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Gene Section
Review

GAST (gastrin)

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Identity

Other names: GAS

HGNC (Hugo): GAST

Location: 17q21.2

DNA/RNA

Note

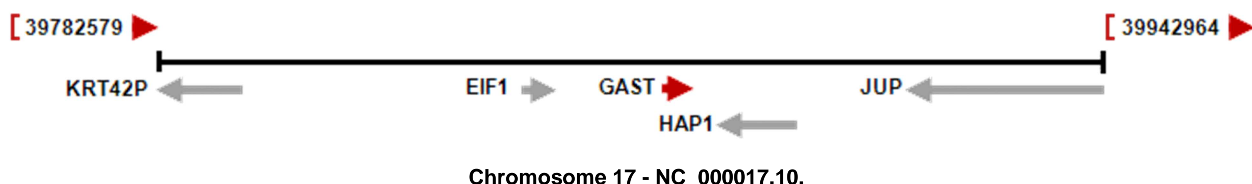
The 4.3 kb gene for human gastrin contains two introns and 3 exons that encode preprogastrin, the gastrin precursor. It is located on chromosome 17(q21), and consists of three exons that contain the code sequence for a prepropeptide of 101 amino acid residues with a calculated molecular mass of 11.4 kDa (see diagram below). The primary structure of human preprogastrin protein consists of an N-terminal 21-amino acid signal sequence followed by a spacer peptide, a bioactive domain, and finally a hexapeptide C-terminal flanking peptide (CTFP). Upon initiation of translation, the signal sequence facilitates the translocation of the elongating polypeptide into the endoplasmic reticulum (ER), where it is subsequently removed by a membrane-bound signal peptidase that cleaves the growing polypeptide chain between alanine residue 21 and serine 22 to generate the 80 amino acid peptide, progastrin. Progastrin is further processed (see protein section below) into the two principal C-terminal alpha-amidated forms of circulating gastrin generated from the proteolytic cleavage of progastrin are gastrin-17 (G17) and gastrin-34 (G34).

Protein

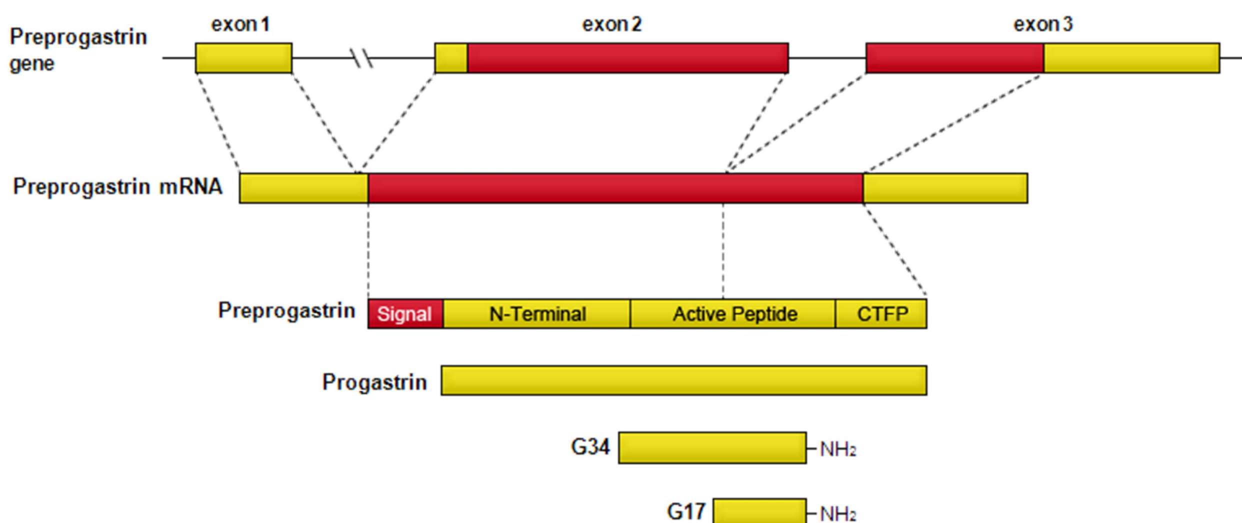
Note

It should be noted that the numbering system of critical amino acid residues involved in peptide cleavage and post-translational modifications of gastrin varies within the scientific literature. This is due to the fact that the numbering system of some authors is based on the sequence of preprogastrin, which includes the 21 amino acids of the signal peptide sequence, whereas the numbering system of others is based on the sequence of progastrin. Our description of prohormone processing will be based on the 80 amino acid peptide sequence of progastrin.

