

Interstitial cells in smooth muscles

Review Series

Kenton M. Sanders*

*Department of Physiology and Cell Biology, University of Nevada School of Medicine,
Reno, NV, USA*



Smooth muscle tissues are more complicated than just contractile cells coordinated by autonomic and enteric neurons. For some time now, data have been accumulating suggesting that additional cell types, known to morphologists generally as 'interstitial cells', may have important physiological and pathophysiological functions in smooth muscle organs. The most extensively studied interstitial cells are the cells known widely as interstitial cells of Cajal (ICC) in the gastrointestinal (GI) tract. There are other types of interstitial cells, however, that include, at a minimum, resident immune cells, enteric glial cells and cells referred to as 'fibroblast-like cells' (FLC). FLC are an extremely interesting group of cells, and thanks to a new technique provided by immunolabelling with antibodies to PDGFR α [1], we know that these cells form networks as complex and extensive as ICC in GI muscles. Interstitial cells of the same general classes and similar morphologies have also been described in smooth muscle tissues outside the GI tract. However, the role of these cells in most organs is obscure.

Gastrointestinal ICC have been associated with functions, such as generation of the pacemaker activity known as electrical slow waves, active propagation of slow waves to provide coordinated contractions of thousands of smooth muscle cells that are electrically coupled to the ICC, transduction of enteric motor neurotransmitter signals, regulation of smooth muscle excitability and participation in responses to stretch. Data supporting the functional roles of ICC have been derived primarily from experiments on two species of rodents (mice and rats) that have mutations in Kit, a receptor tyrosine kinase, the function of which is essential for the development of ICC from mesenchymal precursors [2]. ICC do not develop properly in animals with loss-of-function mutations in Kit, but since total loss-of-function for Kit is lethal, experiments have been conducted on mutants retaining partial function of Kit. Thus, lesions in ICC are non-total in these animals, but there are certain areas of the gut where most ICC are missing and therefore it is possible to evaluate what functions are compromised in these tissues.

An exciting development has come from many clinical studies showing that tissues from human patients with variety of human GI motor pathologies display reduced populations of ICC. With the variety of functions attributed to ICC, it is logical to assume that

loss of or damage to these cells, or breakdown in the electrically coupled networks they form, could negatively affect GI motor function. The aetiology of many GI motor diseases remains unclear, so the possibility that ICC lesions contribute to GI motor dysfunction is an exciting new hypothesis. Of course, we are a long way from establishing cause-and-effect by providing clear demonstrations that ICC loss explains the defects in motor activity observed in GI motility disorders. This is exceedingly hard to accomplish in patients where disease has developed before it is reported. To be frank, we cannot yet say with certainty that the functions attributed to ICC from studies of rodents can be extrapolated to larger animals and humans. This will require developing techniques to lesion ICC in human muscles in culture in a manner that does not affect other cells – obviously not an easy task. Thus, much work is needed to clarify the physiological role of ICC in humans and to determine whether loss of these cells is a cause or an effect of GI pathology.

Several animal models of ICC loss have been utilized to attempt to understand the consequences of losing ICC. These include genetic models in which Kit signalling is compromised either by constitutive loss-of-function of the receptor or ligand, genetic models of type 1 and type 2 diabetes, partial bowel obstruction, bowel resection, ischaemia/reperfusion damage and infections of the GI tract. These animal models clearly demonstrate that motility defects can develop upon loss of ICC and provide strong support for the hypothesis that defects in ICC may be causative in human motility disorders. The fact that so many syndromes of motor dysfunction are associated with loss of ICC suggests that the cellular mechanisms regulating the status of these cells can be negatively impacted by a variety of circumstances. This is obviously the most interesting direction for ICC research. The only common link easily identified in several of the animal models above is inflammation. Thus, it will be necessary to determine the specific molecular signals occurring in inflammation, or other pathological factors, that result in loss of ICC.

