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Editorial Open Access

Interstitial Cells of Cajal and the Promise of Single Cell Molecular Analysis

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Editorial

The interstitial cells of Cajal (ICC) are pacemaker cells organized in networks located in all layers of the intestines [1,2]. Together with the myenteric neurons and the smooth muscle cells, they comprise the machinery that controls the peristaltic movements [3,4]. However, the individual contribution of smooth muscle and ICC to the different motility patterns present throughout the GI tract is not completely described [5]. This task has proven difficult because of the overlapping mechanisms to produce motility in the gut, as well as the close embryonic and anatomic relationship of ICC and myocites, which underlies the myocyte-like differentiation of ICC after several days in culture [6] impeding the generation of pure ICC cultures and the performance of "bulk" molecular analyses.

Recent attempts to purify ICC and define their transcriptomic differences with myocites have identified genes that can be used to discern between the anatomically distinct populations of ICC and myocites at the molecular level [7,8]; unfortunately, the required FACS enrichment of ICC to obtain a transcript library hampers the identification of ICC subtypes with physiological functions. The existence of these subtypes has been suggested previously in W/W (v) mutant mice had a subpopulation of c-Kit-/Ano1+ ICC underlying the normal motor patterns termed "ripples" in the mouse colon [9]. Moreover, ICC subpopulations are being discovered in organs such as the bladder [10], epicardium [11] and in the embryonic intestine [12]. A recent publication point out the myogenic origin of the ripples in the embryonic GI tract, where they looked for c-Kit positive cells and recorded the electrical and mechanical activity of W/W (v) mice [13]; however in the same fashion as with the Ano1+ ICC in the colon, would it be reasonable to think of c-Kit- ICC precursors in the developing embryo which can replace the function of the c-Kit+ ICC ablated by the W (v) mutation? Using single cell RT-PCR in its simplest form combined with electrophysiology and immunohistochemistry we have been able to identify subpopulations of ICC based on their expression of Kv channels in the murine colon, calling for further research into this aspect of ICC biology [14].

When the GI tract suffers from pathological insults, the ICC network is disrupted and the number of ICC in the intestine diminishes. After the injury is resolved, the ICC network is restored together with normal motility in the gut [15-17]. This phenomenon raises the question of the existence of a population of cell progenitors replenishing the lost ICC. Whether this population is part of one of the layers of the ICC or comes from the trans-differentiation of fibroblasts or myocites are questions that can be addressed applying the new molecular tools for single cell analysis.

The electrical activity of ICC originates from the interplay between pumps and channels, generating their oscillating pacemaker activity. Although most of the conductances in ICC are known, there are "orphan" conductances that have not a particular gene associated to them. Such is the case of the maxi channel, which has proven elusive to identify as shown by knockdown studies performed in fibroblasts [18]. To address the identity of the maxi channel, its differential expression between ICC and myocites is and invaluable tool that harbors the potential for this particular discovery, however, the maxi channel is not present in 100% of the ICC which difficult knock-down studies. Carbachol and other agonists that elevate intracellular calcium have shown to activate the maxi channel [19] and very recent developments in spatially resolved, quantitative mRNA profiling in single cells [20-22] could detect the increase of messengers in a transcriptomic scale, allowing identification of the genetic entity –or entities- that upregulates in response to pharmacologic stimulus.

In summary, the study of ICC physiology as well as the study of GI motility can tremendously benefit from the implementation and use of the single cell molecular analysis tools available today. The accumulated knowledge in the field has produced many unique experimental settings and approaches which, combined with the use of more precise molecular tools, opens possibilities for solving questions that have stood for more than 100 years.

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