European Review for Medical and Pharmacological Sciences 2010; 14: 320-326

Small bowel nonendocrine neoplasms: current concepts and novel perspectives

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Abstract. – Although small bowel nonendocrine neoplasms are rare, their incidence has increased dramatically over the past 30 years. Small bowel malignacies can be classified depending upon their cellular origin into four principal histotypes: carcinoid tumors, adenocarcinomas, lymphomas and mesenchymal tumors. Until a few years ago, the treatment of small bowel tumors had remained relatively unchanged, with little progress in the development of effective adjuvant therapies and in the improvement of long term survival over time. Recently, the growing interest in the understanding of the mechanisms underlying carcinogenesis has offered novel insights for the diagnosis and therapy of small bowel tumors.

This review summarizes the state-of-the-art of small bowel nonendocrine tumors and the recent advancements in the knowledge of their molecular pathogenesis and cellular origin, with particular emphasis on stem cell research field.

Key Words:

Adenocarcinoma, GIST, Intestinal stem cells, Cancer stem cells.

Introduction

The small intestine represents 75% of the length and 90% of the luminal surface of the gastrointestinal (GI) system. Nonetheless, small bowel neoplasms are rare throughout the world, accounting for less than 5% of the total annual cancer incidence of the digestive system (0.4% of total cancer cases and 0.2% of cancer deaths in the U.S.). However, the incidence of small bowel tumors is increasing worldwide: from 1975 to 2000 the rates augmented by almost 50%[1]. A recent study has demonstrated that the incidence of all histologies has increased, but most of the change is a result of a more than 4-fold raise in the incidence of carcinoid tumors[2].

Although small bowel tumors are becoming more common, the treatment options have remained limited, and survival after resection of these tumors has not significantly changed over the last 20 years[2]. This lack of progress for small bowel cancers, compounded by an increasing incidence, underscores the need for the development of novel systemic treatments, based on a better understanding of the pathophysiology and molecular characteristics of these tumors. Novel insights toward the understanding of the processes underlying small bowel carcinogenesis might derive from the recent advancements in the knowledge of the molecular pathogenesis and cellular origin of tumors, with particular emphasis on the stem cell research field.

Novel Insights in Carcinogenesis: Tumor As a Stem Cell Disease?

Stemness may be defined as the capability of extensive self-maintenance and differentiation[3]. Stem Cells (SC) exist in all multicellular organisms and play a central role in tissue genesis, regeneration and homeostasis, by providing new elements to increase tissue mass during pre- and post-natal growth, and by replacing cell loss due to senescence or damage[4]. SC possess a hierarchy of potentialities: from the totipotency of the zygote and its immediate progeny, to the pluripotency of embryonic stem cells and finally to the multi/unipotency of adult SC[5]. The latter reside in every tissue, at the apex of the flow of cell differentiation; they can give rise to tissue-amplifying cells (progenitor cells), which abandon the SC compartment, proliferate and undergo further differentiation to generate mature cells, that re-

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place those lost for senescence or tissue damage. Moreover, recent studies have shown that adult SC are endowed with an unexpected plasticity, as circulating adult progenitor cells have been demonstrated to differentiate into mature cells of other tissue types[6].

SC are promising tools for treating a broad spectrum of human pathologies. This has led to the concept of Regenerative Medicine, which is based on SC potentials to facilitate the repair of injured organs. However, SC might also be involved in cancer development and progression[7]. Indeed, in the last decades, mounting evidence has suggested that cancer can be considered a *stem cell disease*, because SC might be implicated in the cellular origin and in the hierarchical organization of tumors[8].

Stem cell origin of tumors. Carcinogenesis is a multi-step process, involving the accumulation of genetic mutations which lead to the transformation of normal cells into cancer cells. Because of SC properties (self-renewal and high-clonogenicity), mutations within the SC compartment may result in cancer transformation. Presumably, fewer mutagenic changes are required to transform a SC, in which the machinery to specify and regulate self-renewal is already active, as compared to more committed progenitors, in which self-maintenance must be activated ectopically[4].

