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NUTS AND BOLTS

A network map of the gastrin signaling pathway

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Abbreviations

CCKAR	Cholecystokinin A receptor
CCKBR	Cholecystokinin B receptor
ECL	Enterochromaffin-like
PPI	Protein-protein interaction
PTM	Post-translational modification
HPRD	Human protein reference database
SBML	Systems biology markup language
PSI-MI	Proteomics standards initiative for molecular interaction
BioPax	Biological pathway exchange

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Introduction

Gastrin is the primary hormone that induces gastric acid secretion (Edkins 1906). In humans, the gene encoding for gastrin is located on chromosome 17q21 (Lund et al. 1986). This hormone is produced by the G-cells of the antrum of stomach as preprogastrin, which comprises of 101 amino acids and is cleaved between Ala-21 and Ser-22 to yield progastrin (Reeve et al. 1984). Progastrin is then sequentially cleaved by prohormone convertase and carboxypeptidase E to yield glycine-extended gastrins- a 35-amino acid gastrin-34-Gly (G34-Gly) or an 18-amino acid gastrin-17-Gly (G17-Gly) in endocrine cells (Varro et al. 1995; Lacourse et al. 1997). G34-Gly and G17-Gly are amidated at their carboxyl terminal groups by the enzyme peptidyl alpha-amidating monooxygenase to form amidated gastrin.

Gastrin interacts with the membrane-bound G-protein coupled cholecystokinin receptor group consisting of Cholecystokinin A receptor (CCKAR) and Cholecystokinin B receptor (CCKBR). CCKAR possesses high affinity for cholecystokinin and has a negligible affinity for gastrin (Ferrand and Wang 2006; Dufresne et al. 2006). However, CCKBR has a high affinity for gastrin and their carboxyl amidated analogues. CCKBR is expressed in the brain, smooth muscle cells, and parietal cells (Kopin et al. 1992; Berna et al. 2007). In addition to this, gastrin has also been reported to interact with annexin 2, and thereby exerts proliferation effects in gastrointestinal cancers (Singh et al. 2007; Singh 2007; Sarkar et al. 2012).

The release of gastrin is induced by gastrin-releasing peptide, a neurotransmitter which acts on its basolateral receptor in the G-cells. Binding of gastrin to CCKBR present in parietal and enterochromaffin-like (ECL) cells (Schmitz et al. 2001; Kulaksiz et al. 2000)induces gastric acid secretion by parietal cells as well as histamine release by ECL cells (Dockray et al. 2005). The released histamine reaches parietal cells by paracrine diffusion where it binds H2 receptors and induces gastric acid secretion. The secretion of gastric acid inhibits the release of gastrin hormone rendering a negative feedback control, further preventing excess acid secretion. In addition, low pH value in the stomach inhibits gastrin release through stimulating somatostatin secretion by antral D-cells (Bloom et al. 1974).

Gastrin is a well-known growth factor for the gastrointestinal tract. Gastrin stimulates proliferation of gastric mucosal cells (Hansen et al. 1976), maturation of parietal cells and enterochromaffin-like cells (Jain and Samuelson 2006), and promotes islet differentiation in the pancreas (Wang et al. 1993). It has also been shown to stimulate proliferation of gastric (Ishizuka et al. 1992) and colon cancer cells (Watson et al. 1989). Gastrin modulates invasion (Wroblewski et al. 2002), apoptosis (Przemeck et al. 2008; Todisco et al. 2001) and migration (Noble et al. 2003) in epithelial cells. Both glycine-extended gastrin and amidated gastrin have been reported to induce angiogenesis (Clarke et al. 2006; Lefranc et al. 2004). Moreover, the hypergastrinemic state has been associated with diverse physiological disorders in humans and other mammals. These include atrophic gastritis (Lehy et al. 2000), pernicious anemia (Orlando et al. 2007), excess acid secretion leading to duodenal ulcer disease in *Helicobacter pylori* infection (Berna et al. 2006; Jensen 2002; Scarpignato et al. 1996) and gastrinoma (Kloppel and Anlauf 2007).

Recently, a number of research groups have explored the feasibility of using gastrin to treat various diseases. Gastrin has been used in combination therapy with epidermal growth factor to increase beta-cell mass which reversed hyperglycemia in diabetic mice (Suarez-Pinzon et al. 2005). Gastrin-stimulated beta cell neogenesis when used in combination with glucagon-like peptide 1 in human pancreatic duct cell transplanted in immunodeficient diabetic mice (Suarez-Pinzon et al. 2008). Gastrins and their receptors have been suggested as potential targets to treat gastrointestinal and pancreatic cancers (Rengifo-Cam and Singh 2004). Gastrin has also been shown to have therapeutic promise as it inhibits the growth of cholangiocarcinoma cells by promoting apoptosis (Kanno et al. 2001).

