

Manifestation of Novel Social Challenges of the European Union in the Teaching Material of Medical Biotechnology Master's Programmes at the University of Pécs and at the University of Debrecen

Identification number: TÁMOP-4.1.2-08/1/A-2009-0011



Manifestation of Novel Social Challenges of the European Union
in the Teaching Material of
Medical Biotechnology Master's Programmes
at the University of Pécs and at the University of Debrecen
Identification number: TÁMOP-4.1.2-08/1/A-2009-0011



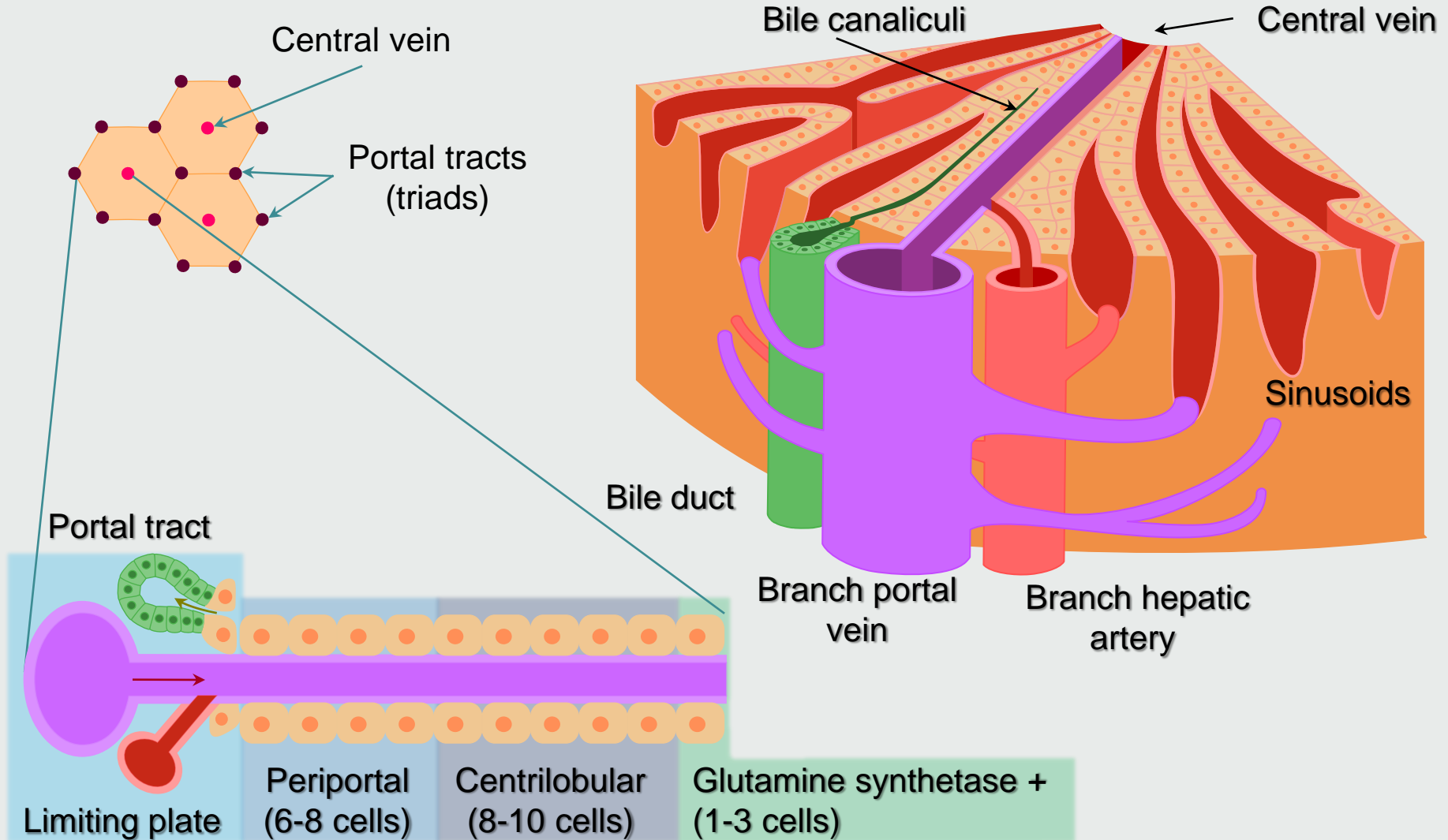
Dr. Péter Balogh and Dr. Péter Engelmann

