

Repair

- Liver Regeneration

- Remarkable capacity to regenerate...growth after partial hepatectomy,
- Prometheus, which was eaten every day by an eagle sent by Zeus as punishment for stealing the secret of fire and regrew every night.
- Two major mechanisms:
 - Proliferation of remaining hepatocytes...following partial hepatectomy
 - Restores up to 90% resected liver
 - Cytokines (IL-6) produced by Kupffer cells + GFs (HGF) produced by many cell types.
 - Repopulation from progenitor cells.
 - When the proliferative capacity of hepatocytes is impaired (chronic liver injury).
 - Progenitor cells reside in specialized niches called canals of Hering.

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- **Mechanisms of Healing by connective tissue**

- **HEMOSTASIS:** Within minutes after injury... hemostatic plug stops bleeding and provides a scaffold for infiltrating inflammatory cells.
- **INFLAMMATION:** Acute and chronic inflammatory responses: neutrophils, M1 and M2 macrophages.
- **EPITHELIAL proliferation:**
 - Within 24 to 48 hours, epithelial cells from both edges migrate and proliferate along the dermis, depositing basement membrane components as they progress. The cells meet in the midline beneath the surface scab, yielding a thin but continuous epithelial layer that closes the wound.
 - **FGF-2** promotes the epithelial cell migration to cover epidermal wounds
- **ENDOTHELIAL** and other vascular cells proliferation: Angiogenesis
- **FIBROBLAST proliferation**
 - Migration and proliferation of fibroblasts into the site of injury (**PDGF, FGF-2, and TGF-β**)
 - Deposition of ECM proteins (**TGF-β**)
- **Granulation Tissue**= proliferating fibroblasts, loose connective tissue, blood vessels and scattered chronic inflammatory cells. Pink, soft, granular.
- **Remodeling**
 - C.t. in the scar continues to be modified and remodeled:
 - By matrix metalloproteinase (**MMPs**) (**ZINC**). (# by **TIMPs**)
 - Regression of blood vessels
 - Fibroblasts acquire smooth muscle contraction function to minimize scar size. (**MYOFIBROBLASTS**)

A family of enzymes related to MMPs is called ADAM (a disintegrin and metalloproteinase).

ADAMs are anchored to the plasma membrane and cleave and release cytokines and growth factors, such as TNF, TGF-β, and members of the EGF family.

ADAM10...cut off and +++ [HER2](#) receptor...Therapeutic ADAM inhibitors = anti-cancer therapy.

ADAM17...cut off and +++ TNF...Inflam.

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- Angiogenesis is the process of new blood vessel development from existing vessels.
- By day 5, it reaches its peak

- Steps

- VD (**NO**) and increased permeability induced by **VEGF**
- Separation of pericytes from the surface and breakdown of the BM
 - Formation of a vessel sprout
- Migration of endothelial cells toward the area of tissue injury
- Proliferation of endothelial cells just behind the leading front (“tip”) of migrating cells
 - **Fibroblast growth factors** (FGFs), mainly **FGF-2**, stimulates the proliferation of endothelial cells.
 - **Notch** signaling through “cross-talk” with VEGF, it regulates the sprouting and branching of new vessels
- Remodeling into capillary tubes (**Angiopoietins 1 and 2**)
- Recruitment of peri-endothelial cells (pericytes for small capillaries and SMCs for larger vessels) to form the mature vessel (**PDGF**)
- Suppression of endothelial proliferation and migration and deposition of the basement membrane (**TGF- β**)