Hierarchical organization of tumors. Within established tumors, the great majority of the cancer cells cannot sustain the tumor mass, nor establish secondary lesions. Only a minority of cancer cells appear to be tumor-initiating and possess the metastatic phenotype. These cells have the property of self-renewal, can differentiate into any cell within the tumor population, and can migrate, establishing metastases. Given the similarities between tumor-initiating cells and normal SC, the tumor-initiating cells have been termed cancer stem cells (CSC). CSC mimic SC properties to sustain the growth and spread of the tumor, while eluding the intrinsic and extrinsic controls that regulate homeostasis within SC populations. The unique properties of CSC explain the failure of traditional chemotherapic strategies aimed to the reduction of tumor mass by targeting proliferating cells: CSC are usually quiescent and thus refractory to these treatments[8]. Biologically distinct populations of CSC have been identified in cancers within the hematopoietic system, breast, brain, prostate, lung, and also colon and liver[8].

Small Bowel Neoplasms: Current Concepts

The mucosal layer of the small bowel consists of absorptive, glandular, and neuroendocrine cells that line the crypts and villi. The crypt epithelium functions in cell proliferation and cell renewal. Lamina propria contains lymphocytes, macrophages, and IgA-secreting plasma cells. Mucosa-associated lymphoid cells are scattered throughout the mucosa of the small intestine, and in the ileum aggregate as macroscopic Peyer patches[9].

Under carcinogenetic stimuli, every resident cell with proliferative potential within the intestinal mucosa can give rise to tumors. Therefore, small bowel malignacies can be classified depending upon their cellular origin into four principal histotypes:

Carcinoid tumors: derive from neuroendocrine cells and represent 30-40% of small bowel cancers (main location: ileum and distal jejunum);

Adenocarcinomas: derive from enterocyte precursors and represent 30-50% of small bowel cancers, most commonly involving duodenum and proximal jejunum;

Lymphomas: represent 15-20% of small bowel cancers and are usually non-Hodgkin lymphoma of the ileum and distal jejunum;

Mesenchymal tumors: derive from GI stromal cells and represent about 10% of small bowel cancers.

Small Bowel Adenocarcinomas

Small bowel adenocarcinomas (SBA) represent approximately 25% of all small bowel neoplasms and about 30-50% of all malignant tumors in this anatomic location. Clinical manifestations of SBA are usually nonspecific and appear late in the course of the disease. Currently, the primary treatment modality for SBA remains surgery. However, because of the advanced stage at presentation, the overall prognosis for SBA is poor, with a 5-year survival rate of about 30%. The predominant location is duodenum and proximal jejunum; duodenal adenocarcinomas usually arise in the periampullary region, suggesting that biliary secretion might play a role in tumor development. Macroscopically, SBA may appears as polypoid, infiltrating, or annular-constricting lesion. Several studies have suggested that SBA originate via an adenoma-carcinoma sequence, similar to that described for colon cancer. Moreover, as described for colon cancer, SBA can de-

velops as a sporadic tumor, or in the context of genetic syndromes[10].

Sporadic SBA. Some of the target genes involved in SBA carcinogenesis have been identified[10]. In particular, as described for colon cancer, K-ras mutation seems to play an early an important role in SBA carcinogenesis and it has been reported in 14-83% of SBA. Conversely, p53 mutation seems to be a late event in both colon and small bowel tumor progression and might be critical for the transition adenoma-carcinoma. Other genes that are involved in SBA carcinogenesis include APC, β-catenin, E-cadherin, and 18q alleles, that presumably participate in the adenoma-carcinoma sequence. The risk of neoplastic transformation for an adenoma increases with villous histopathology components and higher grade of dysplasia. Several studies have demonstrated that lifestyle factors – tobacco and alcohol consumption[11], dietary habits[12] –, and bowel diseases – celiac disease and small bowel Crohn disease – significantly increase the risk of development of SBA[13,14]. Moreover, it has been proposed that the small intestinal bacterial overgrowth (SIBO) might increase the risk of SBA development, since intestinal anaerobic bacteria possess enzymes (β-glucuronidase, b-glucosidase, sulfatase, reductases, and decarboxylases), which act on various substrates (bile acids, fatty acids, etc.) and might produce carcinogenetic agents[15].

