and macrophages were already described by Lars Thuneberg and then reviewed by Mikkelsen [6]; she will now report these old findings enriched with new ones she and her coworkers personally collected as well as those reported in the literature on the cell-to-cell contacts between ICC and macrophages, mast-cells and immune cells, on the molecules these cells release and on their effects on gut motility in normal and pathological conditions; the last ones being a topic few explored notwithstanding its relevant importance for prognosis and therapies.

The more recent studies are considering the possibility of ICC plasticity, in the sense of a transient dedifferentiation or transdifferentiation of these cells or reappearance after their lost, likely due to a simple ICC recover or to an ICC new generation [7]. ICC lost by apoptosis without a significant reduction in ICC number has been demonstrated in the human colon [8], thus predicting the existence of ICC stem cells. To confirm this fantastic possibility, there is the need to identify the ICC stem cells. Very recently, my group demonstrated that in the gut, other than the ICC, and intermingled with them, there are also the so-called interstitial Cajal-like cells (ICLC), and hypothesized these cells might directly or indirectly influence gut motility, and also be the progenitors for cells of mesenchymal origin such as the ICC [9]. Studies exploring this fascinating possibility are of high importance, especially in view of a direct ICLC implication in certain disorders of gut motility and in the origin of ICC tumours (GIST); the hope is to can have in a quickly incoming future a review on this potential new player in gut motility.

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