Transdifferentiation and regenerative medicine – Lecture 8

LIVER REGENERATION FROM STEM CELLS



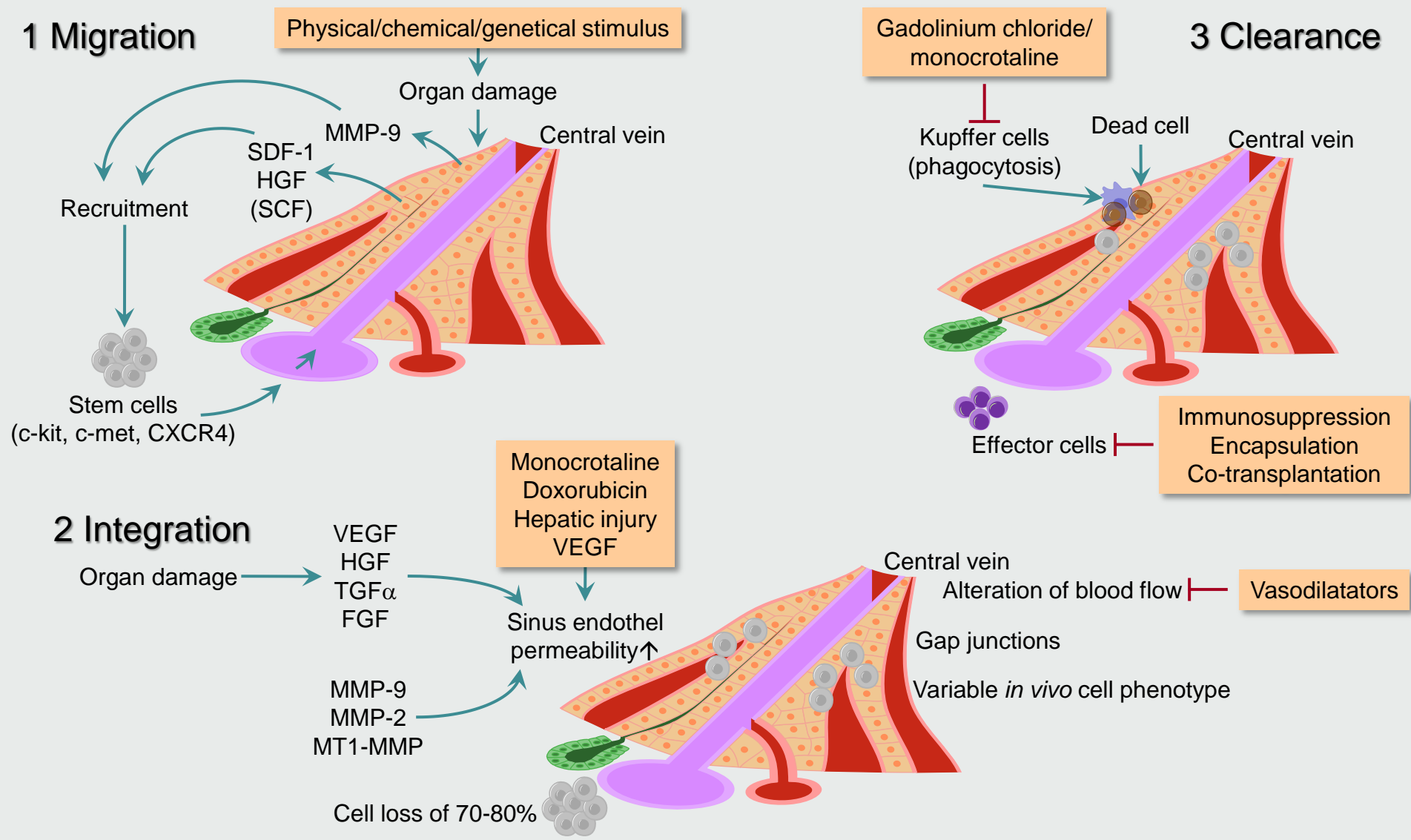