Genetic syndromes. These cases of SBA are usually characterized by familial history, younger age at diagnosis and association with other malignancies.

Most patients affected by *Familiar Adenomatous Polyposis (FAP)* develop duodenal and periampullary polyps, and only a minority (5%) develop cancer. The way in which the wild-type APC allele is inactivated (the "second hit") differs from colonic polyps, in terms of the number of 20-amino acid repeats. For periampullary neoplasias a familial segregation without correlation with a specific germline APC mutation has been noted. Downstream in the molecular pathway, mutations in K-ras have been noted in periampullary polyps[16].

Hereditary Non-Polyposis Colorectal Cancer (HNPCC), due to DNA mismatch repair disfunction germ line mutations (hMLH1and hMSH2), is associated with an increased risk of developing extra-colonic carcinomas in endometrium, pancreas, renal pelvis, stomach, liver and biliary tract, and ovary, and central nervous system gliomas, and also small intestine. SBA are located primarily in the duodenum and histopathologically their main features are: poor differentiation, prominent lymphocyte infiltration, and mucin production[17].

Finally, the *Peutz-Jeghers Syndrome* is associated with an increased risk of small bowel cancers and other malignancies (gastrointestinal tract, breast, ovarian, uterine cervical, ovarian, testicular, and lung). This disease is characterized by hamartomatous polyp formation in the GI tract, due to an autosomical dominant disorder (germ line mutation in the serine/threonine kinase gene, STK11/LKB1, a tumor suppressor gene on 19p13.3). The Peutz-Jeghers syndrome most prominent feature is the distribution of melanin pigmented lesions on lips, perioral region, hands, and buccal mucosa[18].

Non-Hodgkin Lymphomas

This tumor histotype includes a broad spectrum of lymphoproliferative neoplasms arising from B cells, T cells, and natural killer cells, that can be classified into Immunoproliferative Small Intestinal Disease (IPSID) and Enteropathy-associated T-cell Lymphoma (EATL). The latter represents about 5% of all gastrointestinal tract lymphomas and commonly arises in adults of about 60 years of age, in the proximal jejunum. From a genetic point of view, chromosomal gains of 9q, 7q, 5q, and 1q and losses of 8p, 13q, and 9p have been documented. Macroscopically, EATL might appear as multifocal GI ulcers or deceptively bland intestinal perforations. The adjacent mucosa can be thickened or completely normal. Histologically, EATL can be made of small to medium-sized cells (pleomorphic small cell lymphoma and monomorphic small to medium-sized cell lymphoma) or of large cells (pleomorphic medium and large cell lymphoma, immunoblastic lymphoma, and anaplastic large cell lymphoma)[19,20]. EATL most common clinical symptoms include abdominal pain, weight loss, malabsorption, and protein-losing enteropathy. A striking association has been reported between EATL and celiac disease[21]. In 2001 we published an epidemiologic study showing that 1.353 adult patients with active celiacy were diagnosed in 10 Italian GI Units over a period of 10 years. Of those, 60 patients (4.4%) were over-65 years old and EATL was present in 8.3% of cases[22].