After signal peptide cleavage, progastrin undergoes additional post-translational modifications as it transits from the ER through the Golgi to the trans-Golgi network before it is sorted into immature secretory vesicles of the regulated exocytosis (secretory) pathway. The modifications include O-sulfation at tyrosine residue 66 of the propeptide by tyrosylprotein sulfotransferases and/or phosphorylation at serine 75 by a calcium-dependent casein-like kinase. Although O-sulfation is thought to occur primarily in the trans-Golgi network, a recent study provides evidence suggesting that it may continue through later compartments of the regulated secretory pathway.



Chromosome 17 - NC_000017.10.



Schematic representation of the preprogastrin gene, its mRNA, and the peptide precursor preprogastrin. The gene is transcribed as a 303 nucleotide RNA transcript and the mRNA is processed into a 101 amino acid (aa) preprohormone. The preprogastrin peptide consists of a 21-aa signal sequence, which is co-translationally cleaved, a N-terminal spacer, the active peptide and the C-terminal flanking peptide (CTFP). Progastrin is formed after removal of the signal peptide.

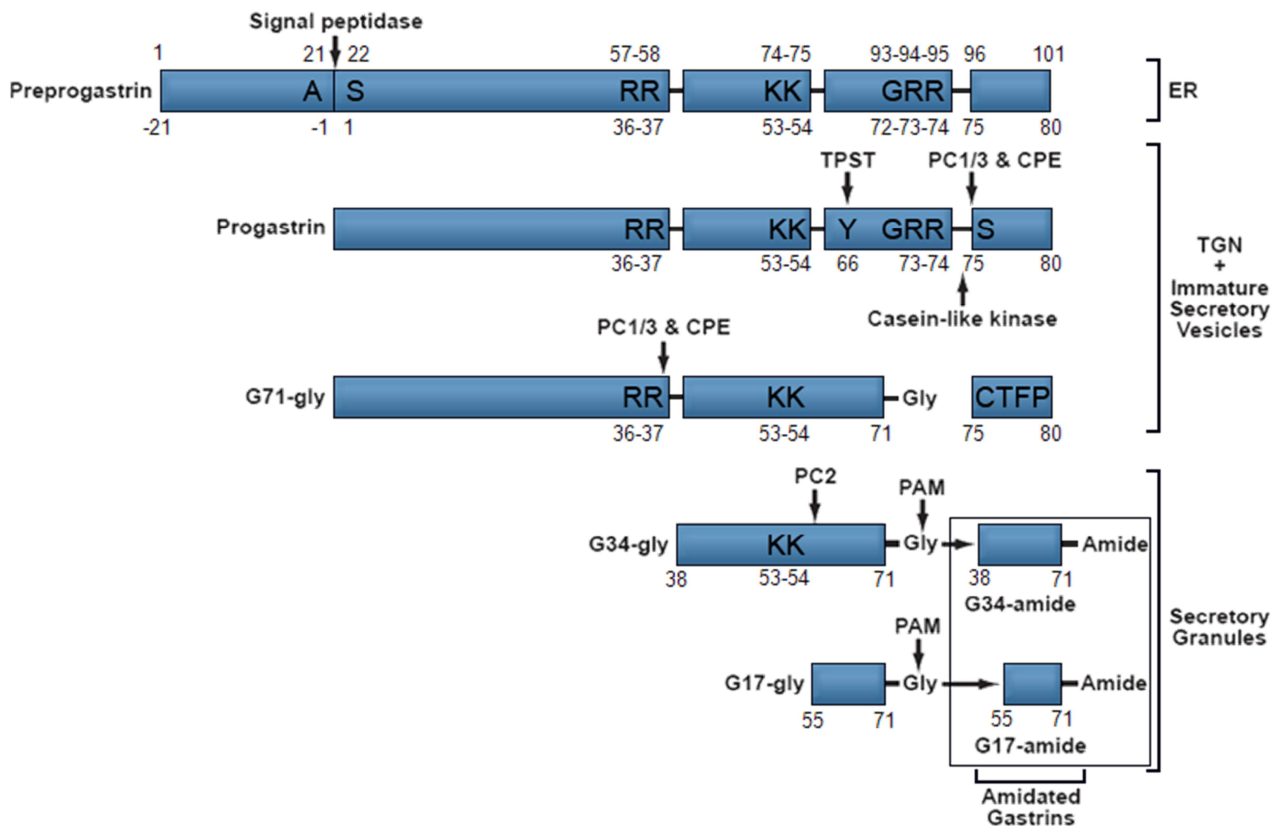
The extent of gastrin O-sulfation varies with species and cellular localization of peptide synthesis within the GI tract as well as the developmental stage of the tissues. For example, in adult humans, approximately half of the gastrin peptide synthesized in G cells of the antrum and duodenum, and released into the circulation are sulfated, whereas all of the gastrin peptide produced by the fetal pancreas appears to be sulfated. Functionally, sulfation of gastrin enhances endoproteolytic processing of progastrin, and may promote protein-protein interactions and peptide sorting between secretory pathways. However, unlike sulfation of the related peptide, cholecystokinin (CCK), sulfation of gastrin does not significantly affect its affinity for its physiologic receptor.

