A Review on Molecular Factors Affecting Stomach Development

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Abstract: Stomach as a highly important portion of the GIT which is responsible for storage, digestion of food, immune defense, and hormonal organization of metabolic homeostasis; it originates from posterior foregut. The transcription factors such as Forkhead Box A (Foxa1/2/3), Gata Binding Protein (Gata4/6), Hnf1 Homeobox B (Hnf1b), and Sry- Box Transcription Factor 2 (Sox2) have a crucial role in gastric specification. Endodermal foregut patterning and regionalization, mesenchymal differentiation and cell lineage specification of stomach are affected by many essential factors such as Retinoic acid (RA) signalling, Wingless-related integration site (Wnt) signals, fibroblast growth factor (FGF) signals, Bone morphogenetic protein (*BMP*) signalling, sonic hedgehog (*Shh*) signalling and GATA family .There is a lack for understanding the organ lineage relationships and lineage-specific markers during stomach development and differentiation. The objectives of this review are to focus on the normal development and the mesenchymal differentiation of the stomach and to highlight the relatively limited information we have about genes and transcription factors associated with stomach specification, regionalization, and differentiation of component cell lineages.

Keywords: Stomach, Specification, Regionalization, Transcription Factor, Lineage-specific markers, Genes, Cell lineage specification.

INTRODUCTION

The objectives of this review are to focus on the normal development and the mesenchymal differentiation of the stomach and to highlight the relatively limited information we have about genes and transcription factors associated with stomach specification, regionalization, and differentiation of component cell lineages.

Gastro-intestinal tract (GIT) is a part of the digestive system and include a set of hollow organs which are esophagus, stomach, small intestines and large intestines, associated glands such as the liver and pancreas are bound to the digestive tract by excretory ducts [1]. Stomach is a curved muscular portion of the proximal GIT which is responsible for storage, digestion of food, immune defense, and hormonal organization of metabolic homeostasis [2,3].

The GIT originates as endodermal tube covered by the splanchnic mesoderm, the stomach lining epithelium, secretory and ductal cells of glands are derived from the endoderm, whereas the lamina propria which composed of connective tissue and muscularis mucosa as well the underlying submucosa containing adipose tissues, blood vessels and lymphatics constituents and the muscularis externa are obtained from the mesoderm, while the enteric ganglia is ectodermal in origin [1,4-6]. Consequently, these tissues arranged into four main histological layers: mucosa, submucosa, muscularis externa and serosa [7].

The primitive gut is formed through cephalocaudal and lateral folding of the embryo, in which a portion of the endoderm-lined yolk sac cavity is incorporated in the embryo, it includes four main parts, pharyngeal gut, foregut, midgut, and hindgut [1]. Therefore, the embryonic stomach originates from posterior foregut, which lies caudal to pharyngeal tube and extends as far caudally as the liver evolution; a complex order of epithelial-mesenchymal interactions is in charge of promoting the gastric fate [1,3].

The stomach as a derivative of the posterior foregut undergoes important modifications in its dimensions, position, rotation and form during morphogenesis [8]. Stomach development varies in shape, size, epithelial lining and glandular mucosa in different species, in horse, carnivore and pig, the stomach is composed of a single compartment, while in ruminants, the simple gastric primordium develops to four chambered structure [7].

The understanding of the processes that regulate the specification of cells within the gastric epithelium during embryonic development could be essential to interpret the disease etiology, the resultant future organ identity is assembled within the simple undetermined gut tube through the combination of signaling pathways from mesodermal tissues opposite to the endoderm and the endodermal progenitors, those pattern of transcription factor enable successive organ-specific differentiation for regional identity[3,9].

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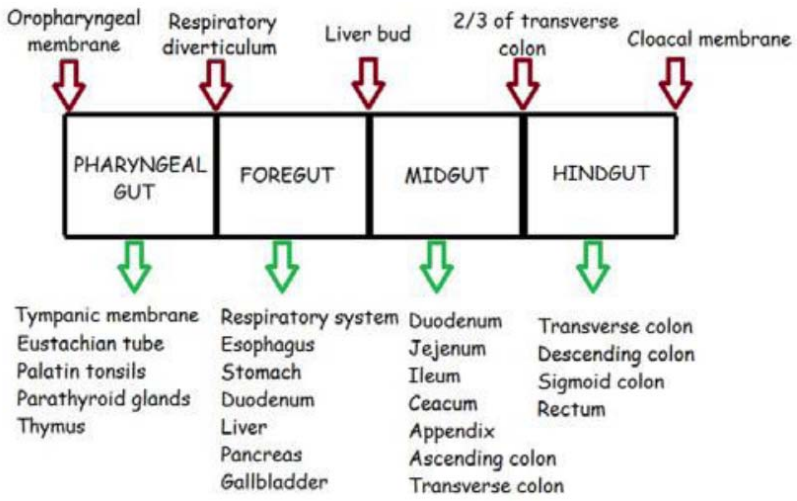

Figure 1: Main parts of the primitive gut tube and the organs derived from these regions are summarized (drawn by [1]) (Eşrefoğlu *et al*. Development of the Esophagus and Stomach 2017).

DISCUSSION

Stomach Primordia

The gut has not undergone histodifferentiation into stomach or intestinal phenotype by the embryonic day 14 (E14) in mice, although the gene expression changes occur at E12 suggest modification as the origin of consequent epithelial histogenesis [10]. The stomach morphologically differentiates from the foregut tube around embryonic day 9.5 (E9.5) and the expansion of the pre-gastric mesenchyme allows the domain of the stomach to be visible beginning at E10.5, by E11.5, the stomach is distinctly enlarged [11].

In pig, [12] stated that, the stomach originates as a spindle-shaped dilation of the caudal region of the foregut, becoming apparent during the third week of gestation. In domestic animals, the stomach develops as a fusiform dilation of the caudal part of the foregut and is recognised early in embryological development [7]. In rabbit, [13] specified that, the primordium of stomach appears at the 10th day of gestation as an enlargement of the foregut.

Regarding to the formation of the stomach curvatures, the dorsal border of the stomach grows faster than the ventral one, resulting in formation of dorsal thick convex and ventral thin concave curvatures, later, the dorsal curvature develops into the greater curvature and the ventral to the lesser curvature of the stomach as reported by [12,13].

Stomach development like other gastrointestinal organs, requires numerous steps such as patterning of the definitive endoderm and regional specialization of the primitive gut tube, followed by specification and differentiation of component cell lineages [3,14].

During endodermal specification, a highly conserved transcription factors is activated to promote the endodermal cells development before regionalization, and their expression in nascent endoderm is vital to generate foregut progenitors that develop the stomach [9].

Embryonic Stomach Specification

Endodermal Foregut Patterning and Regionalization

Retinoic acid (RA) signaling pathways have compound spatiotemporal role that control foregut identity by patterning the anterior posterior axis of the endoderm, RA signaling regulates the posterior endoderm specification mainly at the foregut midgut border during late gastrulation, therefore it is essential to control stomach development [9,15].

Low anterior Wingless-related integration site (Wnt) signals limited by Secereted frizzled related protein 5*(Sfrp5*) promotes the foregut fates and initiate cellular morphogenesis, while high posterior Wnt specifies the hindgut domain [16]. WNT and fibroblast growth factor (FGF) signals produced by the mesoderm promote the expression of posterior endodermal genes such as *Caudal type homeobox2 (Cdx2*) that develop the small and large intestines, Bone morphogenetic protein (*BMP*) signalling initiates posterior over anterior endodermal fates, sonic hedgehog (*Shh*) signaling pathways is concerned in gastric development through epithelial to mesenchyme signaling, however *Shh* is

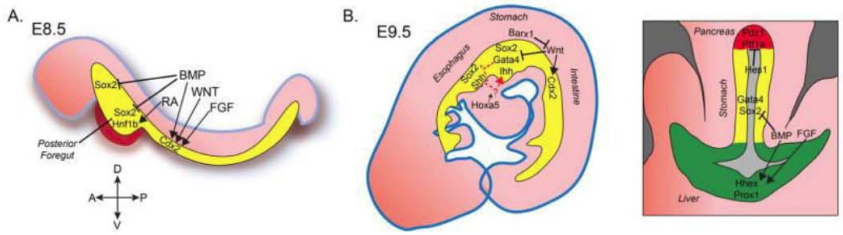

Figure 2: Schematic overview of developmental mechanisms leading to stomach specification [3].

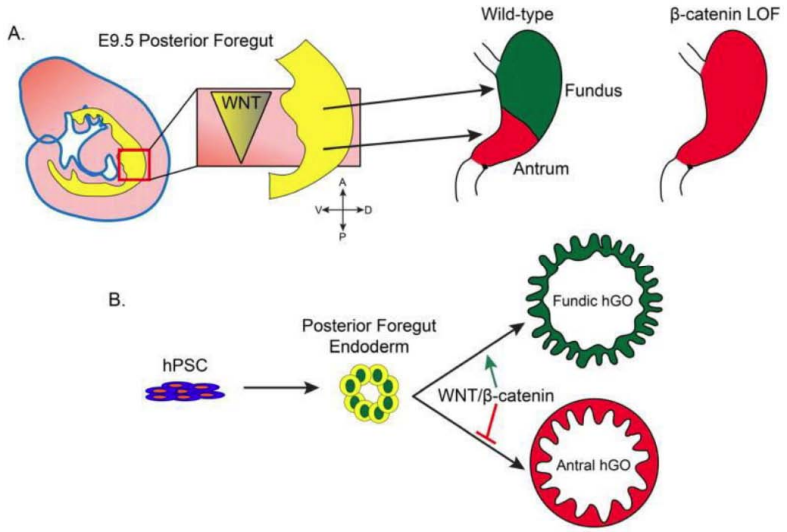

Figure 3: Summary of WNT-mediated gastric patterning mechanisms *in vivo* and *in vitro* [3].

reported being not involved in gastric specification [3,9].

Transcription factors generally expressed such as Forkhead Box A *(Foxa1/2/3)*, *Gata Binding Protein (Gata4/6)*, *Hnf1 Homeobox B (Hnf1b)*, and *Sry- Box Transcription Factor 2 (Sox2)* all could show an essential role in gastric specification [9]. *Fox A* family is expressed all over the early endoderm which is essential for the development of the pancreas, liver, and intestine, they are involved in promoting *Pancreatic and Duodenal Homeobox 1(Pdx1)* expression in the foregut that is expressed only in the posterior foregut, so *FoxA* factors could be involved in regionalizing the stomach, *Pdx1* promotes the development of the antrum and pylorus of posterior stomach, anterior duodenum, dorsal and ventral pancreatic buds, and proximal extrahepatic biliary system [3,9,15,17].

GATA family have been expressed in the nascent endoderm which have roles in endoderm specification and early patterning, *GATA*1, 2, 3 are critical in hematopoiesis in vertebrates, whereas *GATA*4, 5, and 6 are significant in cardiac and gut development [18]. *Gata4* and *Gata6* are expressed all over the definitive endoderm, also they are expressed in the foregut during endodermal regionalization, the expression area of *Gata4* exists at the future forestomach -glandular stomach boundary to specify the glandular stomach, *Gata4* plays a unique role in promoting the cytodifferentiation of definitive endoderm to the gastric columnar glandular epithelium [19]. *Gata4*, *Gata5*, and *Gata6* are transcription factors, that elucidate the GIT epithelium development, *GATA4* and *GATA6*, are considered the essential regulators of GIT epithelial development [6].

Gata4 is present all over stages of human gastric differentiation, and is expressed in the definitive endoderm, posterior foregut endoderm, and mature gastric organoids resembling the development course in mouse [20].

Sox2 is expressed broadly all over the foregut from the anterior endoderm to the future border of gastric antrum and duodenum, it has a crucial role in anterior foregut and stomach specification and so it elucidates the development of some foregut organs like the stomach, esophagus, trachea, and lung, *Sox2* establish the junction between the squamous esophagus,

forestomach and glandular stomach by suppressing genes expression in the posterior epithelium (anterior gastric boundary) [21]. *Sox2*, is a member of the Sry-like HMG box family, which is expressed in the early dorsal foregut endoderm as the gut tube splits into the esophagus and trachea, it is highly expressed during esophagus epithelial stratification and extends into the murine forestomach, so this transcription factor is required for the differentiation and morphogenesis of the esophagus, while it's expression is comparatively low at the glandular stomach, possibly that the *Sox2* level reserved in the developing glandular stomach is appropriate to a proper epithelium development [6].

Sox2, *Gata4* and *Pdx1* are expressed during development of the antrum, therefore termed with antral gastric progenitors, while the corpus progenitors *Sox2* and *Gata4* promotes the corpus region development, therefore [9] mentioned that broadly expressed genes such as *Sox2*, *Gata4*, and *Pdx1* are expressed concurrently in other organs as well as the stomach as essential factors that define the future stomach regions.

Hnf1B is expressed in the definitive endoderm and concerned in stomach specification, knockout of *Hnf1B* leads to gene expression modification within the posterior gastric progenitors initiating loss of *Pdx1* and Indian hedgehog (*Ihh*) [3,9,23].

The transcription factor *Cdx2* is expressed from the hindgut to elucidate the small and large intestines

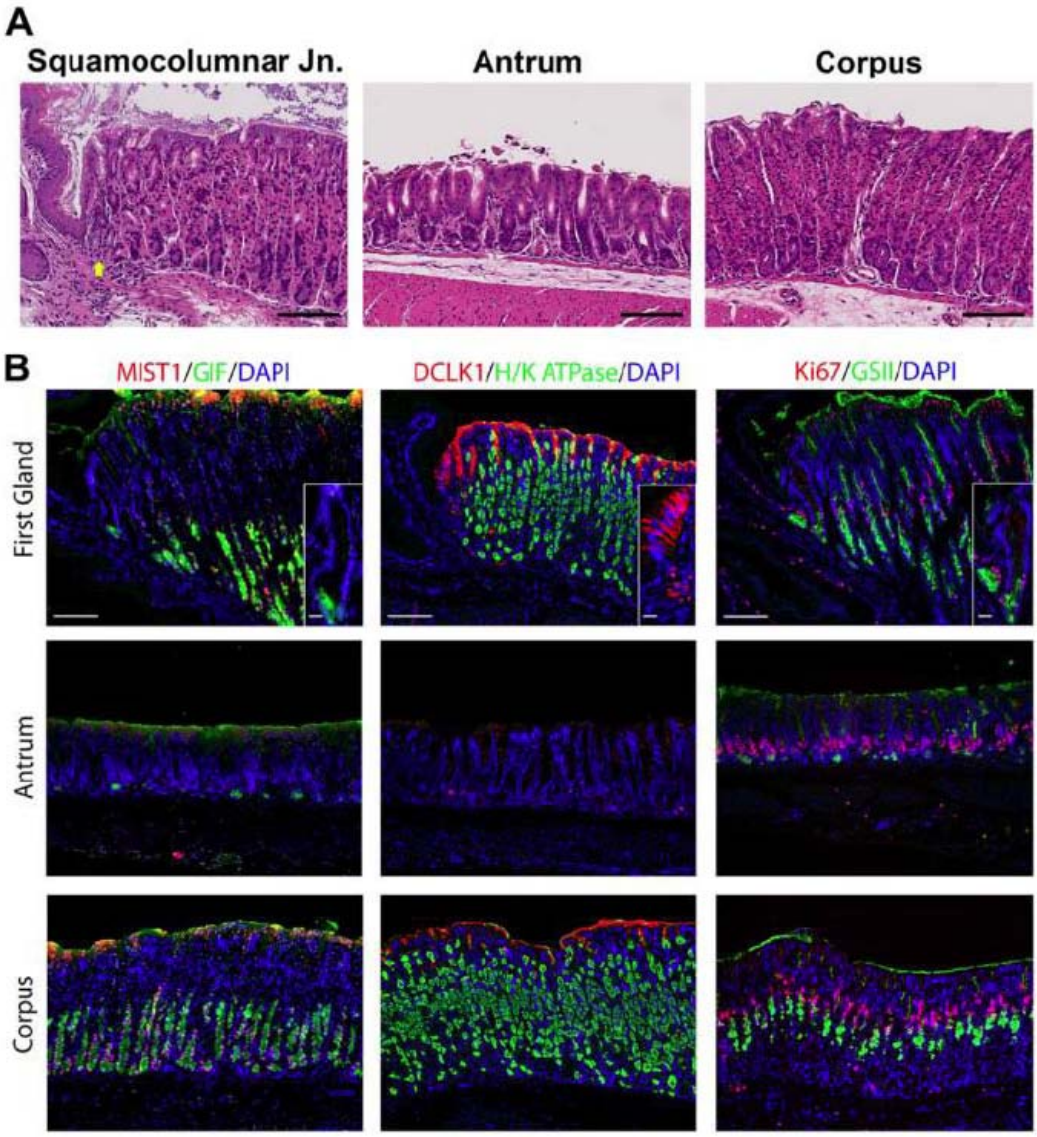

Figure 4: Comparison of gastric corpus markers in the first gland, antrum, and corpus of the stomach. A. Hematoxylin and eosin staining of the squamocolumnar junction region, the antrum, and the corpus [22].

development [24]. Both *Cdx2* and *Sox2* establish the junction between the glandular stomach and the duodenum (the posterior gastric boundary), *Sox2* ectopic activation in the hindgut repress the morphology of the intestines and leads to the glandular stomach features without suppression of *Cdx2* [11,25]. The ectopic *Cdx2* expression in the glandular stomach mucosa in mouse results in the genes expression of intestine and emerging of intestine-like goblet cells [6], therefore, it is crucial that the developing gut must have properly balanced *Sox2 Cdx2* expression. *Cdx2* function act together with that of *Tumor protein p63 (p63*) and *Sox2* in regionalizing the epithelium of GIT, *Cdx2* expressed highly in the midgut and hindgut to elucidate the development of columnar epithelium in the intestines, while both *Sox2* and *p63* expression in the foregut to regulate the development of stratified epithelium in the esophagus and forestomach [6].

Mesenchymal Differentiation

During gastric organogenesis, the mesenchyme is distinguished into numerous layers like the lamina propria, muscularismucosae, submucosa, tunica muscularis and serosa [26].

GIT regionalization including the stomach depends mostly on the epithelial-mesenchymal interaction, the epithelial and mesenchymal cell signaling events are critical for the organization of GIT development [18]. Hedgehog (*Shh*/*Ihh*) signals derived from the gastric epithelium influences the mesenchymal growth and differentiation, in addition to their primitive role in foregut growth, which is continued in the adult [27]. *Shh* and *Ihh* are generally expressed all over the foregut, midgut, and hindgut endoderm early in development, later, *Shh* is mainly expressed in the esophageal and forestomach regions, while *Ihh* is mostly expressed in the hind-stomach and intestinal regions, so that *Shh* and *Ihh* expressions are important to be balanced in order to outline the stratified squamous and gastric columnar epithelia in the stomach [6].

Barx homeobox 1 (Barx1) belongs to homeobox genes family which send positional information to the embryos and have a role in patterning the mammalian gut, *Barx1* is expressed in embryonic gastric mesenchyme and guides the differentiation of endoderm for the subsequent histodifferentiation of stomach mucosa [10,28]. This transcription factor is expressed in the esophageal and gastric mesoderm during the time of stomach morphogenesis and gut endoderm specification, therefore it elucidates the morphology and patterning of fetal stomach [9], it elucidates the expression of wnt signaling antagonists (*Sfrp5*) in the stomach mesenchyme which repress intestinal transformation into the gastric epithelium so it allows the stomach specific epithelium development as shown previously in murine model [10,29,30].

In mice, *Barx1* absence leads to obvious foregut shortening and unclear gastric squamo-glandular, distorted corpus-antral margins, and defects like reduced stomach size, escaped leftward rotation, fundic dysmorphogenesis and pyloric sphincter agenesis. *Barx1* controls stomach morphogenesis and helps to specify the stomach epithelium. However, *Barx1* levels in the stomach decline sharply after epithelial specification [28]. *Barx1* is down regulated in the stomach after E18.5 of gestation [10].

Nk3 Homeobox 2 (Bapx1 (Nkx3-2)), Nk2 Homeobox5 (Nkx2-5), Gata3, Six Homeobox2 (Six2), Nuclear receptor subfamily 2 group f member2 (Nr2f2) and *Sox9* are transcription factors for the pylorus region [11,31,32]. Bapx1 is homeobox transcription factor that is derived from the mesenchyme in the distal hind-stomach and necessitates Barx1 in which their expressions are essential for the pyloric region development in mice [6,11].

Bmp4 drives from the inner mesenchyme, that differentiates into the lamina propria, muscularis mucosae and submucosa, this expression factor in the mesenchyme is controlled through *shh* expression in the epithelium [26].

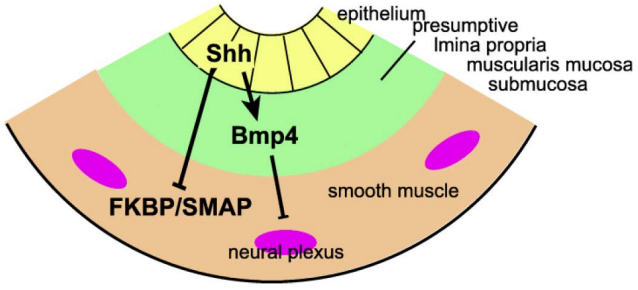

Figure 5: The stomach epithelium of the chicken embryo regulates the concentric differentiation of mesenchymal components in the vertebrate gut [26].

Cell Lineage Specification

There are specific epithelial cell types in the stomach which produce acid, enzymes for digestion, and hormones that permit chemical and mechanical digestion of food and control gastric motility [3,9]. The neck mucus cells and surface pit (foveolar) cells secrete mucus, while chief cells secrete enzymes such

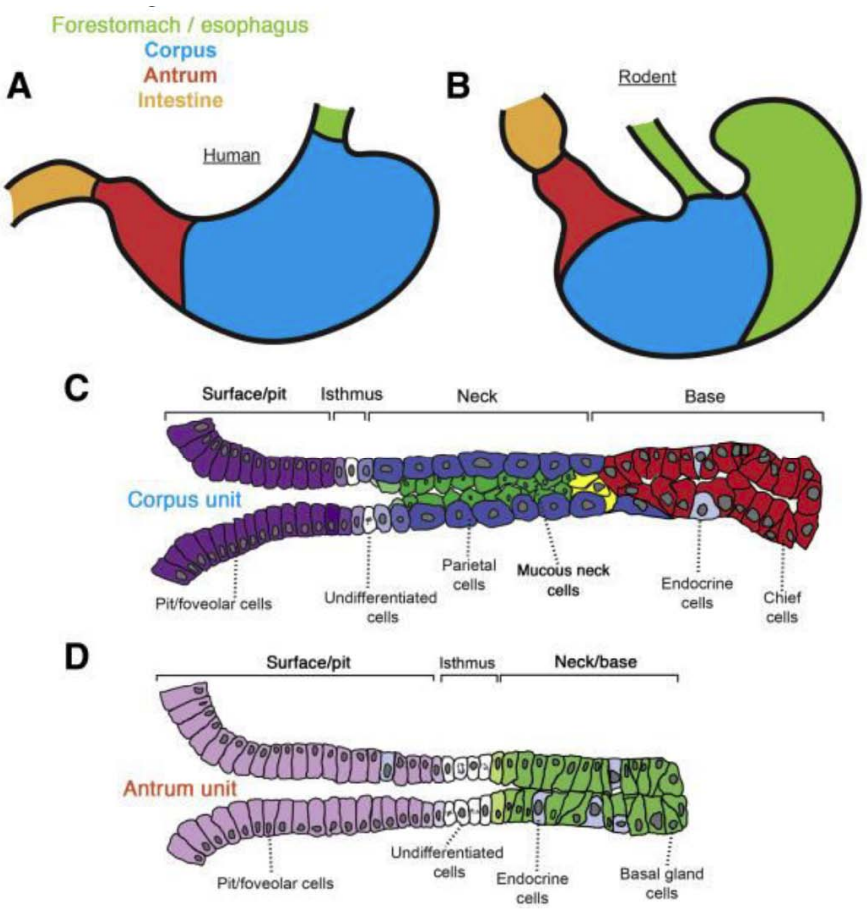

Figure 6: Architecture of the adult stomach and the organization of corpus and antral units [9].

as pepsinogen, parietal cells secrete acid to control the pH of stomach, and the enteroendocrine cells secrete hormones into the lamina propria including gastrin (G cells), these specific epithelial cells distribution within the gastric gland differs along the proximal to distal axis of the glandular stomach [6]. In rodents, all epithelial cell types are present in glands of the fundic stomach,while chief cells and parietal cells are absent in the antral stomach, G cells exist entirely in the antral stomach glands of mice and humans as well as the basal gland cells [9].

The gastric epithelium remains as a simple epithelium without apparent differentiation between the two stages of endodermal specification and cell lineage specification in the stomach, to our knowledge, there is a lack for the specification factors of chief, parietal, pit, mucous neck cells, therefore the markers such as Potassium-transporting ATPase subunit beta *(Atp4b*), Trefoil Factor 1 *(Tff1)*, Progastricsin (*Pgc)*, and *Gif* can characterise the final differentiation of those cells [9].

The morphogenesis of the gastric units starts during late fetal life time, when the endoderm goes through cytodifferentiation to an epithelial formation with numerous short infoldings which have the morphologic structures of differentiated pit, neck, Enteroendocrine and parietal cells [33].

Cell lineage specification and glandular formation are essential to form the mature stomach, and it already begins in the fetus, but the final organization of mature glands is completed after birth, transcription factors representative of different cell types such as endocrine, parietal, and chief cells are expressed nearly at E14.5–E16.5(E: Embryonic day) and small glands are invaginated into the mesenchyme from the gastric epithelium, the expression factor *Shh* regulate gland growth in the adult mouse stomach , BMP and Notch signalling is crucial for glandular proventricular organization in chicken [26,34]. BMP signaling is required in maintenance of the gastric epithelium [35]. *FGF10* expression factor drives from the mesenchyme and regulates stomach maintenance, morphogenesis, and cellular differentiation [3].

The neuroendocrine cells that govern the gastric acid secretion and epithelial cells proliferation, are

