Development of the Gastrointestinal System

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• Jamie
**Competencies:** Upon completion of this section of the course, you must be able to:

- Know the segments of the primitive gut tube.
- Compare the different subdivisions of the gut tube and describe what adult structure(s) arise from each subdivision.
- Understand the rotation of the different segments of the gut tube.
- Know the consequences of abnormal rotation of the gut including volvulus.
- Compare and contrast the cells that give rise to the neural, muscular and connective tissue elements of the different parts of the gut.
- Understand the developmental defects associated with the epithelization of the gut tube.
Background

- Start with the trilaminar embryo.
- Find the oral plate and the cloacal plate.
Lateral Body Folding

• The consequence of lateral body folding leaves the embryo with a gut suspended by a dorsal mesentery.
Head

Back

Midgut

Hindgut

Tail

Connecting Stalk

Foregut

Vitelline Stalk

Allantois
One consequence of the tail folding is the incorporation of the allantois.

Allantois forms the cloaca.

Distal allantois remains in connecting stalk.

By day 35 the connecting stalk and the yolk sac stalk fuse to form the umbilical cord.
Primitive Gut

• Stomodeum - ectoderm at cranial end of gut.
• Foregut - endoderm and splanchnic mesoderm
• Midgut - endoderm and splanchnic mesoderm
• Hindgut - endoderm and splanchnic mesoderm
• Proctodeum - anal pit - ectoderm at caudal end of GI tract.
• SHH secreted from the endoderm
• HOX genes influence cephalic – caudal regions of the gut tube.
Foregut derivatives:

- pharynx (with derivatives tonsils, tongue, salivary glands, etc.)
- lower respiratory system
- esophagus
- stomach
- duodenum (proximal to bile duct)
- liver, biliary system and pancreas
Development of the esophagus

The cephalic foregut is partitioned by the tracheoesophageal septum.
Formation of the Stomach

• During the 4th week caudal foregut begins to dilate
• Initially oriented in the median plane.
Growth of the Stomach

- During the next two weeks:
  Dorsal wall of stomach grows faster than the ventral wall
Rotation of the Stomach

- As the stomach grows:
  - The ventral surface rotates to the right.
  - The dorsal border moves to the left.
Rotation of the Stomach

◆ As the stomach grows:
  • The left side becomes the ventral surface.
  The right side becomes the dorsal surface.
Rotation of the Stomach

• Cranial region moves inferiorly and to the left.
• Caudal region moves superiorly and to the right.
• Long axis of stomach becomes nearly transverse.
Vagus Nerve

• The rotation of the stomach leaves the:
  Left vagus nerve on the ventral surface of the stomach (Anterior Vagal Trunk).
  Right vagus nerve on the dorsal surface of the stomach (Posterior Vagal Trunk).
Since the foregut distal to the esophagus is supplied by the celiac artery, branches of this artery supply the stomach.
Duodenum

• Derived from:
  Foregut up to the Bile duct (first and second parts).
  Midgut from bile duct to jejunum.
Growth of the Duodenum

- Grows as a C-shaped loop that projects ventrally.
Rotation of the Duodenum

- As the stomach rotates so does the duodenum.
Rotation of the Duodenum

- As the duodenal loop rotates it rotates to the right.
Rotation of the Duodenum

- Eventually comes to lie in a retroperitoneal position.
Duodenal Development

- During the 5th and 6th weeks
- The duodenal lumen becomes plugged by epithelial cells.
- Later recanalized.
Development of the Liver

- During the 3rd week the liver bud develops.
- Liver bud also known as hepatic diverticulum.
- Endodermal cells grow toward septum transversum.
Development of the Liver

- Endodermal cords mix with cells of vitelline veins to form liver parenchyma.
- Hemopoietic cells, Kupffer cells and connective tissue from mesoderm of septum transversum.
Liver Function

- Early function is hemopoiesis.
- Activity diminishes during the last 2 months of gestation.
Development of the Bile Duct

- As the liver develops, the epithelium between the liver and the foregut narrows and forms the bile duct.
Development of the Gall Bladder

• A diverticulum develops from the bile duct giving rise to the gall bladder and the cystic duct.
Development of the Gall Bladder

- Bile duct becomes solid, then the lumen opens again.
Development of the Pancreas

- Pancreas originates as two pancreatic buds.
Development of the Pancreas

• Dorsal pancreatic bud is in dorsal mesentery
• Ventral pancreatic bud is near the bile duct.
Development of the Pancreas

• During rotation of the duodenum the ventral bud moves dorsally.