Structure of the hepatic lobe



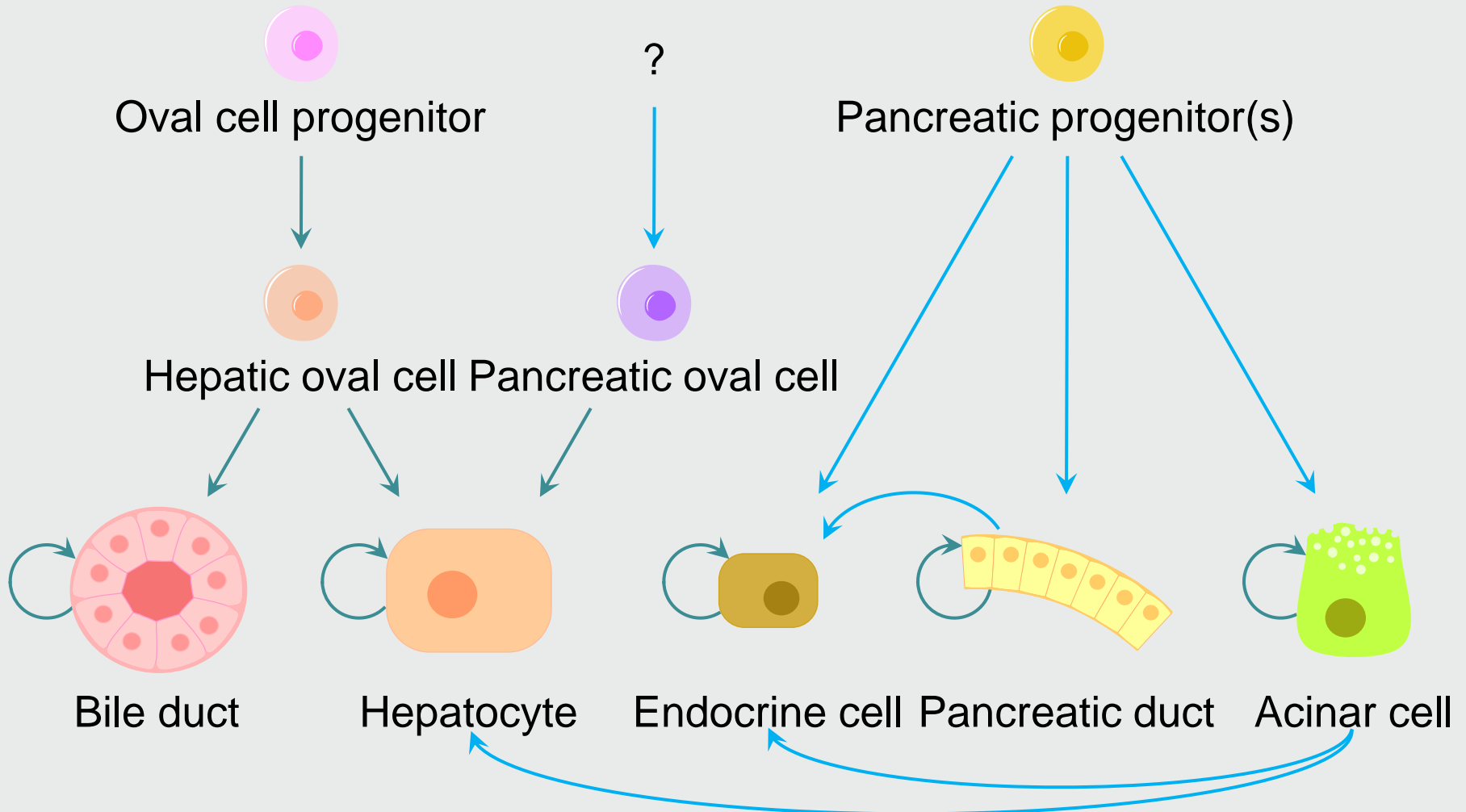
Clinical necessity of liver regeneration

