INTERSTITIAL CELLS OF CAJAL: A REVIEW REGARDING MORPHOLOGY, LOCATION AND FUNCTIONAL SIGNIFICANCE IN DIFFERENT SYSTEMS OF THE BODY

Essay
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ABSTRACT

Interstitial cells of Cajal (ICC) aroused much interest among neuroanatomists at the beginning of the century. These small cells are organized into networks, found in a variety of smooth muscle tissues and are now considered by many authors to be responsible for the pacemaker activity of the gut and may have novel physiological functions. This review discusses the presence of ICCs outside the gastrointestinal tract in different systems of the body especially in urinary tract, female genital system and placenta, and the new possible roles in these organs. It is important now to discover the conditions that are responsible for ICCs loss and develop new therapies to relieve patients of this problem.

Key words: interstitial cells of Cajal – ICC – urinary system– female genital system –functional significance – c-kit.

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LIST of ABBREVIATIONS

∝-SMC:	**Alpha smooth muscle actin**
µm:	**Micro meter**
AA1:	**Anti-tryptase antibody 1**
ACK2:	**Anti-kit antibody**
ATP:	**Adenosin tri-phosphate**
CC1:	**Chymase-containing mast cell 1**
cGMP:	**Cyclic guanosine monophosphate**
C-kit:	**Stem cell factor receptor**
COX-2:	**Cyclo- oxygenase 2**
CSF:	**Colony stimulating factor**
e.g:	**For example**
E:	**Embryonic day**
ER-∝:	**Estrogen receptor alpha**
EM:	**Electron microscopy**
FITC-avidin:	**Fluorescein-isothio-cyanate labeled avidin**
FT:	**Fallopian tube**
GIST	**Gastrointestinal stromal tumor**
GIT:	**Gastrointestinal tract**
GTP:	**Guanosine Triphosphate**
Hx & E:	**Hematoxylin and eosin**
IC:	**Interstitial cell**
ICC- CM:	**Interstitial cell of Cajal – circular muscle**
ICC- DMP:	**Interstitial cell of Cajal – Deep muscular plexus**
ICC- IM:	**Interstitial cell of Cajal – Intramuscular muscle**
ICC- LM:	**Interstitial cell of Cajal –longitudinal muscle**
ICC- MY:	**Interstitial cell of Cajal – Myenteric**
ICC- SM:	**Interstitial cell of Cajal – Submucosal**
ICC- SMP:	**interstitial cell of Cajal – Submucosal plexus**
ICC:	**Interstitial cell of Cajal**
ICC-AP:	**Interstitial cell of Cajal- Auerbach's plexus**
ICC-SS:	**Interstitial cell of Cajal – Subserosa**
ICLC:	**Interstitial Cajal like cell**
IF:	**Immunofluroscence**
IGF-1:	**Insulin- like growth factor 1**
iNOS:	**Inducible nitric oxide synthase**
KDa:	**Kilo dalton**
M2 and M3:	**Muscarinic receptors**
mm:	**Mille meter**

NCLM:	**Non convential light microscope**
NK1 and NK3:	**Neurokinin receptors**
NO-cGMP:	**Nitric oxide- Cyclic guanosine monophosphate**
NOD:	**Non obese diabetic**
NOS:	**Nitric oxide synthase**
PR-A:	**Progesterone receptor A**
P2X2	**Specific purinergic receptor**
PCJ:	**Pelvi-calyceal junction**
PDGF:	**Platele derived growth factor**
Pt stain:	**Pararosaniline-toluidin blue**
RIC:	**Renal interstitial cell**
RNA:	**Ribonucleic acid**
RP:	**Renal pelvis**
SCF:	**Stem cell factor**
sGC	**Soluble guanylate cyclase**
SI/SI^d:	**Mutant phenotype mouse**
SMC:	**Smooth muscle cell**
TEM:	**Transmission electron microscopy**
UPJ:	**Uretero-pelvic junction**
UT:	**Urinary tract**
UUT:	**Upper urinary tract**
VIP 1:	**Vasoactive intestinal polypeptide receptors 1**
Vs:	**Versus**
W/W^v	**Mutant phenotype mouse**
W:	**White spotting gene**

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Historical Introduction

At the end of the nineteenth century **Ramon Cajal** observed unique cells at the terminus of the autonomic nervous system in the acini of salivary glands, in the connective tissue of the pancreas, between the glands of Lieberkuhn, in the intestinal villi and within the tunica muscularis of the gastrointestinal tract (GIT). He used methylene-blue vital staining and Golgi impregnation method. These cells had processes that formed a network that was intercalated between nerve terminals and effector cells. Although **Cajal** could not see an axon among the cytoplasmic processes of these cells, he considered them possible accessory neurons. Cajal believed that the structures he identified had a role in peripheral neurotransmission due to their anatomical locations and named them interstitial cells of Cajal (ICCs) ***(Cajal, 1911)***). As time passed due to the lack of diagnostic criteria, ICCs were considered as fibroblast, myoid cells or schwann cells**.** The embryonic origin of interstitial cells had remained a controversial issue ever since their discovery.