Gastrointestinal Stromal Tumors (GIST)

GIST are tumors whose behavior is driven by mutations in the Kit or platelet-derived growth

factor receptor A (PDGFRA) gene, in mesenchymal cells within the gastrointestinal tract. Some use the term to describe any GI submucosal mesenchymal tumor that is not myogenic (e.g., leiomyosarcoma) or neurogenic (e.g., schwannoma) in origin. Others are more restrictive and use the term when specifically referring to GI mesenchymal tumors that express the stem cell factor receptor cKit (CD117) and/or the CD34 antigen. GIST likely originate from interstitial cells of Cajal or their CD117+/CD34+ stem cell-like precursors. Cajal cells are GI pacemakers, that mediate interactions between autonomic nervous system and smooth muscle cells, regulating GI motility and nerve function. Cytologically, GIST can be classified into 2 broad categories: spindle cell and epithelioid. Spindle cell GIST are characterized by nuclear palisading or prominent perinuclear vacuolization pattern. Epithelioid GIST may have either a solid pattern or a myxoid pattern. Although GIST may differentiate along either or both cell types, some show no significant differentiation at all. The number of mitotic figures may be used to histologically grade GIST: tumors with less than 1 mitotic figure per 50 high-powered fields (HPF) are correlated with benign behaviour, while a finding of more than 10 per 10 HPF denotes high-grade malignancy[23].

The most common presentations of GIST are acute (melena or hematemesis) or chronic (anemia) bleeding, GI obstruction, or appendicitis-like pain. Smaller GIST are often incidental findings during surgery, radiologic studies, or endoscopy. Approximately 20% to 25% of gastric and 40% to 50% of small intestinal GIST are clinically malignant. Metastases commonly develop in the abdominal cavity and liver, rarely in bones, soft tissues, and skin, and extremely rarely in lymph nodes and lungs. Less than 5% of GIST are associated with one out of three tumor syndromes: neurofibromatosis type 1 (NF1), Carney triad (gastric GIST, paraganglioma, pulmonary chondroma) and the so-called familial GIST syndrome. In sporadic GIST (80% of cases), somatic mutations in Kit or PDGFRA present only within the tumor tissue, whereas in the rarer familiar forms constitutional mutations are present in all cells of the body[24]. The first line of treatment for GIST is almost always the surgery. Radiation and chemotherapy are not typically used to treat GIST, and traditional cytotoxic chemotherapy treatment is ineffective in advanced, overtly malignant GIST. The recent approval of the targeted agent Imatimib has been a major advance in treatment (*vide infra*).

Small Bowel Neoplasms: Novel Perspectives

Like other specialized tissues in the body, the GI mucosa experiences continuous cell loss, also enhanced by the high rates of mechanical attrition. Mucosal proliferation plays a fundamental role in the maintenance of the gut integrity. In physiological conditions, cell division mirrors cell loss, both under steady-state and stressed conditions, with dynamic control mechanisms. Most of the epithelial cells are replaced every 2 to 5 days, which represents a high proliferation rate, second only to the hematopoietic system[25]. According to the unitarian hypothesis, the intestinal cell renewal depends on a small population of multipotent SC (GISC) situated within the intestinal crypts and the gastric glands. The intestinal SC are supposed to reside in the basal region of the crypts of Lieberkuhn, at the origin of the well established crypt-to-villus hierarchical migratory pattern. From their niche, intestinal SC give rise to transit-amplifying cells that migrate upwards and progressively maturate, losing their proliferative capability, to become fully-differentiated villous epithelial cells[6]. The molecular identity of GISC and the nature of signals regulating their proliferation and commitment remain largely unknown, even though the first steps towards their discovery are now beginning to be made. Indeed, the epithelial-mesenchymal cell signalling pathways regulating the GISC proliferation and differentiation are emerging, as are putative biomarkers, such as integrin subunits, Musashi-1 (Msi-1), Lgr5, Enhancer of Split Homolog-1 (Hes), side population, FoxP4, Eph, and EphA6[26].

A better comprehension of the GISC markers and of their niches is essential to achieve new insights on their biology. In the last few years great efforts have been made to evaluate the role of GISC in small intestine neoplasms genesis and organization, especially for SBA and GIST.

SBA Cellular and Molecular Pathogenesis

Gutierrez-Gonzalez et al.[27] have shown that all cells within a small intestinal crypt in humans are derived from one common stem cell. Partially-mutated crypts revealed some novel features of Paneth cell biology, suggesting that

either they are long-lived or a committed Paneth cell-specific long-lived progenitor was present. Moreover, the authors demonstrated that mutations are fixed in the small bowel by fission and this has important implications for adenoma development.

