TOPIC HIGHLIGHT

WJG 20th Anniversary Special Issues (8): Gastric cancer

Proteinase activated-receptors-associated signaling in the control of gastric cancer

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Abstract

Gastric cancer (GC) is the fourth most common cancer in the world and the second cause of cancer-related death. Gastric carcinogenesis is a multifactorial process, in which environmental and genetic factors interact to activate multiple intracellular signals thus leading to uncontrolled growth and survival of GC cells. One such a pathway is regulated by proteinase activated-receptors (PARs), seven transmembrane-spanning domain G protein-coupled receptors, which comprise four receptors (*i.e.*, PAR-1, PAR-2, PAR-3, and PAR-4) activated by various proteases. Both PAR-1 and PAR-2 are over-expressed on GC cells and their activation triggers and/or amplifies intracellular pathways, which sustain gastric carcinogenesis. There is also evidence that expression of either PAR-1 or PAR-2 correlates with depth of wall invasion and metastatic dissemination and inversely with the overall survival of patients. Consistently, data emerging from experimental models of GC suggest that both these receptors can be important targets for therapeutic interventions in GC patients. In contrast, PAR-4 levels are down-regulated in GC and correlate inversely with the aggressiveness of GC, thus suggesting a negative role of this receptor in the control of GC. In this article we review the available data on the expression and role of PARs in GC and discuss whether manipulation of PAR-driven signals may be useful for interfering with GC cell behavior.

Core tip: In recent years, a large body of evidence has been accumulated to support the role of proteinase activated-receptors (PARs) in the control of gastric cancer (GC). In particular, it has been demonstrated that both PAR-1 and PAR-2 may trigger intracellular signals which ultimately sustain gastric carcinogenesis, whereas the exact role of PAR-3 and PAR-4 in the initiation and progression of GC remains to be ascertained. Despite these promising and novel observations, further experimentation is needed to better characterize the mechanisms underlying the expression and function of PARs in GC and their potential as therapeutic targets.

Sedda S, Marafini I, Caruso R, Pallone F, Monteleone G. Proteinase activated-receptors-associated signaling in the control of gastric cancer. *World J Gastroenterol* 2014; 20(34): 11977-11984 Available from: URL: http://www.wjgnet.com/1007-9327/full/v20/i34/11977.htm DOI: http://dx.doi.org/10.3748/wjg.v20.i34.11977

GASTRIC CANCER

Gastric cancer (GC) is the fourth most common cancer in the world and the second cause of cancer-related death worldwide[1]. Most GCs arise in the antrum and lesser curvature of the stomach, even if tumors may involve the proximal stomach and gastroesophageal junction[2]. GC is

more frequent in men than in women. There are geographic and ethnic differences in the incidence of GC around the world, as well as trends in each population over time, suggesting that gastric carcinogenesis can be influenced by environmental, host and genetic factors[2-5]. Environmental risk factors for GC include salt and salt-preserved foods, high meat diet, nitroso compounds, obesity, smoking, *Helicobacter pylori* (*H. pylori*)-related gastritis, gastric surgery, whereas consumption of fruits, vegetables and fiber are supposed to be protective factors[6-12]. Many host-related factors can enhance GC risk, including blood group A, hypertrophic gastropathy (including Ménétrier's disease), immunodeficiency syndromes, pernicious anemia, family history of GC, chronic atrophic gastritis, and concomitant cancer syndromes (including hereditary non-polyposis colorectal cancer, familial adenomatous polyposis, Li-Fraumeni syndrome, hereditary diffuse gastric cancer and Peutz Jeghers syndrome)[13,14]. Moreover, many polymorphisms of genes involved in inflammation [interleukin (IL)-1B, IL-1RN, IL-8], detoxification of carcinogens (GSTs, CYP2E1), folate metabolism (MTHFR), intercellular adhesion (E-cadherin) and cell cycle regulation (p53) are associated with GC. In particular, polymorphisms of IL-1B gene (IL-1B-511*T) and of the IL-1 receptor antagonist gene (IL-1RN*2/*2) and homozygotes for MTHFR677T have been associated with an increased risk of GC; carriers of both IL-1B-511*T (IL-1B-511*T/*T or IL-1B-511*T/*C) and *H. pylori* virulence factors (vacAs1-, vacAm1-, and cagA-positive) have a further increased risk of GC as compared to carriers of each of these polymorphisms[15,16].

The most common type of GC is adenocarcinoma and in the subsequent paragraphs the term GC is used to indicate gastric adenocarcinoma. According to the Lauren classification two variants of gastric adenocarcinoma can be considered: the intestinal type, which is the most frequent and has a morphology similar to adenocarcinomas arising in the intestinal tract, and the diffuse type, which is less common and is characterized by a lack of intercellular adhesions and the consequent inability to form glandular structures[17]. The intestinal type of gastric adenocarcinoma is supposed to generate from a preexisting chronic gastritis, which leads to chronic atrophic gastritis, intestinal metaplasia, dysplasia and eventually to adenocarcinoma. In contrast, diffuse type GC has no clearly defined pre-cancerous lesions[18].

Most patients with GC are asymptomatic and may have an advanced incurable disease at the time of presentation. Indeed, at the time of diagnosis, approximately 50% of patients may have a disease that extends beyond loco-regional confines, and only one-half of these patients can receive a potentially curative resection[19]. Thus the overall 5-year patient survival rate is about 25%. Surgically curable early GC are usually asymptomatic and detected during screening programs, which are not widely performed, except in countries which have a very high incidence, such as Japan, Venezuela and Chile[20-22]. Weight loss and persistent abdominal pain are the most common symptoms at initial diagnosis, associated with anorexia, nausea, early satiety. Dysphagia is common in patients with cancers arising in the proximal stomach or at the esophagogastric junction. Other symptoms and signs include occult or overt gastrointestinal bleeding, the presence of a palpable abdominal mass, left supraclavicular adenopathy (Virchow's node), a periumbilical nodule (Sister Mary Joseph's node), a left axillary node (Irish node) or a mass in the cul-de-sac on rectal examination (Blumer's shelf). The most common metastatic distribution occurs in the liver, peritoneal surfaces and non-regional or distant lymph nodes. Less common is the involvement of ovaries (Krukenberg's tumor), central nervous system, bone, lung or soft tissues. Paraneoplastic manifestations include dermatologic findings such as diffuse seborrheic keratoses (sign of Leser-Trelat) and acanthosis nigricans, or microangiopathic hemolytic anemia, membranous nephropathy, hypercoagulable states (Trousseau's syndrome) and polyarteritis nodosa[23-34].

PROTEINASE-ACTIVATED RECEPTORS IN THE GASTROINTESTINAL TRACT

Proteinase-activated receptors (PARs) are seven transmembrane-spanning domain G protein-coupled receptors, comprising four receptors (*i.e.*, PAR-1, PAR-2, PAR-3, and PAR-4) and activated by various proteases. PAR activation is an irreversible phenomenon in which the protease binds to and cleaves the amino-terminal exodomain of the receptor, thus generating a new amino-terminal sequence that binds the core receptor and activates transmembrane signaling to internally located G-proteins[35]. Whereas PAR-1, -3, and -4 are activated by thrombin, PAR-2 is activated by multiple trypsin-like enzymes, such as trypsin itself and mast cell tryptase[36,37]. Moreover, PAR-1 can also be activated by plasmin, coagulation factor Xa and activated protein C. These ligands recognize and cleave the *N*-terminal exodomain of PAR-1 between Arg41 and Ser42. Following PAR activation, the G-proteins trigger a cascade of downstream events leading to engagement of integrins, cell adhesion, migration and mitogenesis[38-42]. Activation of PARs can also be triggered by proteases derived from mites, cockroach, bacteria and fungi, and this phenomenon could be relevant for the pathogenesis of PAR-associated diseases (*e.g.*, asthma and atopic dermatitis)[43,44].

PARs are expressed by epithelial cells, enteric neurons, smooth muscle cells, fibroblasts and immune cells in every region of the gastrointestinal tract and accessory organs, including the salivary glands, stomach, intestine, pancreas and liver[45-52]. Activation of PAR-2 in parotid gland acinar epithelial cells stimulates the secretion of both mucin in a non-cholinergic, non-adrenergic and tyrosine kinase dependent manner and salivary amylase through a mechanism that does not involve capsaicin-sensitive nerves[45,53].

Both PAR-1 and PAR-2 control gastric mucosal function. Activation of PAR-1 by thrombin appears to be

cytoprotective in a gastric epithelial cell line through the secretion of mucin and prostaglandin E[54], and in a rat model, where it has been implicated in the protection of the gastric mucosa from ethanol-induced damage[55]. In both studies, the protective effect was dependent upon cyclooxygenase (COX) activity. In contrast, other studies have shown that PAR-1 may be pro-inflammatory as its activation causes plasma extravasation in the stomach[56]. These differences may rely on the model used, since the former study assessed the effect of PAR-1 activation on ethanol-induced damage in rats[55] while the later one evaluated PAR-1 effects in normal mouse stomach[56].