Later, ICCs were intimately found associated with enteric neurons. Therefore, some authors considered them to be of neural or glial nature and thus of neural crest origin. Recently, ICCs have been shown to arise from the local gut mesenchyme and not from the neural crest in both mammals and birds using the chick-quail transplantation. ICCs were identified by means of a chicken *c-kit* nucleic probe which cross-reacts with the quail *c-kit* gene product. This observation was confirmed by culturing neural tissue from chick embryo guts at embryonic day 3-4 (E3-E4) on the chorio-

allantoic membrane of chick hosts at (E7) for 7 days. The typical ICCs as defined at the EM level and by their expression of the *c-kit* receptor were developed in the gut wall in complete absence of enteric innervation ***(Young et al., 1996; Lecoin et al., 1996***).

Also the positivitiy of ICCs to the intermediate filament vimentin and the lack of neural crest markers such as S-100 protein and neurofilament are compatible with their mesodermal differentiation ***(Kindblom et al., 1998).*** So it could be concluded that the ICCs were of mesodermal origin and developed independently from enteric neurons with which they later established anatomical and functional relations.

Aim of the work

This essay aims to throw light on:

- Histological and ultrastructural identification of ICCs.
- Distribution and sites of ICCs in different systems of the body.
- Significance of these cells in some systems of body especially in the urinary tract, Fallopian tube and placenta.

Histological structure of the upper urinary tract (UUT)

Confocal and low magnification (< × 5000) electron microscopy were used to establish the general organization of the wall of the guinea-pig and human upper urinary tract ***(Szabó, 1992; Klemm et al., 1999)***.

The histological findings are; a compact layer of transitional epithelium lines the luminal surface of the uper urinary tract. Adjacent to the epithelial cells is "lamina propria "a loosely arranged layer that contained collagen, fibroblasts, blood vessels and unmyelinated axon bundles". The epithelial layer and lamina propria extended the full length of the upper urinary tract, both being relatively narrow in the renal pelvis compared to the ureter. In all regions of the upper urinary tract, the lamina propria is surrounded by a layer of smooth muscle cells of varying thickness and arrangement. In the pelvi-calyceal junction, fewer of the smooth muscle cells formed bundles, in the renal pelvis, the smooth muscle cells are more loosely arranged into bundles which are randomly oriented to each other and branch to connect with adjacent bundles forming a single plexiform muscle layer, but in the ureter formed tightly packed bundles to create a compact layer of muscle **(Fig. 1)**. Small blood vessels and axon bundles were found between bundles of smooth muscle cells in all regions. Surrounding these layers is an outer adventitia made up of connective tissue and fibroblasts and containing blood vessels, nerve bundles and lymphatic vessels.

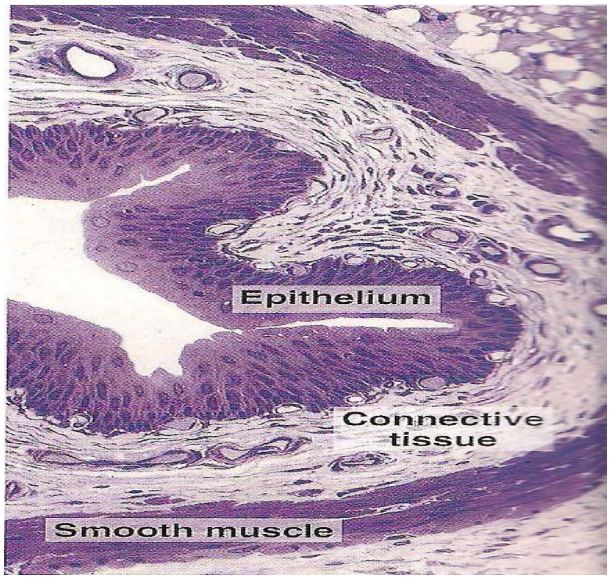


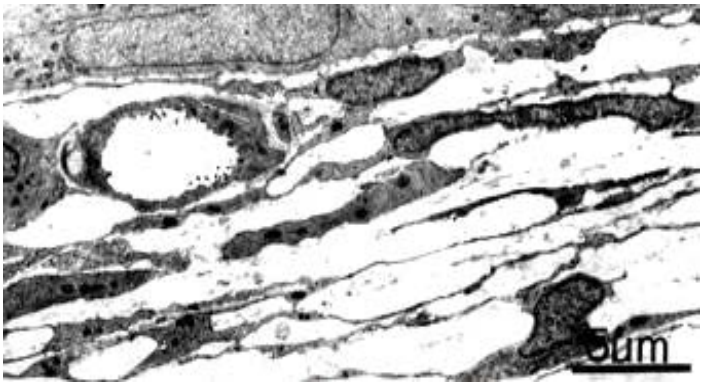
Figure (1): Photomicrograph showing the main components of the ureter which consists of an inner layer of transitional epithelium, a highly vascularized connective tissue a smooth muscle layer, and an outer layer of connective tissue (pt stain). Low magnification ***(Junqueira & Carneiro, 2003 a)***

