ETH zürich

D-BIOL



Tissue Repair Part III

Prof. Dr. Joel Zindel
Assistant Professor (TT) for Tissue Repair
April 20th 2026

Notes for this lecture



Central concepts — exam-relevant



How we know: We look at the experimental data behind central paradigms. These slides are epistemologic in nature—**how we know what we know**—and should not be memorized for the exam.



Nerd factor: Historical or medical perspective or fun. Not to be committed to memory—although sometimes the most random facts stick best.

Resources: Robbins Basic Pathology, Tenth Edition, Chapter TISSUE REPAIR

Disclaimer on Generalizability: The molecular and cellular paradigms described herein (e.g., the iNKT-mediated macrophage switch and the CSF1-PDGF circuit) represent high-fidelity models of tissue repair. While these 'logic gates' appear conserved across vertebrates, much of the foundational experimental data is derived from specific injury models (predominantly liver and skin). Application to other organ systems should account for tissue-specific niche factors and varying immune cell ontogenies.

Agenda – Tissue Repair

This agenda organises key concepts by when they are discussed — not as strict biological boundaries.

LECTURE 1

Injury

seconds – minutes

- **Definitions:** homeostasis, injury, regeneration, repair, and failure modes.
- The molecular basis of injury and injury detection: DAMPs, PAMPs, and LAMPs.

LECTURE 2

Inflammation

min – hours – days

- Injury detection
- macrophage cloaking and threshold gating
- Coagulation and Complement
- Thromboinflammation

LECTURE 3

Granulation tissue

hours – days – weeks

- The macrophage switch: macrophages subtypes in repair
- Macrophage-fibroblast circuit
- Provisional Matrix
- Angiogenesis
- Neural regulation of repair
- Collagen III
- Failure modes

LECTURE 4

Remodelling

days – weeks – months

- MMP/TIMP balance, collagen I/III
- Myofibroblast resolution
- Fibrosis vs. regeneration

Phases are overlapping and tissue-dependent — complement, macrophages, and adaptive immunity span multiple lectures and are discussed in context.

Learning Objectives — Lecture 3: Granulation Tissue

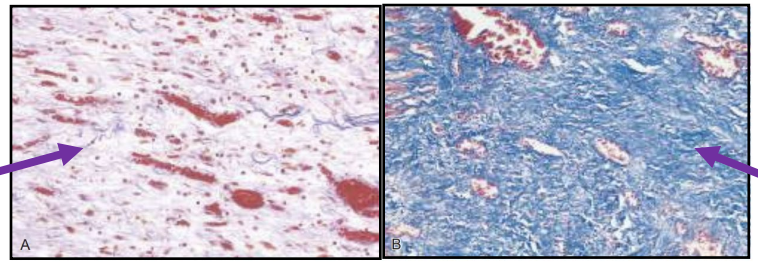
- Students can **describe** the **macrophage-fibroblast two-cell circuit** — key signals, three stable states, separatrix — and explain why injury requires circuit reconstruction from scratch.
- Students can **explain** the **monocyte-to-macrophage class switch**, clarify that CX3CR1 is a maturation not a polarisation marker, and describe the iNKT/CD1d/IL-4 mechanism with its tissue-specific generalisations.
- Students can **distinguish Folr2+ repair macrophages from Trem2+/Spp1+ scar-associated macrophages** by phagocytic cargo, signature, and tissue outcome.
- Students can **define the myofibroblast as a phenotype**, describe **αSMA stress fibre formation**, name two precursor sources including MMT, and explain the mechanical positive feedback loop driving persistence.
- Students can **compare the chemical and mechanical views of myofibroblast activation** — driver, persistence mechanism, therapeutic target, weakness — and state the synthesis.
- Students can **distinguish Model A (functional repair) from Model B (regeneration)** in terms of speed, fidelity, and cellular requirements

