MOLECULAR GENETICS AND PATHOLOGICAL ASPECTS OF GASTRIC CANCER

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Introduction

Gastric cancer is the second most common cause of cancer-related mortality worldwide with 700,349 deaths annually, and is the third most common malignancy worldwide[1]. It may be subdivided into 3 distinct subtypes—proximal, diffuse, and distal gastric cancer—based on histopathologic and anatomic criteria. Each subtype is associated with unique epidemiology.

The incidence of gastric adenocarcinoma has been declining for decades, but its prognosis still remains poor[2]. Epidemiological studies have shown that environmental factors such as Helicobacter pylori, diet, and smoking play a significant role in gastric carcinogenesis[3]. However, host genetics are thought to contribute as well. For example, although H. pylori infection is known to be associated with an increased risk of gastric cancer, the risk is much higher in subgroups of infected patients who have atrophic gastritis and extensive intestinal metaplasia, suggesting that host genetics influence how often precancerous lesions appear in H. pylori-infected individuals[4].

Gastric adenocarcinoma is divided into two distinct types—intestinal (well-differentiated) and diffuse undifferentiated—which have distinct morphologic appearance, epidemiology, pathogenesis, and genetic profiles[5][6]. A molecular basis for this difference is now apparent[7]. The morphologic differences are attributable to intercellular adhesion molecules, which are well preserved in intestinal-type tumors and defective in diffuse carcinomas. The main carcinogenic event in diffuse carcinomas is loss of expression of E-cadherin, a key cell surface protein for establishing intercellular connections and maintaining the organization of epithelial tissues. Biallelic inactivation of the gene encoding E-cadherin, CDH1, can occur through germline or somatic mutation, allelic imbalance...
therapy targets. These therapeutic strategies include epidermal growth factor receptor inhibitors, antiangiogenic agents, cell cycle inhibitors, apoptosis promoters, and matrix metalloproteinases inhibitors. The agents targeting the human epidermal growth factor receptor HER 2 and epidermal growth factor receptor 1 (EGFR1), vascular endothelial growth factor (VEGF), MET and regulators of cell cycle are being integrated into therapeutic studies with the goal of improving therapeutic options for this disease [8].

Gastrointestinal stromal tumor (GIST) is one of the most common mesenchymal tumors of the gastrointestinal tract, accounting for 80% of gastrointestinal mesenchymal tumors [6]. However, they are rare with respect to all GI malignancies, as they constitute only 1-3% [8]. At presentation, nearly half of malignant GISTs are metastatic, however less than a third of GISTs are classified as malignant [8]. Prior to 1998, GISTs were diagnostically problematic, being mistaken for smooth muscle tumors such as leiomyoblastomas, leiomyomas and leiomyosarcomas [9].

Cell biology and immunohistochemical studies in the late 1980s revealed that these tumors were in fact not derived from smooth muscle [9]. Rather, these studies pointed to the interstitial cells of Cajal as the cell of origin of GISTs. The interstitial cells of Cajal are the pacemaker cells of the gastrointestinal tract. They regulate intestinal motility and peristalsis and are found in-between the autonomic nervous system and the muscular wall of the GI tract. These cells have immunophenotypic and ultrastructural features of smooth muscle and neuronal cells similar to GISTs [9]. Like GISTs they stain positive by IHC for platelet-derived growth factor receptor (PDGFRA). Regardless of site of involvement, most GISTs express the CD34 antigen (70-80%) and the CD117 antigen (72-94%). A relatively new immunohistochemistry marker, DOG1, which was discovered using gene expression profiling is highly specific for GISTs. Negativity for both DOG1 and KIT has been observed in only 2.6% of GISTs of the gastrointestinal tract [11]. The term GIST is now generally used to specify a mesenchymal tumor of the gastrointestinal tract that contains either a KIT or PDGFRA driver mutation and displays a characteristic histology which includes spindle, epithelioid, and rarely pleomorphic cells [12]. KIT is a transmembrane tyrosine kinase receptor that plays an important role in the maturation of hematopoietic cells, melanocytes, and interstitial cells of Cajal [9].