On account of the functional significance of different natural forms of gastrin, we have assembled signaling pathway reactions induced by them upon binding to gastrin receptor(s) in different human cell types. These manually curated signaling events are made available through NetPath (http://www.netpath.org/) (Kandasamy et al. 2010) in different formats for analysis by the scientific community.

Material and methods

Annotation of gastrin signaling events

A literature survey was performed using PubMed to retrieve articles related to gastrin signaling, using the search term 'Gastrin'. Signaling events observed under the stimulation of various gastrins including progastrin, glycine-extended gastrins and amidated gastrins were identified from literature. These events were categorized into protein-protein interactions (PPIs), enzyme-catalyzed events, site-specific post-translational modifications (PTMs), changes in protein localization across subcellular compartments and plasma membrane, activation/inhibition events with respect to their activity and gene regulation events. For manual curation of these events, we considered the NetPath annotation criteria as previously described for the series of NetPath pathways (Raju et al. 2011a; Soman et al. 2013). We used the software PathBuilder, developed by our group, to manually document the signaling events (Kandasamy et al. 2009). Information pertaining to protein–protein interactions, enzyme-catalyzed

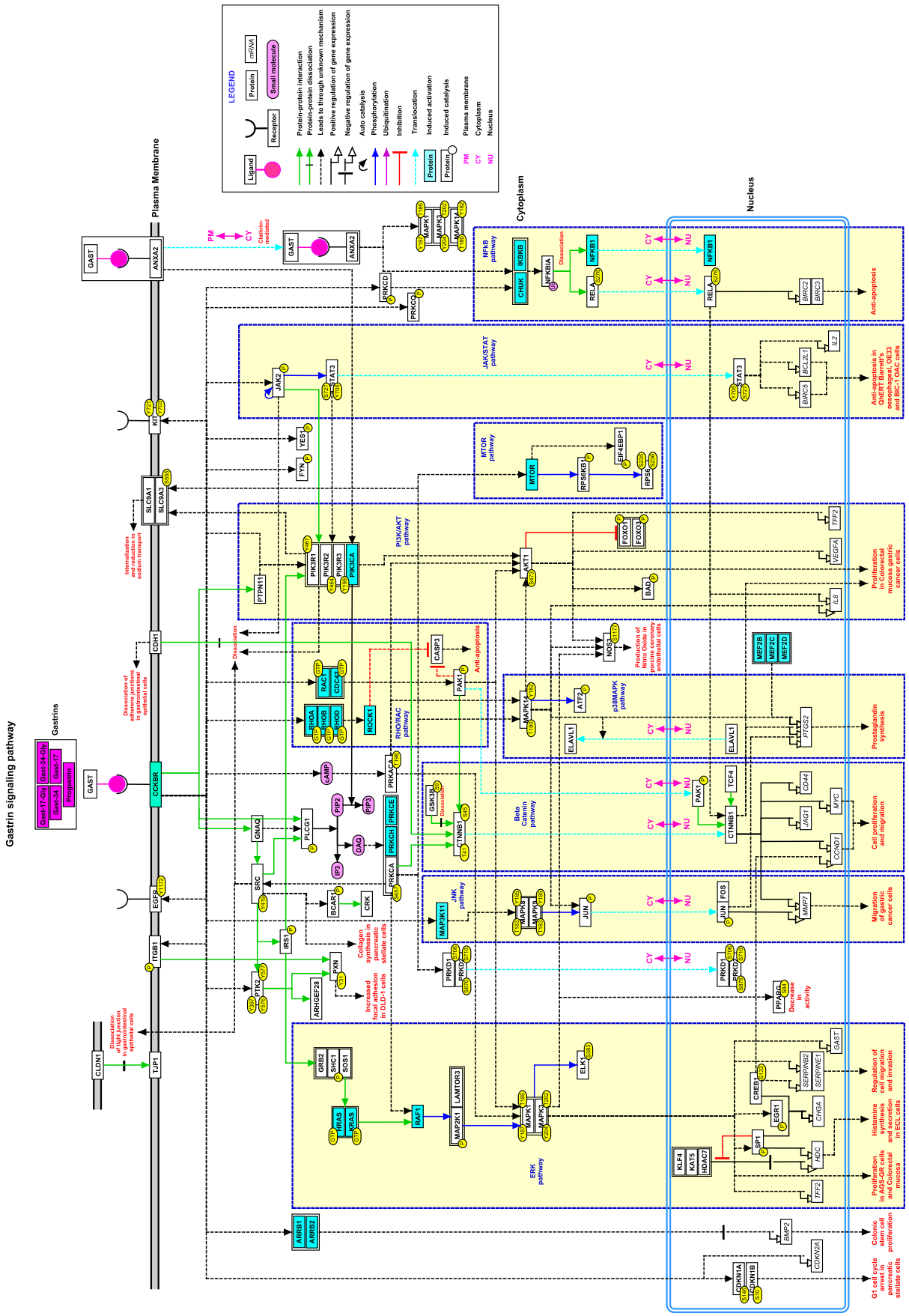

Fig. 1 Schematic representation of the gastrin signaling pathway: this map represents the reactions of the gastrin signaling pathway present in NetPath. The different types of reactions are color coded as described in the legend. The signaling pathways are also distinguished by *colored boxes*

reactions, translocation events, and the activation/inhibition reactions of protein was captured from articles studying human and other mammalian cell/cell lines. The genes that were reported to be regulated by gastrins in different human cell types were also documented. Transcription factors/co-activators or repressors of gastrin regulated genes identified specific to gastrin signaling were also included. Each reaction annotated in gastrin signaling pathway has been linked to the respective research article from which the data was extracted or curated. We have also provided a textual description for each reaction specifying the cell lines and the form(s) of gastrin used for the simulation.

Visualization of gastrin signaling pathway

A pictorial representation of the pathway reactions was drawn using PathVisio (van Iersel et al. 2008). The reactions induced by gastrins were topologically arranged from the receptors to the specific transcriptionally regulated genes and their functional role using the information obtained by inhibition, activation, silencing and/or mutation studies. The molecules regulated by multiple signaling modules such as ERK1/2, PI3K/AKT or p38MAPK were also represented. Considering the complexity in visualization of the gastrin signaling map, we also represented a simplified version of the map as described previously (Raju et al. 2011a, b).

Results and discussion