PARs have numerous effects on intestinal epithelial function, depending upon the site of expression. Studies from cell lines have demonstrated that PAR-1 is expressed on both basolateral and apical surfaces of a duodenal crypt cell line. Activation of basolateral PAR-1 stimulates apically directed chloride secretion in a calcium-dependent manner[57]. This effect is due to Src-kinase-associated epidermal growth factor receptor (EGFR) kinase transactivation which stimulates MAP kinase-induced activation of phospholipase A2. The subsequent liberation of arachidonic acid stimulates chloride secretion via a mechanism dependent upon both COX-1 and COX-2[58]. In contrast, activation of apical PAR-1 in the same cell line activates a different Src-independent signaling pathway, which leads to apoptosis and increased permeability of epithelial monolayer[59]. PAR-2 is also expressed on intestinal epithelial cells[51,60] and its activation in isolated segments of rat jejunum stimulates chloride secretion in a manner independent of enteric nerves, suggesting that the effect is directly on the epithelium[61]. Similar results were seen following activation of PAR-2 in human colonic explants[62].

Activation of PAR-1 in submucosal secretomotor neurons of mouse colon suppresses chloride secretion[63]. PAR-2 activation on enteric nerves may change the electrophysiological properties of these neurons, either causing excitation[64] or enhancing excitability induced by other activators[65]. Furthermore PAR-2 might have a role as a mediator of neurogenic inflammation in the intestine[66] and could mediate intestinal hyperalgesia[67]. PAR-1 can also activate intestinal myofibroblasts and promote prostaglandin (PG)-E2 secretion[50]. Both PAR-1 and PAR-2 are expressed by intestinal mast cells[68,69] but their role in controlling the activity of these cell types remains to be ascertained.

In the pancreas, PAR-2 is expressed on both acinar cells[53] and duct epithelial cells[48], and its activation stimulates amylase secretion and electrolyte transport respectively. The contribution of PAR2 in the pathogenesis of pancreatic disorders is not yet fully understood even though some forms of experimental pancreatitis are characterized by activation of PAR-2[70].

Role of PARs in the control of epithelial cell proliferation and cancer

PAR-1- and PAR-2-driven signals stimulate cellular proliferation and differentiation[71] and therefore could contribute to the uncontrolled cellular growth in the various organs. Indeed, abnormal PAR-1 expression has been seen in highly invasive breast cancer, advanced-stage prostate cancer, oral squamous cell carcinoma[72] and colon cancer[73] and has been associated with pancreatic cancer cell differentiation[74] and invasion signals in kidney and colon cancer cells through activation of a Rho-A-dependent pathway[75]. Similarly, activation of PAR-2 leads to proliferation of colonic epithelial cancer cells[76] and proliferation and invasion of pancreatic cancer. PAR-2 is also over-expressed by breast, gallbladder, lung, kidney, uterine and cervical cancers and glioblastoma tumors[76-78], but it remains unclear the exact contribution of this receptor in the pathogenesis of these cancers. In contrast, PAR-2 exerts a tumor protective role in skin carcinogenesis. The role of PAR-3 and PAR-4 in human cancer is less clear, even if experimental data suggest that PAR-4 contributes to hepatocellular carcinoma cell migration, fibrotic response in the lung cancer, growth of prostatic and colonic tumor cells and hematogenous metastasis of melanoma cells[79-82].

PARS AND GASTRIC CANCER

PAR-1

Human GC are marked by elevated levels of PAR-1 and there is evidence that PAR-1 expression correlates with depth of wall invasion and peritoneal dissemination and inversely with the overall survival of patients[83]. Consistently, PAR-1 is over-expressed in MKN28, MKN74 and NUGCIII GC cell lines, whereby its activation by α-thrombin leads to nuclear factor-κB (NF-κB) activation and increased expression of downstream target genes (*e.g.* tenascin-C, Bcl-2, cIAP1, EGFR), which regulate GC cell growth, apoptosis and diffusion[84]. The factors/mechanisms which control PAR-1 expression in GC are not fully understood even though it has been demonstrated that galectin-3, a 31-kilodalton member of carbohydrate-binding proteins over-expressed in GC patients, is involved in the control of PAR-1. In particular, it was shown that silencing of galectin-3 in GC cell lines down-regulates PAR-1 and consequently reduces migration of tumor cells, while over-expression of galectin-3 increases PAR-1 expression. Analysis of basic mechanisms by which galectin-3 regulates PAR-1 revealed that galectin-3 directly interacts with Fra-1 and c-Jun in the AP-1 complex, thus promoting up-regulation of AP-1 transcriptional activity and enhanced binding of the AP-1 complex to the PAR-1 promoter. At the same time, galectin-3 increases production of matrix metalloproteinases, which could further enhance GC cells invasion by promoting both PAR-1 activation and extracellular matrix degradation[85].