The binding of stem cell factor to the extracellular domain of the receptor results in phosphorylation of several tyrosine residues and activation. Once activated KIT phosphorylates other proteins and transcription factors leading to activation of signal transduction cascades, such as the Ras/MAP kinase pathway [13]. These activated pathways ultimately lead to several cellular modifications including changes in cell adhesion, migration, KIT mutations are seen in 85% to 95% of GISTs, almost always resulting in ligand-independent activation. The mutations tend to cluster in 4 exons: exon 9 (extracellulardomain), exon 11 (intracellular juxtamembrane domain), exon 13 (split kinase domain), and exon 17 (kinase activationloop) [9].

Exon 11 mutations are the most common, representing 60% to 70% of the cases. Exon 9 mutations are present in 10% of cases and are associated with smallbowel location and a more aggressive clinical behavior.

Exon 13 and 17 mutations are rare, each representing approximately 1% of GIST cases [11]. Thus far KIT and PDGFRA mutations are thought to be mutually exclusive [17]. Approximately 5% to 10% of GISTs harbor PDGFRA mutations involving exons 12, 14, and 18 [18]. Akin to KIT mutations, PDGFRA mutations result in ligand-independent activation [9]. Almost all PDGFRA-mutant GISTs have an epithelioid morphology and are found in the stomach. CD117 expression in PDGFRA-mutant tumors is often weak and focal or entirely
negative. Approximately 5% of GISTs do not harbor either KIT or PDGFRA mutations and yet, can still be positive for CD117 by immunohistochemistry. These are known as "wild-type" GISTs. Most GISTs are sporadic, however, small percentages (less than 5%) do occur in the rare GIST associated tumor syndromes: neurofibromatosis type 1 (NF1), Carney triad, and familial GIST syndrome.

The tumors are frequently multiple, small, and indolent with a low mitotic activity. NF1 patients can go on to develop malignant GISTs, which can be confused with malignant schwannomas if immunohistochemical studies are not carried out.1 GISTs in NF1 patients likely have a different pathogenic pathway, since they rarely if ever have the c-kit and PDGFRA mutations as seen in sporadic GISTs.14

The Carney triad includes gastric GIST, paraganglioma, and pulmonary chondroma. These GISTs are usually epithelioid. They often occur in children and have a strong female predominance (85%) and the majority are indolent, even in the setting of metastatic disease.12 Rare cases of familial GIST syndrome have been reported.12 Usually, they show autosomal dominant transmission of activating KIT or PDGFRA mutations. Patients with germline KIT or PDGFRA mutations have shown Cajal cell hyperplasia and progression to discrete GISTs.15 Tumors are typically multiple with biological behavior that varies from indolent to malignant. These individuals also develop cutaneous hyperpigmentation and mastocytosis.16 A study using PCR for clonality analysis showed that diffuse Cajal cell proliferations seen in these patients are polyclonal, whereas the GIST tumors are monoclonal.16 This suggests that additional genetic alterations are required before clonal expansion and malignant transformation can occur.12

The therapeutic drug of choice for unresectable, metastatic, or recurrent GISTs is imatinib, a competitive antagonist of the ATP binding site of tyrosine kinases such as KIT, platelet growth factor receptors alpha and beta, ABL, and ABL-related gene product. It causes interruption of the downstream signaling process that leads to cellular proliferation. Ten to twenty percent of GISTs exhibit resistance to imatinib [8]. This resistance has been associated with selection of mutations that in some cases interrupt the binding site of imatinib.17

Patients with the Kit exon 9 mutations often require a higher dose of imatinib, often double the starting dose recommended for exon 11 mutants.18 Resistance is also thought to result from secondary mutations in the KIT and/or PDGFRA kinase domain.

Conclusions

The progress in tailoring new target therapies is based on more understanding of different molecular pathways of tumorigenesis and progression to metastatic disease. In the scope of new targeted cancer therapy approaches, molecular tests and new technologies that can analyze many genes simultaneously with high quality and cost-effectiveness are required to identify patients who will benefit from these therapies. The role of molecular pathology will only increase as clinicians and patients demand more novel diagnostic and prognostic information from the pathologist.

References: