SnapShot: GI Tract Development

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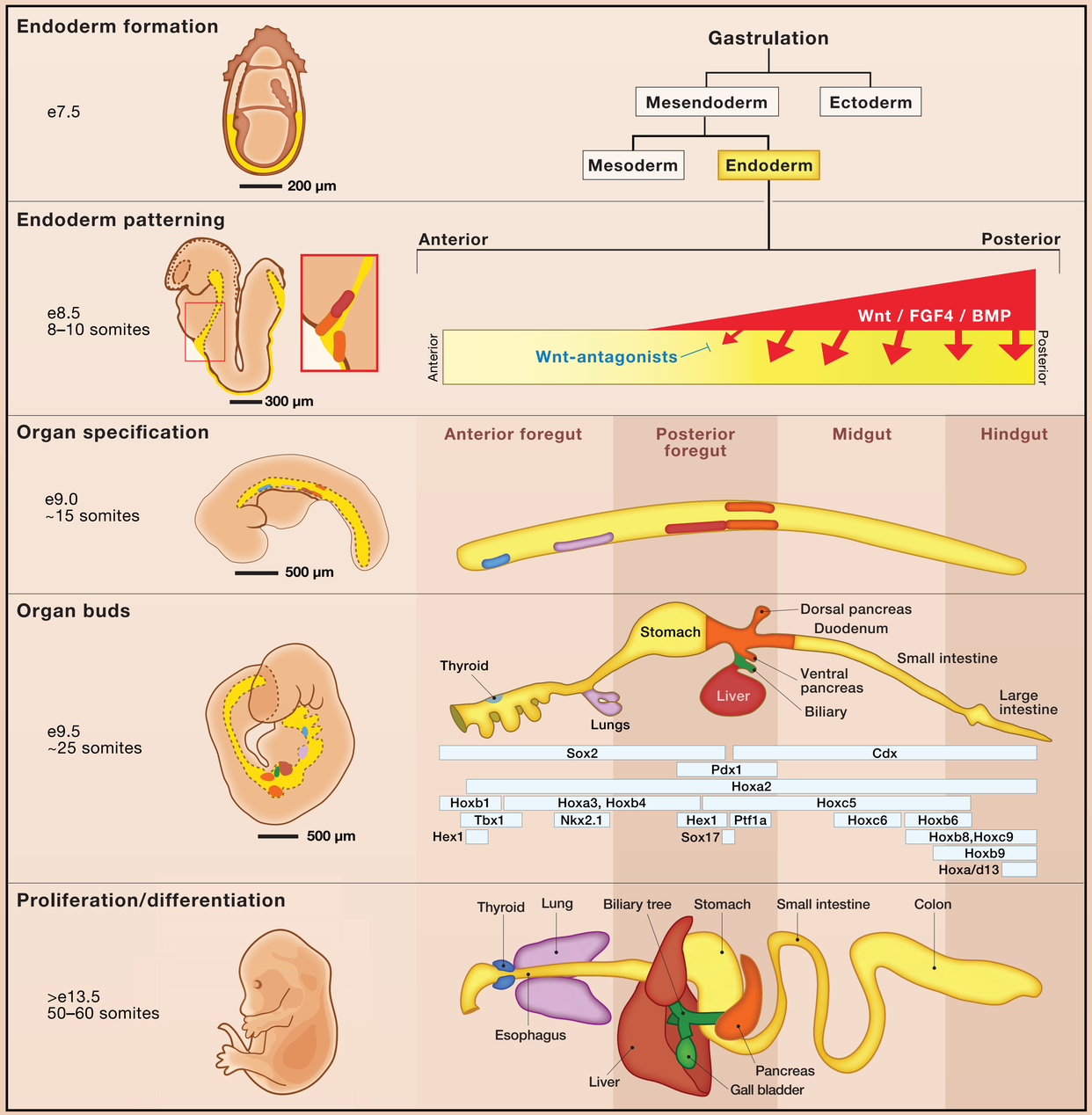
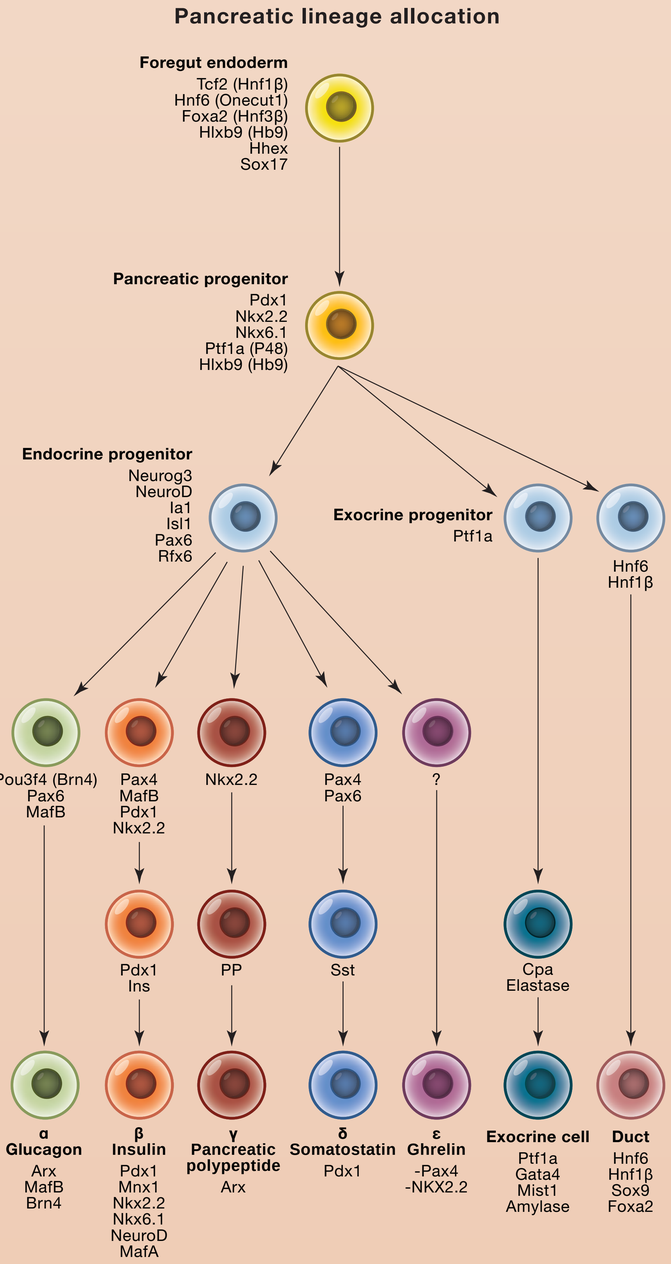
Cell





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The endoderm germ layer contributes to the respiratory and gastrointestinal (GI) lineages during development, giving rise to an array of specialized epithelial cell types lining organs, including the thyroid, thymus, lungs, liver, biliary system, pancreas, and intestines. This SnapShot timelines and summarizes key stages following gastrulation, including endoderm patterning, organ specification, and organogenesis. A lineage tree of the developing endocrine pancreas is outlined to further illustrate this process.

Timeline of Endoderm Formation, Patterning, and Organogenesis

During development in mice (left), the blastula gives rise to the three germ layers (ectoderm, mesoderm, and definitive endoderm) through the process of gastrulation (middle), which occurs between embryonic day 5 and 7.5 (e5–e7.5). After gastrulation, the two-dimensional sheet of definitive endoderm is patterned along the anterior-posterior (A-P) axis and undergoes morphogenesis to form a three-dimensional gut tube that is surrounded by a primitive mesenchyme (e8.5). A-P patterning of the endoderm occurs through reciprocal signaling with the mesenchyme involving growth factors such as Wnts, Fgfs, and Bmps. At this stage in development, these factors largely act to promote posterior fate and repress anterior fate. The anterior endoderm gives rise to the foregut (thyroid, lungs, esophagus, liver, stomach, pancreas), while the midgut and hindgut give rise to the small and large intestines, respectively. The first evidence of organ specification occurs in the early gut tube by the expression transcription factors that begin to demarcate specific organ domains, including the respiratory tract (Nkx2.1), liver (Hhex), stomach (Sox2 and Pdx1), extrahepatic biliary system (Sox17), pancreas (Pdx1 and Ptf1a), duodenum (Pdx1 and Cdx2), and intestine (Cdx2). The spatially restricted expression of these transcription factors predicts where organs will begin to form starting around e9.5. By e13.5, the organs of the respiratory and GI tracts are formed and undergoing growth and differentiation into specialized lineages.

Pancreatic Lineage Allocation: A Transcription Factor Map

Temporal lineage formation of the pancreas involves the expression of unique sets of transcription factors that mark and often direct cell fate decisions (right). All developing cell lineages of the pancreas (acinar, duct, and endocrine) arise from the foregut endoderm, which expresses markers such as Foxa2, Hnf6, and Hlxb9. The pancreatic endoderm becomes specified when the gut tube begins to express Pdx1 and Ptf1a in dorsal and ventral domains of the tube (e8.5–9.0). Morphogenesis of the pancreas initiates with an endodermal thickening (e9.0) and evagination of dorsal and ventral pancreatic buds (e9.5–e10.0) into the surrounding mesenchyme, forming an expanding pool of multipotent pancreatic progenitor cells. The lineage allocation and maturation of specific pancreatic cell subtypes are mediated by a network of signaling pathways and transcription factors. Commitment of progenitor cells to the endocrine lineage occurs following transient expression of Neurog3 and its downstream targets Neurod, Rfx6, and Pax6, whereas exocrine-committed cells express high levels of Ptf1a and carboxypeptidase A (CpA). Allocation of the separate endocrine lineages involves the combinatorial actions of multiple transcription factors. For example, development of mature β cells requires Pdx1, NeuroD, Nx6.1, and MafA. The ductal lineage involves a different set of factors, including Hnf1β and Hnf6. Each pancreatic cell lineage is portrayed with a subset of defining transcription factors throughout development.

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