Gastrointestinal Stromal Tumors, Interstitial Cells of Cajal and their Nomenclature

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Abstract

Currently, gastrointestinal stromal tumors (GIST) have been emphasized considerably in the literature. Following the date of the description of interstitial cells of Cajal (ICC) by Santiago Ramon y Cajal in the late 19th century, this issue has been very popular. Lately, discovery of the association of GISTs with c-Kit mutations in their development, and the significance of drugs such as imatinib, that inhibit c-Kit mutations in their treatment, has increased the interest of researchers. Our aim is to review the nomenclature about ICC and GISTs in the light of literature, to discuss the definition of GIST, which is a heterogeneous, pleomorphic tumor, in its historical progression and in the light of new data, and to suggest the naming these tumors as “tumor of Cajal”, “Cajal tumor” or “Cajal cell tumor” instead.

Keywords: Santiago Ramon y Cajal; Gastrointestinal stromal tumor (GIST); Gastrointestinal autonomic nerve tumor (GANT); Gastrointestinal pacemaker cell tumor (GIPACT); Interstitial cells of Cajal (ICC); Interstitial cells of Cajal Tumor (ICCT); Ic-Kit mutation; Tumor of Cajal; Cajal tumor; Cajal cell tumor

Introduction

Towards the end of the 19th century, Ramon y Cajal (May 1, 1842 – October 17, 1934) described the cells now referred to as the "Cajal interstitial cells" or the "Interstitial cells of Cajal" (ICC) [1,2] Santiago Ramon y Cajal, a Spanish neurohistology expert, working with a light microscope in 1892 described the specialized “interstitial neurons” found in the tubular gastrointestinal tract. His complete work on the nervous system brought him the Nobel Prize in medicine in 1906, which he shared with Camillo Golgi [3,4].

Clinical and histological researches conducted since then have established the importance of ICC.

The current developments in researches concerned gastrointestinal stromal tumor (GIST) research have enhanced the importance of the ICC. Current findings indicate that ICC cells are found outside the gastrointestinal system as well, and extragastrointestinal stromal tumors (EGIST) are encountered [4].

We are aim at placing an emphasis on the significance of ICC in GIST, at reviewing and making suggestions about the nomenclature of these tumors based on historical and current knowledge.

Interstitial Cells of Cajal

The interstitial cells of Cajal (ICC) are “pacemaker” cells that are found in the muscle layer of the intestinal wall. They facilitate the communication between enteric nervous system and the muscle layer of the intestinal wall, thereby ensuring the peristalsis (rhythmic and coordinated contraction) of the intestinal wall [5].

C-Kit positive ICC, are found in the gastrointestinal tractus, both around the myenteric plexus and in the muscularis propria. Contrary to what Cajal postulated, they are not neuronal in origin but mesodermal in origin [6].

The uncertainty regarding ICC lasted for approximately 100 years until it was finally understood that GIST arose from ICC or ICC like cells (interstitial cells of Cajal-like precursor) [7].

For the development and survival of ICC, a tyrosine kinase receptor protein called c-Kit (CD177) is required (8). Consequently, a c-Kit mutation leads to the development of GIST [8].

Gastrointestinal Stromal Tumor

GISTs develop from ICC or their stem cell-like precursors. GISTs are non-epithelial tumors. They are the most commonly seen mesenchymal tumors that constitute approximately 2% of the tumors seen in the gastrointestinal tract [9-14].

GISTs constitute nearly 60% of cases in the stomach (40%-60%), 30% of cases (20%-40%) in the small intestines (ileum and jejunum), less than 5% of cases in the duodenum, and less than 1% of cases in the mouth [14]. They are seen mostly in adults after 40 years of age, and they have a peak in the 6th and 7th decade of life [15-17].

A small percentage (%5) of GISTs forms extra gastrointestinal masses in the omentum, mesenteries, retroperitoneum, rectovaginal septum and undefined abdominal sites [17-18] and very rarely in vulva [19]. These tumors are occasionally designated as extragastrointestinal stromal tumors (EGIST) [17].

Histological Differential Diagnosis and Clinical Implications

Histologically GISTs are usually spindle cell tumors. It is striking to note that they have previously been misdiagnosed as leiomyoma, leiomyoblastoma or leiomyosarcoma for many times. Though rare,
epithelioid and pleomorphic variants have also been described [14,20,21]. The term GIST was first proposed by Mazur and Clark in 1983 [22]. In 1984, Herrera defined gastrointestinal autonomic nerve tumors (GANT) as “plexosarcoma” [23-25]. In 1998, Kindblom defined gastrointestinal “pacemaker” cell tumors as “gastrointestinal pacemaker cell tumors—GIPACT” [12].

