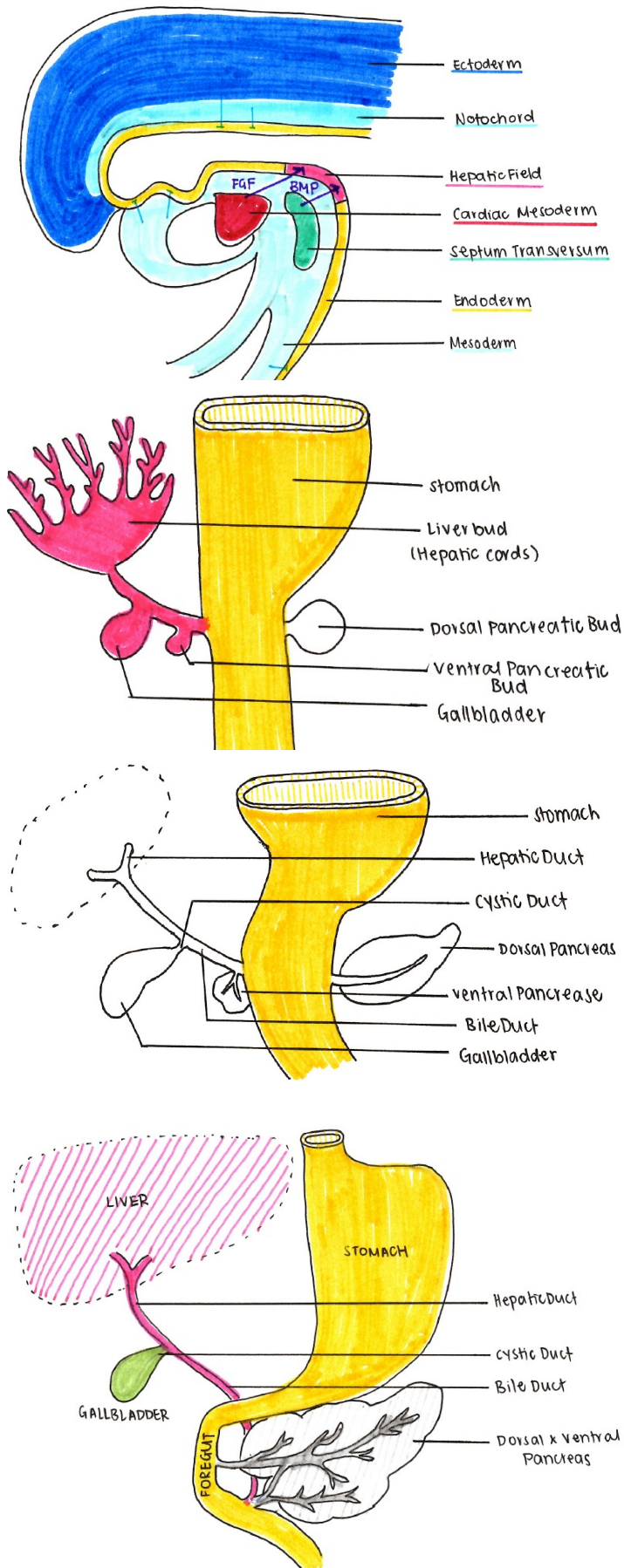


## Induction of liver development



Liver formation from the gut tube occurs via the setting-up of a hepatic field in the future dorsal foregut region, which will become the liver primordium. This is in part induced by FGFs (1,2,8 and 10) secreted from the cardiac mesoderm, which act as morphogens (in a concentration-dependent manner) to pattern a select area. GATA4 expressed in the septum transversum mesenchyme induces BMP4 expression which is also an important secreted signal for induction of the hepatic field within the endoderm.

Ectoderm, notochord and intermediate (non-cardiac mesoderm) secrete factors which inhibit formation of a hepatic field anywhere else along the endoderm tube. The BMP and FGF signals secreted in specific areas inhibit these inhibitors, lifting repression of hepatic field formation and permitting differentiation of these cells into hepatic and biliary cells, which is mediated in part by activation of hepatic nuclear transcription factors (HNF1/3/4). The endodermal epithelium begins to thicken (termed pseudostratification) as cells change from simple cuboidal to columnar epithelial morphology, involving upregulation of Hhex, a homeobox transcription factor. This marks the initial stage of liver bud outgrowth. Subsequently the laminin-rich basal layer surrounding the hepatic endoderm breaks down; cells downregulate E-cadherin interactions and the delaminated cells migrate to the septum transversum mesenchyme to form the liver bud, induced by signalling from endothelial cells surrounding the outgrowth which has been suggested to be chemotactic in nature. Hhex continues to be expressed and utilised in differentiation of hepatic-field cells into hepatoblasts, bipotent progenitor cells which become hepatocytes (cells of the liver) and cholangiocytes of the intrahepatic bile ducts. Hepatoblasts proliferate rapidly prior to differentiation, and form the outgrowing liver bud which penetrates the mesodermal plate of the septum transversum and invades the space inside. During this process the connection between the liver bud and the connection to the foregut narrows to form the bile duct. The gallbladder and ventral pancreas develop as subsequent outgrowths from this structure. Epithelial hepatic "chords" intercalate with vitelline and umbilical veins in the surrounding mesenchyme to form the hepatic sinusoids; these chords then differentiate into parenchymal liver cells and become the lining of bile ducts. Once the septum transversum has been completely invaded with the liver cells, the mesoderm layer of the septum transversum develops epithelial characteristics – this "mesothelium" surrounds the liver on all sides except cranial, where the mesoderm differentiates into the central tendon of the diaphragm. Proliferation and elongation of the foregut between the stomach and the point of bile duct attachment causes the liver connection to effectively move further down the gut length towards the midgut. Morphological twisting of the gut tube leads to the bile duct being pulled behind the foregut segment.

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