

## Interstitial cells of Cajal: once negligible players, now blazing protagonists

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### SUMMARY

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Cajal in 1889 described a network of anastomosing interstitial cells in the gut muscle coat and hypothesized that they were accessory primitive neurons exerting a direct regulatory effect on smooth muscle contraction. Reticularists (among them Golgi) sustained that this net was not an assembly of individual cells but a true syncytium and the foremost dissidents, such as Kolliker and Dogiel, declared they were connective tissue cells. Keith, the discoverer of the sino-atrial node, suggested that these cells "constitute a pacemaker system of the intestinal muscle". In the period 1925-1960, there were papers still discussing the role and nature of the interstitial cells. The majority of these papers, however, reflect the fight between neuronists and reticularists. Around 1960, the reality of the neurons was established by ultrastructural evidence and interstitial cells degraded to fibroblasts or Schwann cells. By 1970, electron microscopists began to pay attention to these cells (from now named ICC). Among them, I myself concluded that ICC have smooth muscle features and might well be pacemaker cells. In this period, vital methylene-blue staining followed by electron microscopy firmly identified the ICC as myoid cells and the zinc iodide-osmic acid method, used to stain neurons, was also excellent for ICC and, when applied for electron microscopy, confirmed the identity of these cells. In the meantime different ICC populations were found in the gut muscle coat with region-specific location and region-specific features. By 1980, ICC, revealing themselves as myoid cells, a nature far more exciting than former ones, underwent to a booming interest and also physiologists began to study them. At present, it has been proved that one population, distributed throughout the entire gut, plays a pacemaker role; a second population, located intramuscularly in the stomach, is involved in neurotransmission, and a third population, specific of the small intestine, is part of the intestinal stretch receptor. By 1980 up to day, the differentiating steps of these cells were studied and factors implied in their maturation during foetal life and in the maintenance of their differentiated state in adulthood were identified. There has been also a rapidly evolving knowledge of specific molecules which are expressed on ICC, some of which useful for ICC identification under light- and electron microscope with a relative facility, some functionally implicated in neurotransmission and others in metabolic pathways strictly related to specific ICC behaviours. The more recent studies are considering the possibility of an ICC plasticity, transdifferentiation and apoptosis,