• Ventral bud will lie caudal and posterior to the dorsal bud.
Development of the Pancreas

- Ventral bud forms uncinate process and inferior pancreatic head.
- Dorsal bud makes up rest of gland.
- Main pancreatic duct is formed from dorsal and ventral pancreatic duct.

Langman p. 303
• FGF and Activin
  – Secreted by the notochord
  – Repress SHH in endoderm to become pancreas

• Pancreatic and duodenal homeobox 1 (PDX) gene upregulated.
Development of the Pancreas

• Islets of Langerhans develop from parenchymatous tissue during the 3rd month of gestation.
  – PAX 4 and Pax6 specify cells to become:
    • $\beta$ (insulin) cells
    • $\delta$ (somatostatin) cells
    • $\gamma$ (pancreatic polypeptide ) cells
  – PAX4 only:
    • $\alpha$ (glucagon) cells

• Insulin secretion begins at 5 months of gestation.
Development of the Midgut
Development of the Midgut

• During early development there is a rapid growth of both the midgut and its mesentery.
Development of the Midgut

- Midgut forms a primary intestinal loop.
- Loop remains in connection with yolk sac.
- Connection is called the vitelline duct.
- If vitelline duct persists it is called a Meckel’s diverticulum.
Development of the Midgut

Cephalic and caudal limbs of the midgut

Midgut forms a primary intestinal loop.

• Loop remains in connection with yolk sac.

• Connection is called the vitelline duct.

• If vitelline duct persists it is called a Meckel’s diverticulum.
Physiological Umbilical Herniation

- 6th week abdominal cavity can not contain the gut.
- Large kidneys, liver.
- Midgut migrates into the umbilical cord.
Return of the Midgut

• Midgut returns at 10 - 12 weeks

• Reasons:
  – regression of mesonephric kidney.
  – reduced growth of the liver.
  – increased size of the abdominal cavity.
Return of the Midgut

• First to return is the jejunum - on left side.
• As other parts return they are located to the right.
• Cecum is the last part to return.
• Located on the right side under the liver.
• From there it descends and forms the ascending colon and hepatic flexure.
Rotation of the Midgut

- The midgut rotates around the superior mesenteric artery.
- 90 degrees during herniation.
- 180 degrees during the return.
Rotation of the Midgut

Week 6
Development of the Midgut

Week 8

Week 10
Development of the Midgut

Week 11

Later Fetal Period
• Rotation of the gut
Infant omphalocele
An omphalocele is an abdominal wall defect at the base of the umbilical cord (umbilicus); the infant is born with sac protruding through the defect which contains small intestine, liver, and large intestine.

Factors increasing the risk of omphalocele:
- Alcohol
- Tobacco
- Selective serotonin-re-uptake inhibitors (SSRIs)
- Obesity

from the National Birth Defects Prevention Study
Stem Cells

- In crypts of large intestine
- Stem cells give rise to
  - Paneth cells
  - Enterocytes
  - Enteroendocrine cells
  - Goblet cells
- Wnt signaling pathway important
Stem cell differentiation

Notch inhibits endocrine differentiation:
Inhibits adjacent intestinal cell from becoming the same cell as its neighbor
Innervation of the Gut tube

- Vagal neural crest cells innervate the gut tube.
- Additional lumbosacral neural crest cells innervate the hindgut.
Neural plexus

SHH – Mesenchyme differentiation into muscle
Keeps neural crest cells proliferating

GDNF – glial cell line derived neurotrophic factor
Allows:
1. Migration of neural crest cells
2. Differentiation of neural crest cells
Hirschsprung's disease
Congenital megacolon

- Lack of neural crest cells in large intestine
- Causes constriction and lack of bowel movement.
- Proximal to the segment is distension
- More often found in males than females
- Family association in 10 – 15% of the cases.
- 10 – 15% have Down’s syndrome
Development of the Hindgut

- Terminal portion of in contact with the ectoderm via cloacal plate or cloacal membrane.
- Membrane is endoderm of hindgut and ectoderm of anal pit.
- Cloaca is expanded partion of hindgut.
- Cloaca receives the allantois.
• Cloaca is divided into dorsal and ventral parts by urorectal septum.
• divides cloaca into:
  – rectum and anal canal dorsally.
  – urogenital sinus ventrally.
Development of the Cloaca

- By week 7 cloacal membrane fuses with urorectal septum.
- Anal membrane and urogenetial membrane.
Cloaca

- Epithelial-mesenchymal interactions
  - SHH
  - FGF10 also important
  - BMP important signaling in the mesoderm
  - Lack leads to anorectal malformations.