Phosphorylation of serine 75 of progastrin may promote proteolytic processing at the upstream arginine residues at positions 73 and 74 (arginine 73-arginine 74) releasing the C-terminal flanking peptide, and may affect the conversion of glycine-extended gastrin intermediates to mature C-terminal alpha-amidated peptides. However, since phosphorylation is not essential for progastrin processing, its biological significance remains an enigma.

Following sulfation and/or phosphorylation, progastrin exits the trans-Golgi network and enters immature granules of the regulated secretory pathway. The major proteolytic processing of progastrin to its biologically active peptides occurs in the maturing dense core secretory granules of the regulated pathway. Progastrin is cleaved by two types of proteases: endo- and exopeptidases. Endopeptidases, also known as prohormone convertases (PC), typically cleave polypeptides downstream of two adjacent basic amino acid residues at the general motif (lysine/arginine)-(X)n-(lysine/arginine), where n=0, 2, 4, or 6 and X is any amino acid, but usually not a Cysteine. PC1/3 and PC2 are involved in progastrin processing.

The two principal biologically active forms of circulating gastrin are gastrin-17 (G17) and gastrin-34 (G34). In rodent and human G cells of antrum and proximal duodenum, approximately 95% of the progastrin is processed to partially sulfated G17 (85%) and G34 (10%). Although G17 is the predominant product, G34 is the major circulating form of gastrin due to its slower rate of clearance. In both humans, the half-life of circulating G34 is approximately five times longer than that of G17.

The proteolytic processing of progastrin involves convertase-specific cleavage at three dibasic consensus sites. PC1/3 is active early in the secretory pathway in granules with a neutral pH (i.e., pH ≈ 7) and cleaves the prohormone after the arginine 36-arginine 37 and arginine 73-arginine 74 sequences, releasing the C-terminal flanking peptide, and generating G34. The post-cleavage residual basic residues are then removed by carboxypeptidase E, generating what are commonly referred to as the glycine-extended gastrins (i.e., G34-Glycine). In contrast to PC1/3, PC2 is mainly active in mature granules at an acidic pH (i.e., pH ≈ 5). Cleavage of G34-glycine by PC2 after the dibasic amino acid sequence lysine 53-lysine 54 produces G17-glycine. These glycine-extended peptides are substrates for the peptidyl-glycine alpha-amidating monooxygenase (PAM) that utilizes the glycyl residue as an amide donor to alpha-amidate the carboxyl group of the C-terminus of the peptide. The ratio of amidated gastrins to processing intermediates varies considerably across tissues and cell types. Processing intermediates are quite scarce in the gastric antrum, making up only about 1-5% of gastrin gene products, while in the duodenum the value has been reported to be as high



