DECODE LAB

PROGASTRIN

A KEY PLAYER IN CANCER DEVELOPMENT AND A SPECIFIC BIOMARKER OF CANCER

Cancer screening is intended to reduce the number of deaths from cancer and, secondarily, to reduce the incidence of cancer. In accomplishing these goals, the ideal cancer screening test is both sensitive and specific, introduces minimal physical and psychological harm to the patient, detects disease at a preclinical phase and screens for a cancer that has a well-defined treatment.

Most tumor markers are made by normal cells as well as by cancer cells; however, they are produced at much higher levels in cancerous conditions.

Furthermore, there are some limitations to the use of tumor markers:

- Noncancerous conditions can cause the levels of certain tumor markers to increase.
- Not everyone with a particular type of cancer will have a higher level of a tumor marker associated with that cancer.
- Tumor markers have not been identified for every type of cancer.
- Low specificity and low sensitivity, especially at early stages.

Finally, no “universal” tumor marker that can detect any type of cancer has been found so fare.

After ten years of Research & Development, ECS Screening identified Progastrin as a potential universal tumor marker present in the blood of patient and ECS Screening developed an ELISA sandwich test able to detect Progastrin in the blood at high sensitivity and specificity.

A

GASTRIN

As too much or too little acid can cause disease, gastric acid secretion is tightly regulated by a highly coordinated interaction among a variety of effector, sensory, and feedback pathways. The main hormonal and paracrine stimulants of acid secretion are gastrin, released from pyloric G cells; and histamine, released from oxyntic ECL cells (Schubert et al, current opinion in gastroenterology, 2014). Especially, gastrin is released into the bloodstream when food enters the stomach.

Gastrin, mainly present in G cells of the gastric antrum and also in the duodenum, was discovered in 1905 and its structure determined in 1964. Gastrin is synthesized as a 101 amino acid precursor, preprogastrin that, via peptidases and convertases, is processed to Progastrin to yield glycine-extended gastrins (G-Gly) (Dimaline et al, J physiol, 2014) (Fig. 1). Additional processing via peptidyl-glycine α-amidating monooxygenase yields its carboxy terminus amidated forms, mainly G17-NH2 and G34-NH2.

Of note Progastrin and Progastrin-releasing peptide (Pro-GRP) are two completely different proteins even though they share the word «Progastrin». Pro-GRP is the precursor for Gastrin-releasing peptide (GRP), a gut hormone that stimulates the release of gastrin in the stomach.

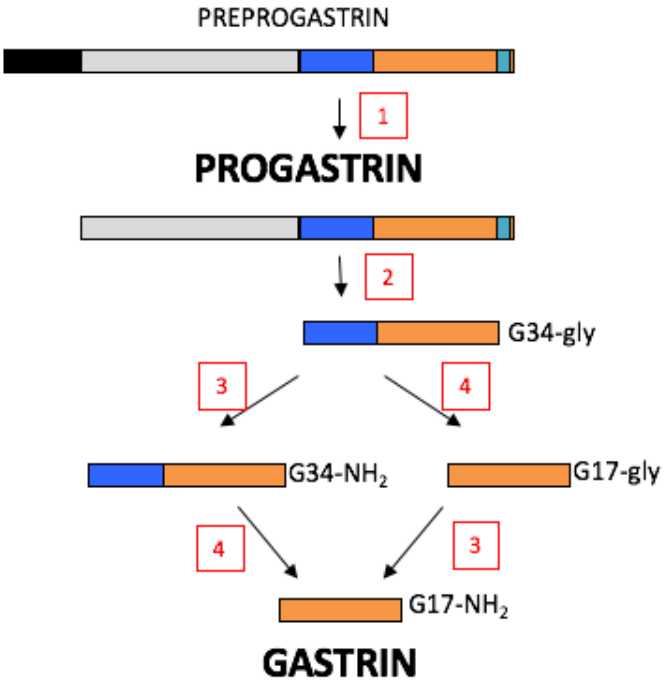


Figure 1

Processing of the products of GAST gene.