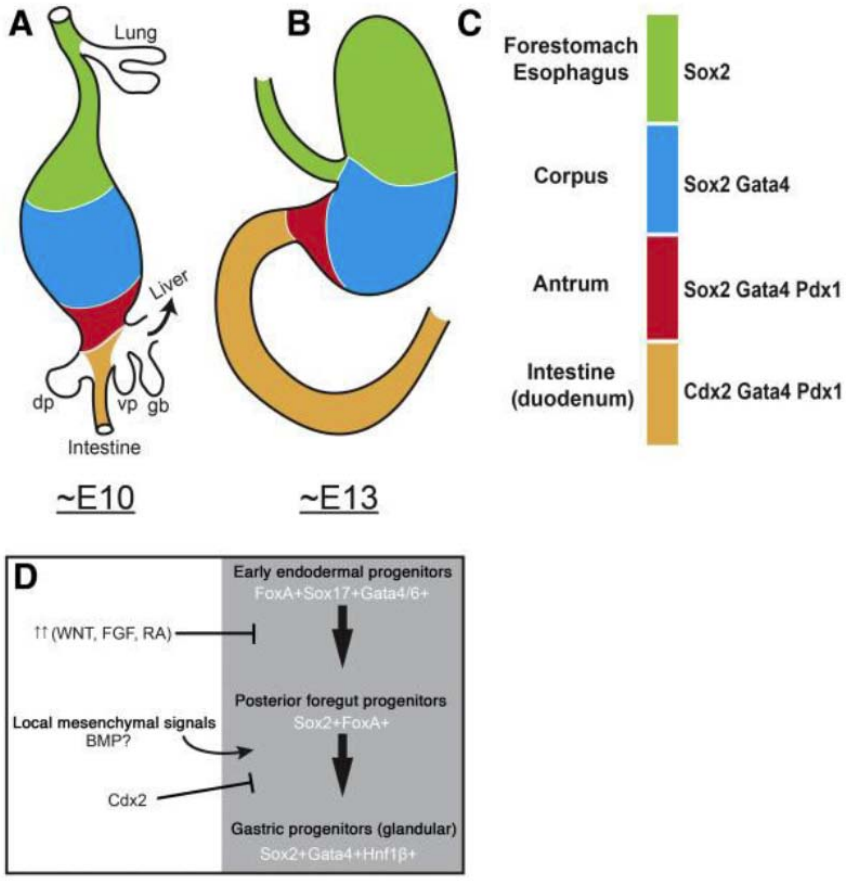

Figure 7: Transcription factor domains in the development of the gastric region [9].

stomach lineages with identified progenitor markers are M*ammalian achaetescute homologue1 (Mash1*) and *Neurogenin 3* (*Ngn3*) [36]. *Ngn3* and *Aristaless related homeobox (ARX)* are essential for differentiation of gastric enteroendocrine cells found in the fundic or antral regions, *Pdx1*, *Nkx6-3*, and *Pax6* are vital in the distal hind-stomach for G-cell differentiation, while *Pax4* is necessary for serotonin and somatostatin producing enteroendocrine in distal gastric region [6].

Wnt signaling has a crucial role in regionalizing epithelial cell type identity within the proximal and distal regions of the glandular hind stomach [6]. The homeobox 1, *Pdx1* is a key marker that distinguishes these regions which is present in the distal glands but not in the proximal glands, when Wnt signaling is blocked early during development in the future fundic stomach epithelium by elimination of B-catenin, the proximal gland marker expression is exchanged by distal gland marker expression by E10.5 in mice [37]. Wnt signaling during development is critical to specify proximal against the distal gastric gland types in mouse stomach, and human stomach development as demonstrated using human pluripotent cell-derived gastric organoids, therefore the regulation of Wnt signaling is vital for gastric gland regionalization in mice and humans [37].

The development of chief cell within the proximal hind-stomach necessitates the transcription factor X-box binding protein 1 (*XBP1*) and its target, Muscle intestine and stomach expression 1 (*MIST1*) [38]. *MIST1* transcription factor regulates the establishment and conservation of a generalized secretory cell architecture in various cell types, together with the gastric chief cell [39]. Estrogen-related receptor gamma (*ESRRG*) regulates the production of parietal cells in proximal glands in mice [40]. The fork head protein (*FOXQ1)* regulates pit cell differentiation [41]. *Gata4* is essential in the development of gastric cell types including parietal cells, chief cells and neck mucus-producing cells [19].

CONCLUSION

To my knowledge, there is a lack for understanding the organ lineage relationships and lineage-specific markers during stomach development and differentiation. So this inspired me an idea for the later

research about genes and transcription factors associated with stomach specification, regionalization, and differentiation of component cell lineages.

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