- Shortage of livers for orthotopic liver transplantation
- Liver cell transplantation – limited amount
- Choice of stem cell candidates – variable success in experimental conditions

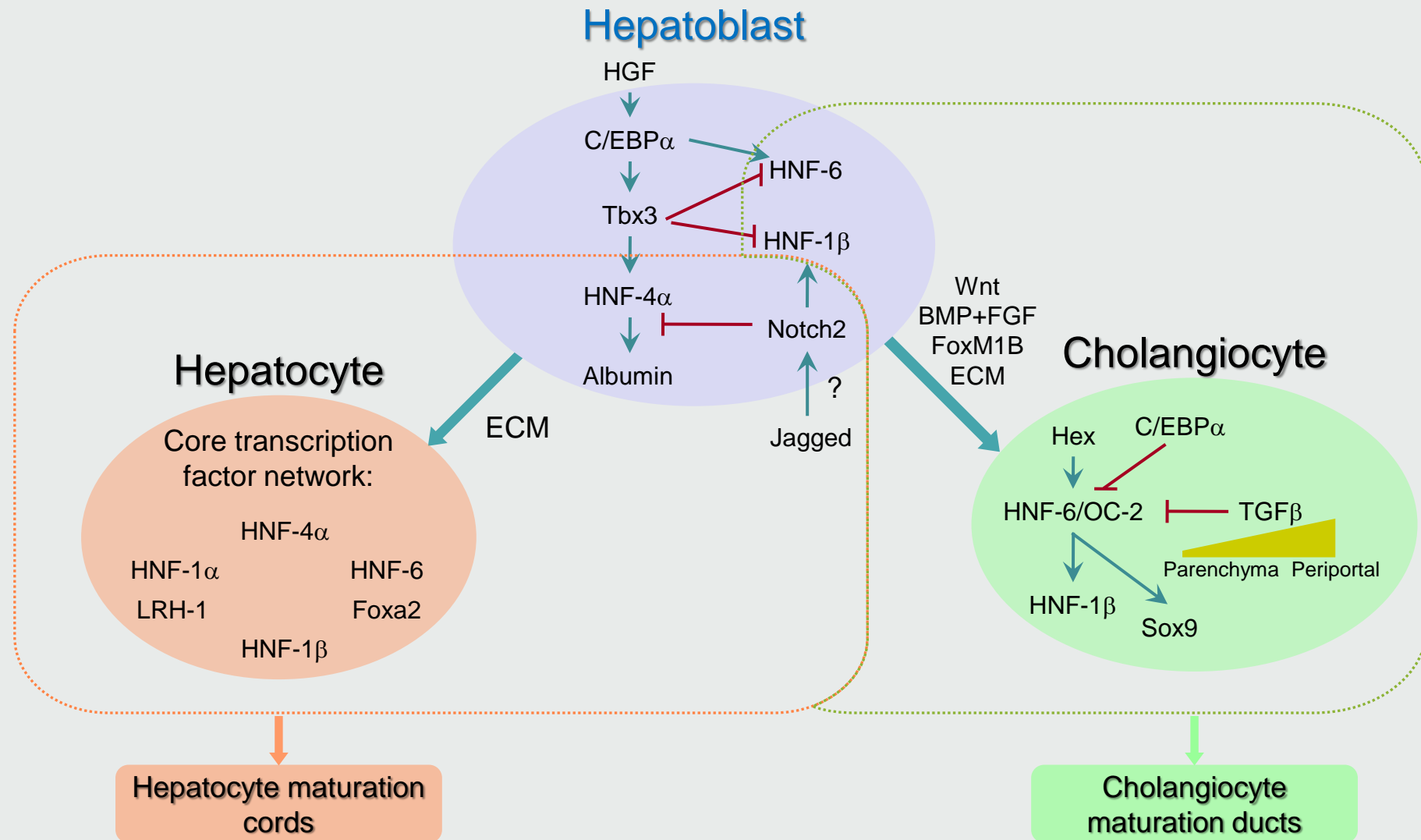
Main phases of liver regeneration



Developmental relationship between hepatic-pancreatic differentiation



Transcriptional control of hepatoblast development



Oval cells – adult liver stem/progenitor cells

- Origin: debated (their precursors are associated with the biliary tree)
- Bipotential differentiation: hepatocyte and cholangiocyte
- Phenotype: shared markers with adult hepatocytes (albumin, cytokeratins 8 and 18), bile duct cells (cytokeratins 7 and 19, OV-6, A6), fetal hepatoblasts (AFP), and haematopoietic stem cells (Thy -1, Sca-1, c-kit).

Cellular targets for hepatic regeneration

- Hepatocytes: metabolic activity of the liver
- Cholangiocytes: formation of bile ducts
- Both derive from embryonic endodermal epithelium.

Stages and forms of liver regeneration

- Surgical partial hepatectomy – from hepatocytes (often polyploid cells)
- Possible sources: hepatocytes, oval cells and extrahepatic stem cells (HSC?)
- Assessment of lineage commitment: albumin, glucose-6-phosphatase, transferrin and transthyretin (hepatic).
- Fibrotic regeneration: transformation of fibrocytes into myofibroblasts
- Parenchymal regeneration: regeneration of hepatocytes

Sequence of parenchymal regeneration of the liver

- Stem cell migration into the liver parenchyma is directed by chemoattractive agents (as SDF-1, HGF and SCF) secreted by damaged liver cells
- Increased MMP-9 expression by host hepatocytes after injury, leading to ECM remodeling and increased vascular permeability