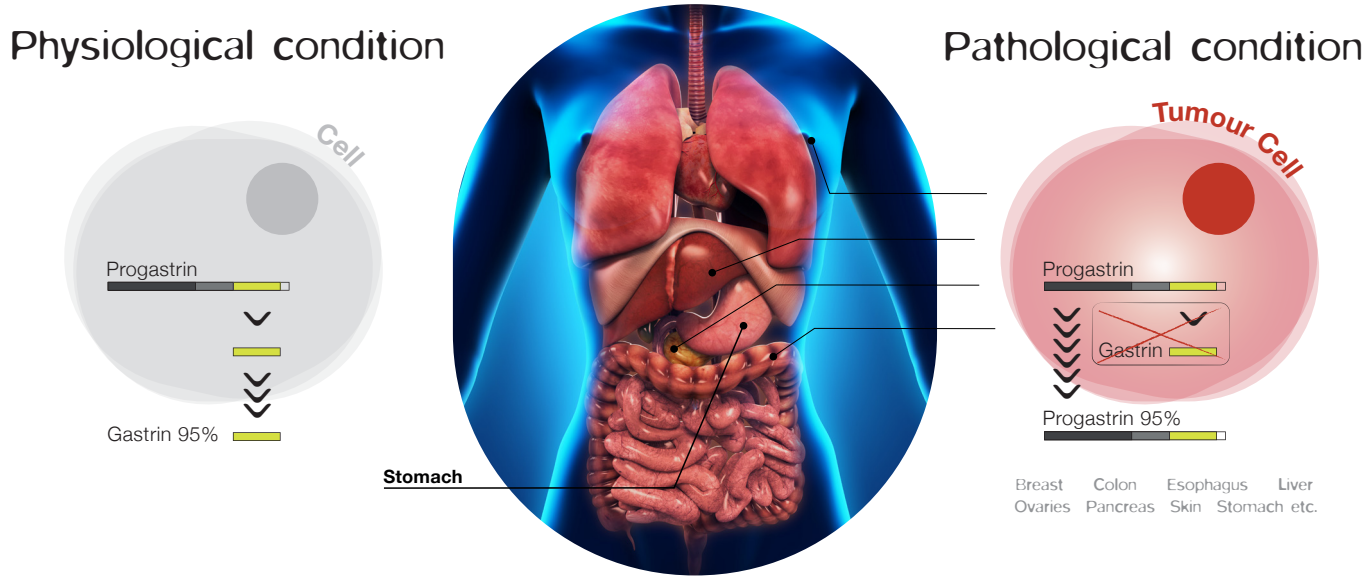
Numbers in red indicate the processing enzymes:

1. signal peptidase,
2. prohormone convertase and carboxypeptidase E,
3. amidating enzyme
4. prohormone convertase

Adapted from Stepan et al , American Journal of Physiology (2001)

B

PROGASTRIN



Other than during digestion, healthy people have no progastrin in their blood*.

**In the stomach, cells produce progastrin, which is maturated into gastrin. During digestion 95% of progastrin is released as gastrin from the cell. A very small amount of progastrin is released as progastrin*

Progastrin is released from the tumoral cell at the beginning of the tumorigenicity and becomes an early marker**

***In the tumour cells, progastrin is not maturated into gastrin. Progastrin is consequently released from the tumoral cell and becomes an early marker. This process is independant of digestion*

In 1993, Van Solinge and collaborators showed for the first time a direct link between cancer and progastrin secretion (Van soling et al, Gastroenterology, 1993). Since then, several research groups in the world studied the role of progastrin in cancer.

The main results are summarized in the following table:

Activity	Publication
Is required for cancer cells proliferation	Pannequin et al, gastroenterology 2007
Modulates the balance proliferation/apoptosis	Pannequin et al, gastroenterology 2007
Is a pro-angiogenic factor in colorectal cancer	Najib et al, Oncogene 2014
Modulates cancer stem cells markers and frequency	Giraud et al, Cancer research 2016
Modulates the WNT pathway	Pannequin et al, gastroenterology 2007
Modulates the NOTCH pathway	Pannequin et al, Cancer research 2009
Modulates the PI3K/AKT pathway	Pannequin et al, gastroenterology 2007

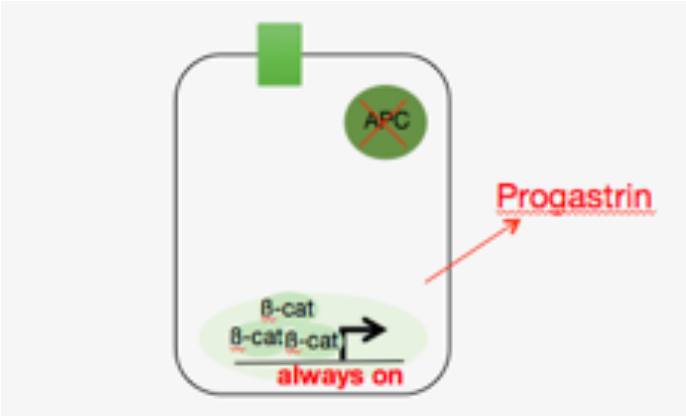
WNT PATHWAY

The gene GAST coding for progastrin is a direct target gene of the WNT/ß-catenin oncogenic pathway (Koh et al, JCI, 2000; Pannequin et al Gastroenterology, 2007). The activation of this oncogenic pathway is an early event in cancer development.

Normal cells

Tunable activation of the Wnt/β-catenin target genes

Cancer cells



Constituvely activated Wnt/β-catenin pathway leading to continuous expression and secretion of Progastrin

Chronic activation of the WNT/ß-catenin oncogenic pathway occurs in almost all human solid tumors (e.g colorectal, liver, breast, ovarian cancers) and is a central mechanism in cancer biology (Waisberg et al, World J hepatho 2016; Yang et al, Laboratory investigation, 2016).

- Induction of cellular proliferation and blocking of differentiation leading to primary tumor growth.
- Induction of epithelial to mesenchymal transition leading to metastasis formation.
- Regulation of cancer stem cell pathways leading to chemoresistance and relapse.