Zhu et al.[28] have successfully attempted to investigate whether cancer stem cells within SBA are the direct progeny of mutated stem cells or more mature cells that reacquire stem cell properties during tumour formation. Using an inducible Cre, nuclear LacZ reporter allele knocked into the Prom1 locus, they showed that Prom1 (CD133) is expressed in a variety of developing and adult tissues. Lineage-tracing studies in mice showed that CD133+ cells are located at the base of crypts in the small intestine, co-express Lgr5, generate the entire intestinal epithelium, and are therefore the small intestinal stem cells. Moreover, activation of endogenous Wnt signalling resulted in a gross disruption of crypt architecture and a disproportionate expansion of CD133+ cells at the crypt base. Lineage tracing demonstrated that the progeny of these cells replaced the mucosa of the entire small intestine with neoplastic tissue that was characterized by focal high-grade intraepithelial neoplasia and crypt adenoma formation.

Marsh et al.[29] have investigated the role of PTEN in small bowel homeostasis and tumorigenesis. PTEN acts as a tumor suppressor in a range of tissue types and has been implicated in the regulation of intestinal stem cells. To study PTEN function in the intestine, the authors used various conditional transgenic strategies to specifically delete this gene from the mouse intestinal epithelium: PTEN loss specifically within the adult or embryonic epithelial cell population did not affect the normal architecture or homeostasis of the epithelium. However, in the context of APC deficiency, it accelerates tumorigenesis through increased activation of Akt, leading to rapid development of adenocarcinoma. Based on these results, the Authors concluded that PTEN is redundant in otherwise normal intestinal epithelium and epithelial stem cells but, in the context of activated Wnt signaling, suppresses progression to adenocarcinoma through modulation of activated Akt levels.

GIST Cellular and Molecular Pathogenesis

Previously said, GIST are thought to originate from interstitial cells of Cajal or their CD117+/CD34+ stem cell-like precursors. The majority of GIST is associated with somatic mutations of cKit and PDGFRA. Advances in the understanding of molecular mechanisms of GIST pathogenesis have resulted in the development of a treatment that has become a model of targeted therapy in oncology: imatinib (IM) mesylate. IM is a small-molecule inhibitor against specific receptor tyrosine kinases, including cKit and PDGFRA. It has been clearly demonstrated that IM has therapeutic benefit for patients with inoperable or metastatic disease[30]. IM might be also used in the prevention of metastasis/relapse in high risk GIST[31]. In this context, it is noteworthy to report the case of a 55 years old woman who had been admitted to our hospital for acute GI bleeding. Endoscopy revealed a double gastric ulceration on a submucosal lesion. A US endoscopy was then performed, showing a hypoechogenic disomogenous mass (13 cm of diameter) from the 4th layer, with hyperechogenic areas and irregular edges. A biopsy was taken from this lesion, that proved to be formed by CD117+/CD34+ spindle cells compatible with an high risk GIST[32]. The patient underwent surgical resection of the lesion followed by 1-year of adjuvant treatment with imatimib mesylate, that successfully prevented relapses and metastases (Figure 1).

Conclusions

Although small bowel nonendocrine neoplasms are rare, their incidence has increased dramatically over the past 30 years. Until a few years ago, the treatment of these tumors had remained relatively unchanged, with little progress in the development of effective adjuvant therapies and in the improvement of long term survival over time. Recently, the growing interest in the understanding of the molecular mechanisms underlying carcinogenesis has offered novel insights for the diagnosis, molecular classification, and therapy of small bowel tumors. We have reason to believe that the future of small bowel malignancy treatment will be based on a deep knowledge of cancer cellular and molecular organization, which will lead to the discovery of novel molecularly targeted agents and to the optimization of the therapeutic strategies, to completely free the patient from the burden of disease.