- Transformation of local microenvironment for the integration and proliferation of the transplanted cells, including local secretion of cytokines/growth factors (HGF, FGF, TGF α). Dead cells will be phagocytosed by Kupffer cells.

Oval cell activation and expansion

- Liver injury activates oval cells (their precursors in the biliary tree?) AND other support cells (stellate cells, macrophages/Kupffer's cells, NK cells, endothelium, etc)
- Homing/intrahepatic migration to the site of injury
- Proliferation and bidirectional differentiation (hepatocyte/cholangiocyte)

Non-hepatic cells for liver regeneration

Autologous: Bone marrow-derived/mesenchymal stem cells – fibroblastic regeneration

Allogenic: Fetal-derived hepatocytes or embryonic stem cell-derived liver cells

Differentiation of iPS cells into hepatocytes

- Induction of iPS cells: transfection with TFs
- Formation of embryoid bodies
- Induction of endodermal commitment: treatment with Activin A and bFGF
- Differentiation into hepatocytes: treatment with hepatocyte growth factor (HGF)
- Assessment: gene expression, albumin secretion, glycogen storage, urea production, and inducible cytochrome activity

Summary

- Depending on the origin/type of liver damage, different regeneration processes operate, thus (a) in loss of liver mass, the regeneration is initiated from hepatocytes, whereas (b) in toxicity from hepato-cholangiocyte progenitors.
- Oval cells as adult-type hepatocyte/cholangiocyte progenitors are most likely to be facultative stem cells, although cells with stem cell activity from extrahepatic sources may also operate in liver regeneration.