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Mini-review

Role of gastrin peptides in carcinogenesis

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Abstract

Gastrin gene expression is upregulated in a number of pre-malignant conditions and established cancer through a variety of mechanisms. Depending on the tissue where it is expressed and the level of expression, differential processing of the polypeptide product leads to the production of different biologically active peptides. In turn, acting through the classical CCK-2R receptor, CCK-2R isoforms and alternative receptors, these peptides trigger signalling pathways which influence the expression of downstream genes that affect cell survival, angiogenesis and invasion. Here we review this network of events, highlighting the importance of cellular context for interpreting the role of gastrin peptides and a possible role for gastrin in supporting the early stage of carcinogenesis.

Keywords: Gastrin; CCK-2R; Growth; Apoptosis; Angiogenesis; Metastasis; Pre-malignant; Progression

1. General introduction

Novel, active peptides derived from the precursor peptide encoded by the gastrin gene have been purified [1] and variant isoforms of the classical gastrin/CCK-2 receptor (CCK-2R) [2–6] as well as potential gastrin receptors unrelated to CCK-2R [7], which bind one of more gastrin peptides or are constitutively active, have been identified. Binding to these receptors triggers signalling through a variety of intracellular pathways [8]. This review will focus on the factors leading to upregulation of the gastrin gene and the role of gastrin peptides in activating downstream transcriptional cascades that contribute to tumour establishment, survival and progression.

Abbreviations: CCK-2R, CCK-2 receptor; ECL, enterochromaffin-like; COX-2, cyclo-oxygenase 2; GI, gastrointestinal; EGF, epidermal growth factor; AMP, adenosine monophosphate; cAMP, cyclic AMP; TNF-α, tumour necrosis factor-α; EGFR, EGF receptor; HB-EGF, heparin binding EGF-like growth factor; IL-1β, interleukin-1 beta; T4SS, type IV secretory system; G34, gastrin-34; G17, gastrin-17; Gly-G17, glycine-extended gastrin; P-TX, pertussis toxin; PKC, protein kinase C; MAPK, mitogen-activated protein kinase; PI3K, phosphoinositide kinase 3; MEK, MAPK/ERK kinase; PKB, phosphokinase B; JAK2, Janus kinase 2; JNK, Jun N-terminal kinase; VEGF, vascular endothelial growth factor; MMP, matrix metalloproteinase; PAI-2, plasminogen activator inhibitor-2; CRE, cAMP -responsive promoter element; PKA, protein kinase A; SRE, serum response element; ODC, ornithine decarboxylase; TFF, trefoil family factors.

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2. Expression of gastrin in pre-malignant lesions and cancer

The main physiological role of gastrin is in the control of acid release within the stomach. The main site of gastrin production is within G cells of the gastric antrum. Endocrine, paracrine, neurocrine and local luminal conditions stimulate release of gastrin from secretory granules within the G cells by explosive exocytosis, leading to release into the circulation from the baso-lateral border (reviewed in [9]). Exocytosis is positively regulated by gastrin-releasing peptide which is expressed within neuronal fibres in the stomach, whilst somatostatin, produced by D cells in response to luminal acid, inhibits gastrin release from G cells [9]. Following release into the circulation, gastrin acts on enterochromaffin-like (ECL) cells in the gastric corpus/fundus stimulating release of histamine which in turn stimulates acid secretion by parietal cells [9]. Gastrin stimulation of ECL cells is via the classical gastrin receptor, CCK-2R. There is some evidence that parietal cells also express this receptor, but it is unclear at which stage in their maturity and, due to difficulties in obtaining pure cell populations whether direct stimulation of acid secretion is achieved [10].

Systemic gastrin, arising from G-cell secretion may play a role in carcinogenesis in an endocrine manner, or gastrin may be locally produced as a result of constitutive expression and secretion by cancer cells leading to paracrine or autocrine activity. Systemic hypergastrinaemia may occur through administration of proton pump inhibitors [11] or infection with *Helicobacter pylori* [12]. Interestingly, whilst hypergastrinaemia resulting from *H. pylori* infection is associated with the occurrence of gastric [13] and colorectal adenocarcinoma [14], administration of proton pump inhibitors has not been clearly linked to adenocarcinoma incidence in patients [15], in spite of the fact that they accelerate tumour progression in animal models [16]. This suggests that gastrin can promote adenocarcinoma formation but only in conjunction with other co-factors, such as a mutant cell phenotype [16] or bacterial pathogenicity factors, or through synergising with inflammatory events associated with *H. pylori* infection [17].

The second source of gastrin that can influence carcinogenesis is through endogenous production by tumour cells from where gastrin may be released into the circulation or act locally. Patients with colorectal cancer have raised serum gastrin levels compared with controls but following resection, the levels return to control values [18]. In the same study, the pre-operative serum levels of gastrin correlate with cancer stage, measured using the Dukes' classification with increasing levels of gastrin associated with more advanced lesions, especially at stages C and D in which there is involvement of local lymph nodes and metastasis. This may reflect increased requirements for gastrin as metastases become established at new sites and explains the higher rates of liver metastasis (58%) observed in patients with high gastrin serum levels (>150 mg/ml) compared with patients with lower gastrin levels (12%) [19]. Gastrin protein expression is particularly high in laterally spreading colorectal tumours categorised as granular [20] which have high expression of *k-ras* mutations and cyclo-oxygenase 2 (COX-2). Gastrin and its receptor(s) are also co-expressed in both gastric [21] and pancreatic cancer [22]. In gastric cancer, approximately 48% of cancers are gastrin positive, with higher rates associated with men and with differentiated adenocarcinoma [21]. Rates are higher in pancreatic cancer with 74% of adenocarcinomas positive [22]. Gastrin protein expression is also found in non-gastrointestinal (GI) cell lines, for example, in bronchogenic carcinomas, and is expressed at higher levels in malignant ovarian tumours compared with normal or benign ovarian lesions [23,24].

Whilst studies have mainly focused on investigating expression in adenocarcinomas, there is growing interest in the role of gastrin in the pre-malignant phase. Eighty to ninety percent of colorectal polyps are gastrin-positive [25] and gastrin expression occurs during progression to the intestinal form of gastric cancer with increasing expression from metaplasia through to high grade dysplasia [26]. Gastrin expression is also raised in the pre-malignant lesion, Barrett's metaplasia/dysplasia, compared with normal tissue from the same patients [27]. These findings suggest that this may be the stage where gastrin expression, which is normally absent in such cells, is switched on and thus further investigation of the underlying mechanism, including links to oncogene/tumour suppressor genes, and the role of gastrin in pre-malignant evolution is warranted.

3. Factors influencing expression of the gastrin gene

Since gastrin expression is upregulated in pre-malignant tissues and adenocarcinomas, the