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Cancer Letters 238 (2006) 15–29
CANCER Letters
www.elsevier.com/locate/canlet

Mini-review

Gastrin and cancer: A review

Audrey Ferrand[a,*], Timothy C. Wang[b]

[a]*IFR31, Institut Louis Bugnard, BP 84225, Unité INSERM 531, Biologie et Pathologie Digestives, 31432 TOULOUSE, Cedex 4, France*
[b]*Columbia University Medical Center, Irving Cancer Research Center, 1130 St Nicholas Avenue, Room 925, 9th Floor, New York, NY 10032, USA*

Received 7 June 2005; accepted 15 June 2005

Abstract

In 1905, a Cambridge physiologist, John Sydney Edkins, initially identified a hormone responsible of gastric acid secretion, which he called gastric secretin, or gastrin. While gastrin's role in acid secretion is now well defined, more recent studies have implicated the various isoforms of gastrin in cancer. Important advances in the last decade have included the recognition of biological activity for processing intermediates such as progastrin and the glycine-extended gastrin. Here, we give an overview of the roles of these peptides in cancer, highlighted by molecular, cellular and integrated studies on animal models for progastrin-derived peptides and their receptors.

Keywords: Gastrin; Cancer; Colon; Pancreas; Stomach; *Helicobacter pylori*

1. Background on gastrin and cancer

In 1905, 3 years after the discovery of the first hormone, secretin, by Bayliss and Starling, Edkins observed that the injection of pyloric mucosa extract induced gastric acid secretion in anesthetized rats. He named the agent responsible for this acid secretion 'gastric secretin' but later contracted the name to 'gastrin' [1,2]. Indeed, gastrin was confirmed by others to be a very potent stimulant of gastric acid secretion. However, after the work of Edkins, it took sixty years until the classic amidated gastrins, G-17 and G-34, were finally isolated and characterized by Gregory and Tracy [3]. During 1970s, the development of radioimmunoassay (RIAs) against amidated

Abbreviations ACF, aberrant crypt foci; COX, cyclo-oxygenase; ECL, enterochromaffin-like; EGF, epidermal growth factor; ERK, extracellular-signal regulated kinase; FAK, focal adhesion kinase; HDC, histidine decarboxylase; JAK, janus kinase; JNK, c-Jun N-terminal kinase; MAPK, mitogen-activated protein kinase; MEK, mitogen activated kinase/ERK kinase; MLCK, myosin light chain kinase; MMP, matrix metalloproteinase; PI 3-K, phosphatidyl inositol 3-kinase; PLC, phospholipase C; STAT, signal transducer and activator of transcription; TGF, transforming growth factor; VMAT, vesicle monoamine transporter 2.

* Corresponding author. Tel.: + 33 05 61 32 2408; fax: +33 05 32 2403.
E-mail address: audrey.ferrand@toulouse.inserm.fr (A. Ferrand).

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doi:10.1016/j.canlet.2005.06.025

gastrin peptides elucidated the nature of the Zollinger-Ellison syndrome, later renamed as the gastrinoma syndrome. These observations established a first link between gastrin and disease. Later studies suggested that gastrin was often upregulated in the setting of acid suppression and *Helicobacter pylori* infection, and a 'gastrin link' was established between *H. pylori* and peptic ulcer disease/gastric cancer.

In the 1980s and 1990s, progress in molecular biology allowed an analysis of gastrin gene expression, and led to the recognition that the gastrin gene was often upregulated in carcinomas with an accompanying increase in circulating amidated gastrin. Thus, the concept of biological activity for incompletely processed gastrins was introduced. In 1994, Seva [4] showed for the first time that a precursor peptide, glycine-extended gastrin or G-gly, previously thought to be an inactive intermediate, was able to induce cell proliferation through a distinct, but specific receptor. Other groups reported similar results for G-gly, and later investigations demonstrated activity for progastrin as well. Finally, the development of antibodies that are able to discriminate among the different gastrin peptides has confirmed the fundamental observation that gastrin gene products are expressed in a variety of epithelial cancers. However, it has largely been the development of transgenic mouse models overexpressing distinct forms of progastrin-derived peptides that have provided the strongest link between gastrin and cancer. This review will summarize these and other studies.

2. Expression and biosynthesis of gastrin peptides

Gastrin peptides are normally produced at high levels by endocrine (G) cells located in the gastric antrum and proximal duodenal mucosa, although lower levels have been detected in the colon (fetal > adult), fetal islets, pituitary and spermatozoa. In humans, the gastrin gene is 4.1 kb and contains two introns of 3041 and 130 bp [5]. Transcription of the gastrin gene gives rise to a 0.7 kb mRNA coding for a 101 amino acids precursor, known as preprogastrin [5,6] (Fig. 1). Between the endoplasmic reticulum and the Golgi apparatus, the preprohormone is converted into progastrin through cleavage of the 21 amino acids N-terminus signal peptide. Progastrin is an 80 amino acids polypeptide. During its processing in endocrine

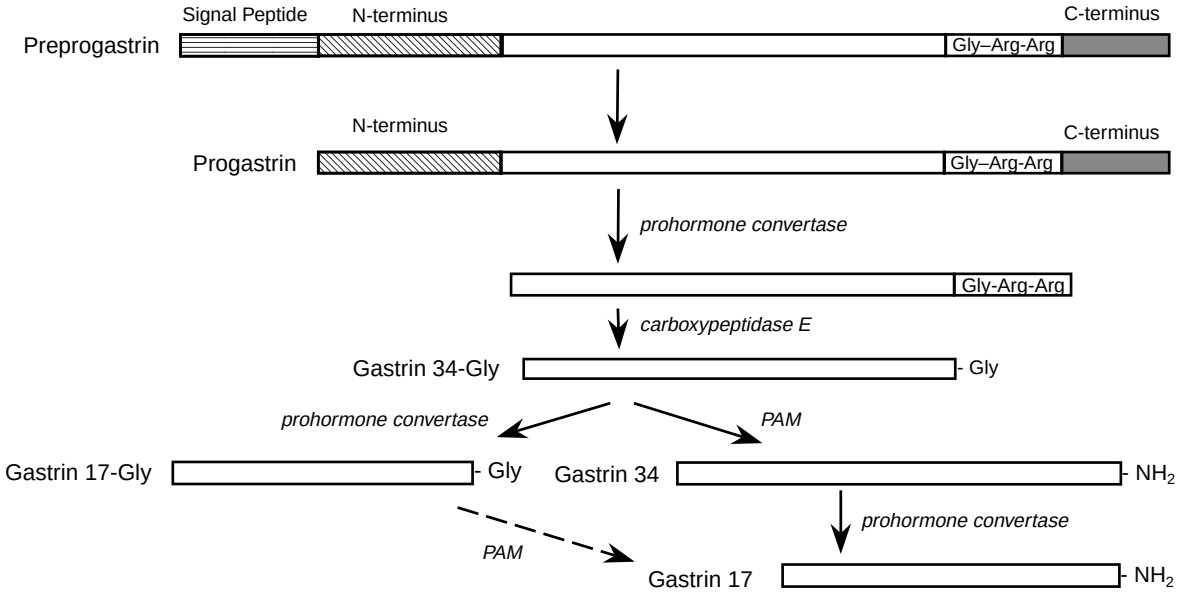

Fig. 1. Progastrin processing. PAM: peptidyl α-amidating mono-oxygenase. The dotted arrow indicates a reaction reported only by certain authors [7] Gastrin 17 sequence: Glu-Gly-Pro-Trp-Met-Glu-Glu-Glu-Glu-Glu-Ala-Tyr-Gly-Trp-Met-Asp-Phe-NH2. Gastrin 17-Gly sequence: Glu-Gly-Pro-Trp-Met-Glu-Glu-Glu-Glu-Glu-Ala-Tyr-Gly-Trp-Met-Asp-Phe-Gly.