We screened over 20,000 research articles from PubMed related to gastrin/gastrin signaling and identified molecules and signaling events reported to be induced by different forms of gastrin from 550 research articles. From these articles, we documented 97 unique proteins that were experimentally identified to be participant in one or more of the 18 PPI's, 60 catalysis events or PTM's, 17 protein translocation events, 24 activation, and 1 inhibition reactions. We have also provided 46 genes (37 upregulated and 9 down regulated genes) identified to be transcriptionally regulated by gastrin(s) in different human cell types.

The gastrin pathway data can be accessed at NetPath (http://www.netpath.org/pathways?path_id=NetPath_154). A pictorial representation of the complete set of curated reactions in gastrin signaling pathway is shown in Fig. 1. The NetSlim version of the map and a detailed description of the gastrin induced signaling events are available at http://www.netpath.org/netslim/Gastrin_pathway.html. This version of the gastrin signaling pathway represents 76 molecules involved in 97 reactions based on the NetSlim criteria (Raju et al. 2011b). An interactive version of this map can be obtained by clicking on "map with citations". Each node (protein) is linked to their corresponding NetPath molecule page; and the edges (relationship among proteins) and the PTMs are linked to their respective PubMed identifiers.

The Gastrin pathway page in NetPath provides information about the pathway, the molecules participating in the pathway and the statistics for the number of molecules and reactions annotated for this pathway. Each molecule has been linked to a molecule page in NetPath which provides a brief description about the molecule. Through the molecule page, every protein captured in NetPath has also been linked to other protein-centric resources including Human Protein Reference Database (HPRD) (Prasad et al. 2009a, b), Entrez gene (Maglott et al. 2011), Swiss-Prot (Boeckmann et al. 2003) and OMIM (Hamosh et al. 2005). The gastrin signaling pathway data can be downloaded from both NetPath and NetSlim in various standard data exchange formats such as BioPAX level 3.0 (Demir et al. 2010), PSI-MI version 2.5 (Hermjakob et al. 2004) and SBML level 2.1 (Hucka et al. 2003). The gene regulation data is available in Microsoft Excel and tab-delimited formats. The pathway maps can be downloaded for customization and analysis in .gpml and .GenMAPP formats from NetSlim.

Conclusions

Gastrin is known to play an important role in gastrointestinal disorders and carcinogenesis. Channeling research on gastrin signaling could provide novel insights into diagnostic, prognostic and therapeutic strategies in gastrointestinal cancers and other disorders. Information on gastrin signaling and the pathway map designed in this study are available in different standard formats compatible with multiple pathway analysis software. Thus, the gastrin pathway data organized in this study will serve as a template for gene set enrichment and pathway analysis of data from multi-omics platforms related to these disorders.

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Conflict of interest No potential conflict of interest declared.

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