Processing of gastrin. The numbering system of critical amino acid residues involved in peptide cleavage and post-translational modifications of gastrin varies within the scientific literature. This is due to the fact that the numbering system of some authors is based on the sequence of preprogastrin, which includes the 21 amino acids of the signal peptide sequence, whereas the numbering system of others is based on the sequence of progastrin. The numbers at the top of the diagram represents the amino acid (aa) sequence for preprogastrin; the numbers at the bottom of the diagram represents the aa sequence for progastrin. The signal peptide is cleaved co-translationally in the rough ER by signal peptidase. In the Trans-Golgi-Network (TGN), progastrin is modified by sulfation at Tyr 66 and phosphorylation of Ser 75 by a casein-like kinase. Prohormone convertases (PC) and carboxypeptidase E (CPE) sequentially convert the prohormone to the glycine-extended forms (G71-Gly, G34-Gly, G17-Gly). Abbreviations: CTFP: C-terminal flanking peptide, TPST: tyrosyl-protein sulfotransferase, PAM: peptidyl-alpha-amidating-monooxygenase.

as 20%. Carboxyl-terminus alpha-amidation is a prerequisite for high affinity binding of gastrin to its cognate receptor, CCK2 receptor.

Mutations

Note

There are no known mutations in the gastrin gene causing a pathologic entity. Overexpression of gastrin, or aberrant expression of gastrin, have both been associated with gastric, colorectal, esophageal and pancreatic cancers.

Implicated in

Gastrinomas

Note

Gastrinomas are neuroendocrine tumors that can arise from the stomach, duodenum or pancreas. Patients with multiple endocrine neoplasia type 1 (MEN1) have a mutation in the menin gene and are at very high risk for developing gastrinomas. In patients with hypergastrinemia due to pernicious anemia or MEN1, tissue and plasma levels of PAI-2 are elevated. Gastrin directly regulates PAI-2 expression in CCK_2 receptor-positive cells, and in neighboring receptor-negative cells, by way of paracrine mediators released from the CCK_2 receptor-expressing cells. Direct regulation involves cell automous activation of CRE and AP-1 transcription factors via a PKC, Ras, Raf, RhoA, and the NFkappaB signaling pathways in CCK_2 receptor-expressing cells by gastrin. The CRE and AP-1 transcription factors, in turn, regulate expression of the genes for IL-8 and COX2. IL-8 acts through a GACAGA site via the activating signal cointegrator 1 (ASC-1) complex, whereas prostaglandins, resulting from the activation of COX2, target the Myc-associated zinc finger protein (MAZ site via the small GTPase RhoA to stimulate PAI-2 expression in adjacent CCK_2 receptor-negative cells.

Inflammation-associated carcinomas

Note

In a rat intestinal epithelial cell model, MAPKs mediate CCK_2 receptor regulation of cyclooxgenase 2 (COX-2). COX-2 is an inducible enzyme catalyzing the rate-

limiting step in prostaglandin synthesis, converting arachidonic acid to prostaglandin H2. A large body of genetic and biochemical evidence support the important role of COX-2 and the subsequent synthesis of prostaglandins in the regulation of inflammation and promotion of tumorigenesis. Gastrin has been shown to increase COX-2 expression in colorectal, gastric, and esophageal cancers.

Gastric cancer

Note

Gastric carcinogenesis is a multistep process that arises from superficial gastritis, chronic atrophic gastritis, progressing to intestinal metaplasia, dysplasia, and finally carcinoma. H. pylori is the most common known cause of chronic gastritis in humans, secretes urease, which converts urea to ammonia, and neutralizes the acid in the stomach. H. pylori initiates a host inflammatory response that is associated with the recruitment of mononuclear and polymorphonuclear leukocytes, and bone marrow-derived cells. Specific inflammatory cytokines from immune cells are required for the initiation and promotion of carcinogenesis. In addition to local inflammation, H. pylori induces the systemic elevation of serum gastrin (hypergastrinemia). The combination of achlorhydria and hypergastrinemia, induced by H. pylori infection, results in gastric bacterial overgrowth, lack of parietal cell differentiation, development of gastric metaplasia, and eventual progression to gastric carcinoma.

Colorectal cancer

Note

Gastrin and gastrin-like peptides are upregulated locally in 78% of premalignant adenomatous polyps, before the appearance of invasive carcinoma, and gastrin expression has been linked to key mutations in the initiation of colorectal carcinogenesis. When the $APC^{min-/+}$ mouse was crossed with a gastrin gene knockout mouse, the hybrid developed fewer intestinal polyps. Gastrin transcription is linked to the Wnt/beta-catenin pathway by a binding site for the transcription factor TCF4 in the gastrin promoter. Induction of the wild-type APC decreased gastrin mRNA expression, while transfection of constitutively active beta-catenin increased gastrin promoter activity.

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