PAR-1 expression is increased in the stomach of patients with *H. pylori* infection and circumstantial evidence suggests that PAR-1 may contribute to down-regulate the host response against *H. pylori*[86]. PAR-1 is encoded by a gene on chromosome 5q11.2-q13.3, which is 27 kilobase

long and has two exons separated by a large intron of 22 kilobase. Three main polymorphisms are known in PAR-1 gene: PAR-1-505 ins/del, PAR-1 IVSn-14 A/T and PAR-1-1426 C/T[87]. The first 2 polymorphisms are involved in the production and activity of PAR-1 and therefore their presence could amplify the local mucosal inflammation thereby promoting the development of *H. pylori*-associated lesions (*e.g.*, ulcers and GC)[88,89]. This hypothesis well fits with the demonstration that in Chinese subjects, PAR-1 IVSn-14 A/T allele is a risk factor for the development of GC[90]. Along the same line, studies in Caucasian, African-American, Asian and Hispanic gastric cancer patients have shown that PAR-1-505 ins/del polymorphism is a prognostic marker in patients with localized GC, whereas no association was found between PAR-1 IVSn-14 A/T and time-to-tumor recurrence or overall survival[89].

PAR-2
Like PAR-1, PAR-2 is highly expressed in primary GC tissue and PAR-2 levels correlate with the depth of tumor invasion, lymphatic involvement, early metastasis (liver metastasis and venous invasion) and poor prognosis of GC[91]. Analysis of PAR-2 in human GC tissue revealed however that additional cell types such mast-cells, vascular endothelial cells, smooth muscle cells, macrophages and stromal fibroblasts, express PAR-2[92]. One of the factors implicated in the activation of PAR-2 in GC cells is trypsin, which plays an important role in GC invasion and metastasis given its ability to catalyze the hydrolysis of proteins and promote extracellular matrix degradation. Trypsin-driven PAR-2 activation promotes GC cell growth and enhances GC cell adhesion to fibronectin via an integrin α5β1-dependent pathway[92]. The mitogenic effect of PAR-2 on GC cells is mediated by Src-dependent EGFR transactivation, which causes phosphorylation of ERK 1/2[93]. In GC, PAR-2 could also regulate angiogenesis, given that trypsin-induced PAR-2 activation in MKN28 cells enhances expression of proangiogenetic factors, such as vascular endothelial growth factor (VEGF) and COX-2, in a dose and time-dependent manner, through a mechanism which appears to be at least in part dependent on MAP kinase activation[78,94,95].

PAR-2 is also over-expressed in the *H. pylori*-colonized gastric epithelium and studies in gastric adenocarcinoma (AGS) cells showed that *H. pylori* can promote the expression and the activation of PAR-2. This later phenomenon could be either directly induced by *H. pylori* or mediated by small amount of tryptase secreted in *H. pylori*-treated AGS cell cultures[96,97].

Activation of PAR-2, but not PAR-1, in MKN45 cell lines up-regulates the expression of IL-8, a chemokine which enhances the recruitment of leukocytes to the stomach, thereby amplifying the mucosal inflammation seen in both *H. pylori*-associated gastro-duodenal ulcer and GC[98].

PAR-4
In the normal gastric mucosa PAR-4 is expressed in neck and deeper glands and its levels are markedly down-regulated in GC. In particular, the diminished levels of PAR-4 in GC associated with the clinically aggressive phenotype of this neoplasia, as PAR-4 is barely detectable in poor-differentiated GC tissue and in tumors with extensive lymph node invasion. The reason why PAR-4 is down-regulated in GC remains unknown. However, studies in AGC cell lines have shown that 5-Aza-2'-deoxycytidine, a demethylating agent, can enhance PAR-4 expression, thus implying a role for PAR-4 promoter hypermethylation in the down-regulation of the PAR-4 gene transcription in GC cells[99].

DISCUSSION
The data described in the present article underline the involvement of PAR-1 and PAR-2 in the processes that sustain gastric carcinogenesis. Although PAR-1 and PAR-2 are also up-regulated in clinical conditions which associate with GC (*i.e.*, *H. pylori* infection), the exact factors and mechanisms involved in the overexpression and activation of these two receptors in human GC are not fully understood. Further studies are therefore needed to address these issues as well as to clarify the exact mechanism(s) by which these receptors promote gastric carcinogenesis. While studies with cultured GC cell lines indicate that both PAR-1 and PAR-2 can directly activate intracellular pathways involved in the growth and diffusion of GC cells, it is conceivable that both receptors may also affect the activation and function of mucosal immune cells, which could in turn affect GC cell behavior. In contrast, preliminary evidence indicates that PAR-4 expression is down-regulated in GC, but the functional relevance of this finding remains to be ascertained. The demonstration that PAR-4 levels correlate inversely with the aggressiveness of GC suggests that this receptor can be a negative regulator of the initiation and/or progression of the neoplasia, even though studies in other systems have documented a dual role of PAR-4 in sustaining tumorigenesis[79,80,82,100-102].

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