There are currently two major hypotheses about the fate of ICC in disease; one suggests that ICC are damaged and undergo apoptosis. Another idea is that ICC do not die, but undergo cellular

*Correspondence to: Prof. Kenton M. SANDERS,
Department of Physiology and Cell Biology,

University of Nevada School of Medicine, Reno, NV 89557, USA.
E-mail: ksanders@medicine.nevada.edu

remodelling and changes in ICC phenotype that cause loss of function. It could be that ICC-like cells in other smooth muscle tissues are also affected adversely by the same disease processes that affect ICC in the GI tract. Thus, investigations into the status of ICC in disease models might provide a fruitful means of investigating the role of ICC in these muscles.

An exciting observation in animal models has been that ICC loss may not be permanent, but under some circumstances these cells might be regenerated or the process of remodelling might be reversed. Restoration of ICC has been associated with restoration of function. Thus, in such models, it may be possible to study the development of ICC lesions as a function of time, and then to carefully determine the means by which ICC repopulate damaged areas and restore function. If cell phenotype is remodelled due to pathological conditions, then the functional phenotype might be restored when the adverse conditions are remedied. A recent study described a population of cells that may serve as stem cells capable of repopulating ICC networks, and these cells may replenish the ICC population continuously [3]. Thus, it is possible that when circumstances exist that are prone to damage ICC, regeneration may not keep pace. But when the pathological circumstances are corrected, normal populations of ICC may regenerate.

This review series is designed to consolidate information obtained from recent experiments into concise concepts about the extent and function of interstitial cells in smooth muscle organs. We will review information about ICC from several smooth muscle organs and contrast the structure and function of ICC and discuss whether ICC loss is generally a feature of the pathophysiology of smooth muscle organs. The articles will

attempt to attract new investigators to the field and to help them understand the present state of the art in this field. We hope to set the stage for future experiments that might provide answers to questions of function and to understand the involvement of these cells in smooth muscle diseases.

Notes

After manuscript acceptance, newer information since appeared. The terms “TELOCYTES” and “TELOPODES”, respectively, were proposed for Interstitial Cajal-like Cells and their prolongations.

- a. **Popescu LM, Faussone-Pellegrini MS.** TELOCYTES – a case of serendipity: the winding way from Interstitial Cells of Cajal (ICC), via Interstitial Cajal-Like Cells (ICLC) to TELOCYTES. *J Cell Mol Med.* 2010; 14: 729–40.
- b. **Faussone-Pellegrini MS, Bani D.** Relationships between telocytes and cardiomyocytes during pre- and post-natal life. *J Cell Mol Med.* 2010; 14: 1061–3.
- c. **Bani D, Formigli L, Gherghiceanu M, Faussone-Pellegrini MS.** Telocytes as supporting cells for myocardial tissue organization in developing and adult heart. May 2010. In press.
- d. **Kostin S.** Myocardial telocytes: a specific new cellular entity. *J Cell Mol Med.* 2010. DOI: 10.1111/j.1582-4934.2010.01111.x.
- e. **Hashitani H, Lang RJ.** Functions of ICC-like cells in the urinary tract and male genital organs. *J Cell Mol Med.* 2010; 14: 1199–211.

For more details please visit: www.telocytes.com

References

1. **Iino S, Horiguchi K, Horiguchi S, et al.** c-Kit-negative fibroblast-like cells express platelet-derived growth factor receptor alpha in the murine gastrointestinal musculature. *Histochem Cell Biol.* 2009; 131: 691–702.
2. **Ward SM, Burns AJ, Torihashi S, et al.** Mutation of the proto-oncogene c-kit blocks development of interstitial cells and electrical rhythmicity in murine intestine. *J Physiol.* 1994; 480: 91–7.
3. **Lorincz A, Redelman D, Horváth VJ, et al.** Progenitors of interstitial cells of Cajal in the postnatal murine stomach. *Gastroenterology.* 2008; 134: 1083–93.