Atypical and typical smooth muscle cells (SMC) in the UUT:

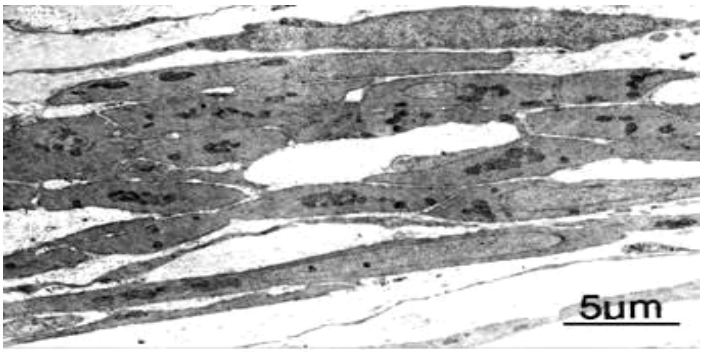
Two types of smooth muscle cells within the muscle wall of the UUT have been identified under the light and electron microscopes: 'atypical' and 'typical' SMC ***(Gosling & Dixon, 1974).***

‘Typical’ SMC are described as having long spindle shaped, contractile filament-filled cells surrounded by a continuous basal lamina and containing a large round or oval shaped nucleus and generally grouped into bundles. In the guinea pig and rat, typical SMC are defined as having more than 60% of their cell area filled with myofilaments. In the pig, ‘typical’ SMC are evident in the major calyx, renal pelvis and ureter. They represent 78–83% and more than 98% of the SMC in the proximal renal pelvis and uretero-pelvic junction (UPJ) respectively. ***Lang & Klemm, (2005)*** stated that gradual thickening of the wall of the UUT of all

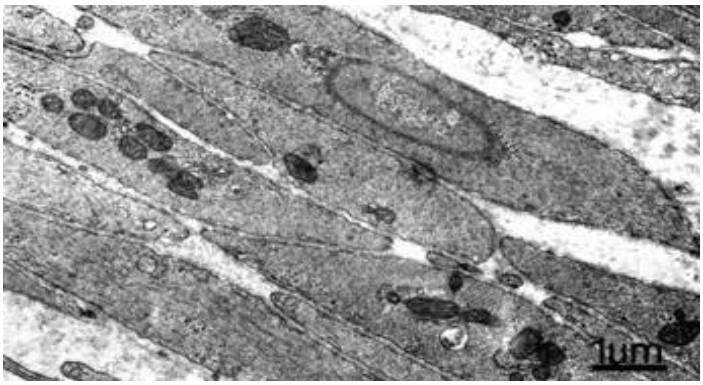
mammals with distance from the pelvi-calyceal junction indicates the increasing presence of 'typical' SMC **(Fig 2)**.



Pelvi-calyceal junction



Renal-pelvis



Ureter

Figure (2): General organization of the upper urinary tract. Low magnification electron micrographs of the rat pelvi-calceal junction, renal pelvis and ureter illustrating the gross arrangement of the smooth muscle cells within each area. Note increased number of SMCs in successive levels. ***(Lang & Klemm, 2005)***

Atypical SMC were recognized by their distinctive irregular morphology, being irregularly shaped due to the presence of many long branching processes. They have been described as long thin cells, smaller than typical smooth muscle cells observed in the upper urinary tract, have a cytoplasm that stained less well with masson trichrome, and have smaller nuclei than typical smooth muscle cells. Furthermore they give negative staining for non- specific cholinesterase. The functional significance of this enzyme is unknown although this enzyme activity used to distinguish the two types of smooth muscle cell. The contractile myofilaments within atypical SMC are arranged in bundles which are separated by large areas of cytoplasm containing Golgi cisternae, granular endoplasmic reticulum and small mitochondria occupying 3% of cell sectional area. Atypical SMC which defined are as having less than 40% of their sectional area filled with myofilaments shows areas of close apposition with each other and with typical SMC ***(Dixon & Gosling, 1982).***

These appositions are being separated by long portions of naked membrane. In uni-calyceal kidneys (mouse, dog, rat, guinea big and rabbit), **'atypical'** SMC were first described as forming a discrete layer which begins at the pelvi-calyceal junction and continues over the length of the renal pelvis and terminate at UPJ. Such atypical smooth muscle cells were never observed in the distal regions of the renal pelvis or in the ureter ***(Gosling & Dixon, 1971)***. In multi-calyceal kidneys (human and big), 'atypical' SMC alone form the muscle coat of each minor calyx. A thin sheet of loosely arranged atypical SMC extends between the minor calyces creating an open network in this area, the space between cells being filled with collagen-rich connective tissue and axon bundles ***(Dixon & Gosling, 1982).*** The observed frequency of 'atypical smooth muscle cells' in the pelvi-calyceal junction is 80 % of cells, proximal (15%) and distal (0 %)