Immunohistochemical, GIST cell are stained positively with c-Kit (95%) and CD34 [10,11]. These tumors can show a weak positivity with some other mesenchymal tumor markers as well. For this reason other mesenchymal, neuronal and neuroendocrine tumors should be in the differential diagnoses from c-Kit negative GISTs. In these cases kinase C theta and DOG1 may be helpful [26].

Currently although tyrosine kinase inhibitors such as imatinib mesylate and sunitinib malate, which arrests the growth of GISTs by inhibiting c-Kit offer a good prognosis, they are resistant to secondary c-Kit mutations. In addition, these drugs are ineffective in GISTs arising from the stem cells of the gastrointestinal tractus. Therefore it is important to differentiate tumor stem cells immunohistochemically [26].

On the other hand, isolating ICC stem cells and investigating their signal pathways along with the reason why they do not respond to drugs such as imatinib mesylate and sunitinib malate is a path with many hurdles. However, in recent years researches regarding differentiation of ICC stem cells and their identification have increased considerably. Tamás and Ordog have shown that ICC stem cells, in comparison to mature ICC have lower concentrations of c-Kit (less expression). It is for this reason that GISTs developing from ICC stem cells do not respond to drugs such as imatinib mesylate and sunitinib malate [27].

ICCs are mesodermal in origin [22]. ICC and smooth muscle cells arise from common precursor cells that express c-Kit (tyrosine kinase receptor). The fully developed smooth muscle cells do not express c-Kit, whereas ICCs continue to express c-Kit. For this reason c-Kit is a specific determinant for ICCs [28,29].

Recent studies have shown that some ICCs develop into ventrally migrating neural tubes [30].

**GIST Subtypes and their Antigenic Properties**

Immunohisto logical, GISTs are categorized as c-Kit-mutant GIST (80%), PDGFRα-mutant GIST (5-8%), “wild-type” GIST (12-15%), c-Kit-negative GIST (5%) and GIST syndromes. In adults GIST syndromes are neurofibromatosis type 1 (NF1), the Carney triad (epithelioid GIST of the stomach, extra-adrenal paraganglioma, pulmonary chondroma), familial GISTs (2008), multiple GISTs, and secondary GISTs (secondary mutations due to imatinib treatment). During imatinib treatment generally in areas I and II of c-Kit or PDGFRα tyrosine kinase, due to imatinib resistant secondary mutations, acquired drug resistance, as metastatic diseases may be seen in such cases [31].

**Conclusion**

GISTs are the most commonly seen mesenchymal tumors of the gastrointestinal tractus, they constitute approximately 2% of all gastrointestinal tumors [14]. Although initially it was believed that GISTs arose from Cajal cells or smooth muscle cells, and that they were mesodermal in origin, today it is understood that they arise from multipotent mesenchymal stem cells [31-33].

Currently GISTs are tumors that appear extensively in the scientific literature, and there are suggestions as to their nomenclature. For example Mazur and Clark defined GISTs as a group of non-epithelial heterogeneous stromal neoplasms [22].

In 1984 Herrera defined gastrointestinal autonomic nervous system tumors (GANT) as “plexosarcoma” (23-25). Recently Kindblom et al. in the light of electron microscope findings defined gastrointestinal pacemaker cell tumors (GIPACT) as “pacemaker tumors” [12] (Table 1).

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In conclusion, GISTs are pleomorphic, heterogeneous, mesodermal stromal tumors of the gastrointestinal tract. The interstitial cells of Cajal (ICC) called, they were first identified in the late 19th century by Ramon y Cajal [1-4]. In light of the advances in the field and the emergence of different viewpoints [33], I believe the time to change the nomenclature of these tumors has come, and instead of GIST calling them Cajal tumors, tumors of Cajal or Cajal cell tumors would be more inclusive and appropriate, previously as indicated in 1999 by Sircar K (ICC tumor/ICCT) [34] and in 2002 by Rhatigan (Cajal tumors, Cajal cell tumors) [35].

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I aim to make a scientifically and histologically contribution to the discussion of these topics. Currently, GIST definition is really widely used in the medical field, in the light of scientific developments, it will be more appropriate to use both Cajal tumor (tumor cells of Cajal) and GIST together, in order to avoid any confusion. In my opinion, there will still be necessary some new perspectives and discussions about this issue.

Therefore, for the clarification of this issue, there is a need for new concepts and new proposals. As a result, the definition of Cajal cell tumor (Cajal tumor) is more specific definition than that of GIST, in

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Table 1: Nomenclature about GISTs with related references; Abbreviations: GIST, gastrointestinal stromal tumor; GANT, gastrointestinal autonomic nervous system tumor; GIPACT, gastrointestinal pacemaker cell tumor
terms of histology and science though GIST is accepted as a general definition.

References