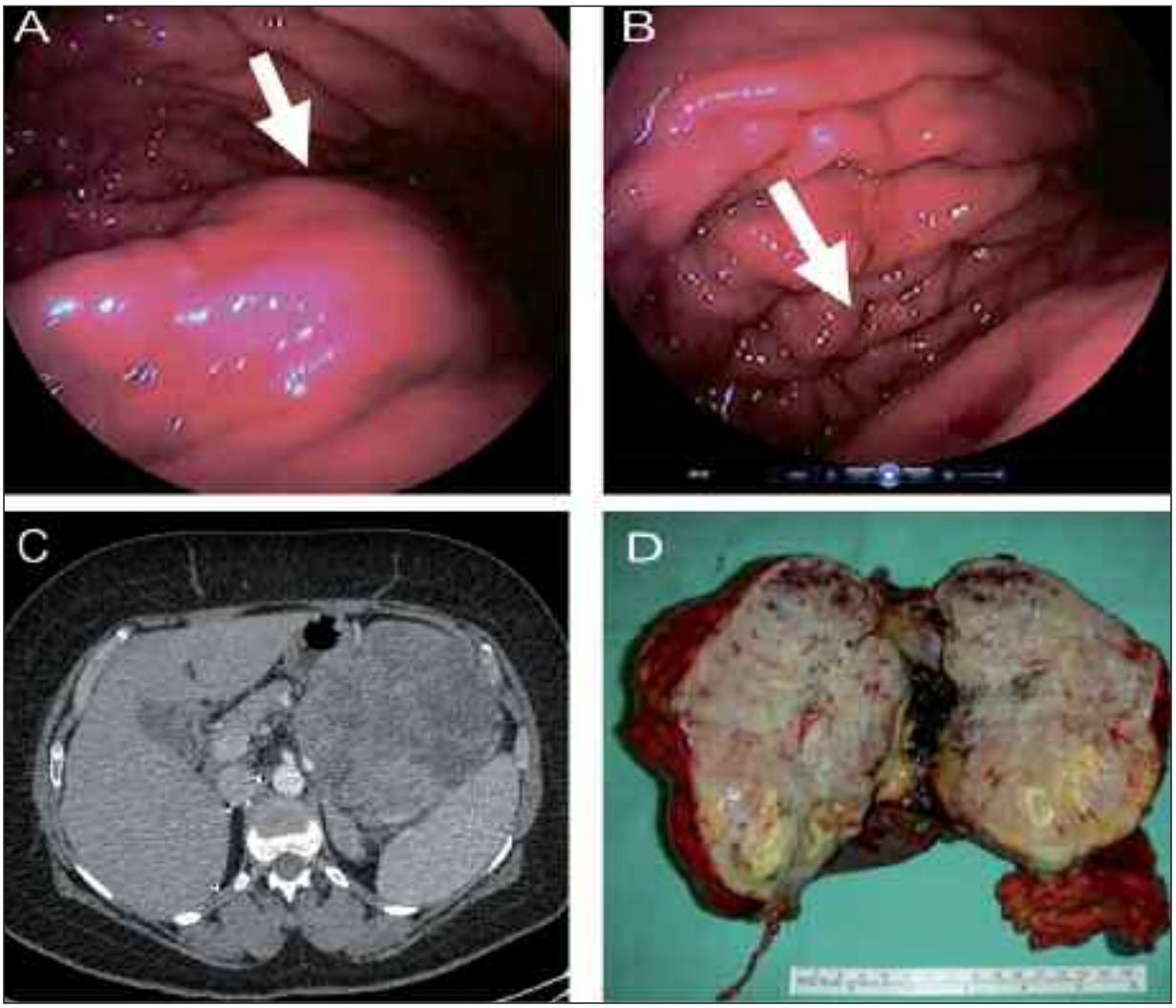

Figure 1. A case of GIST. ***A, B,*** Endoscopic features. ***C,*** CT scan. ***D,*** Surgical specimen.

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