Recap: Phases of Repair

Lecture 1 and 2

Lecture 3

Lecture 4



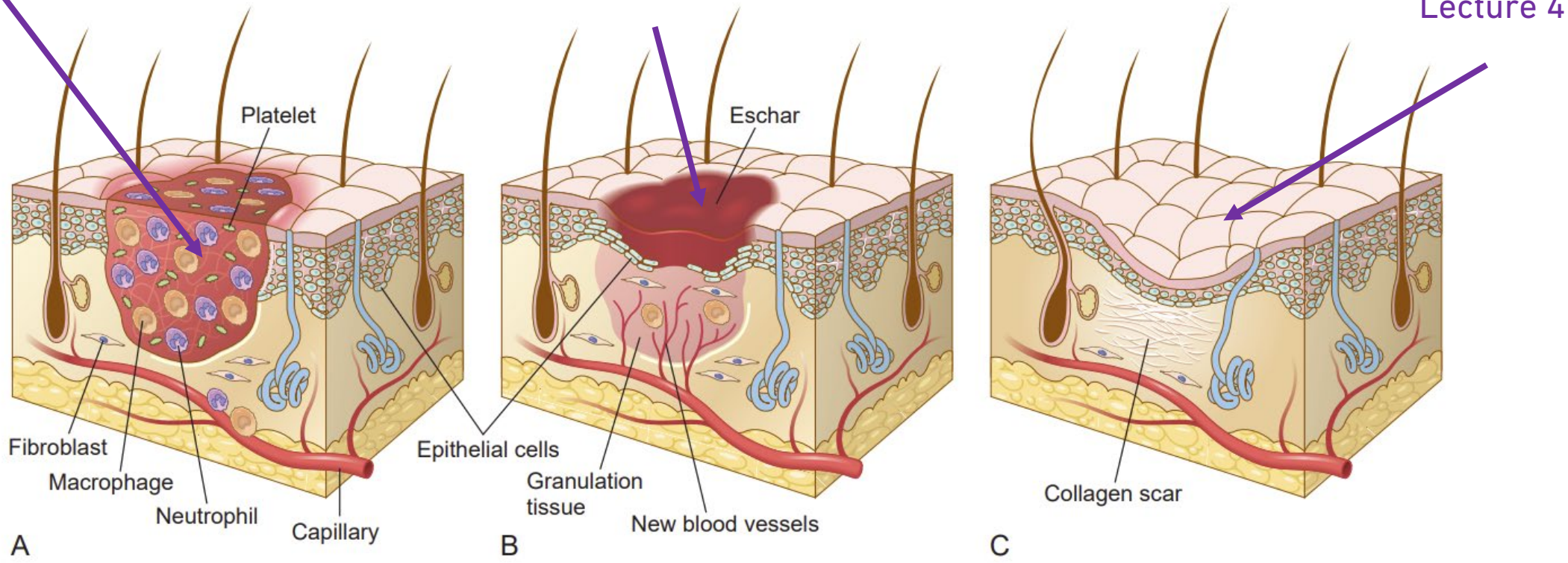
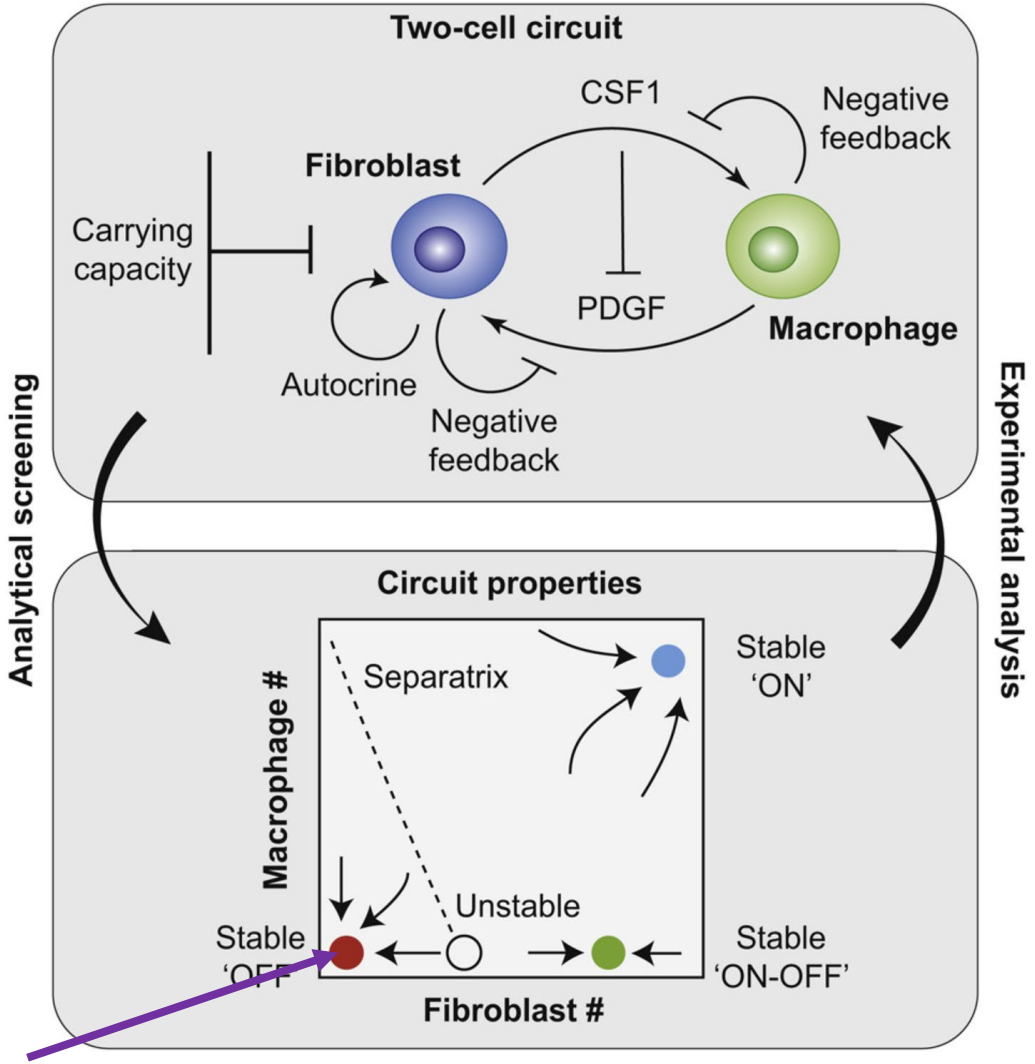


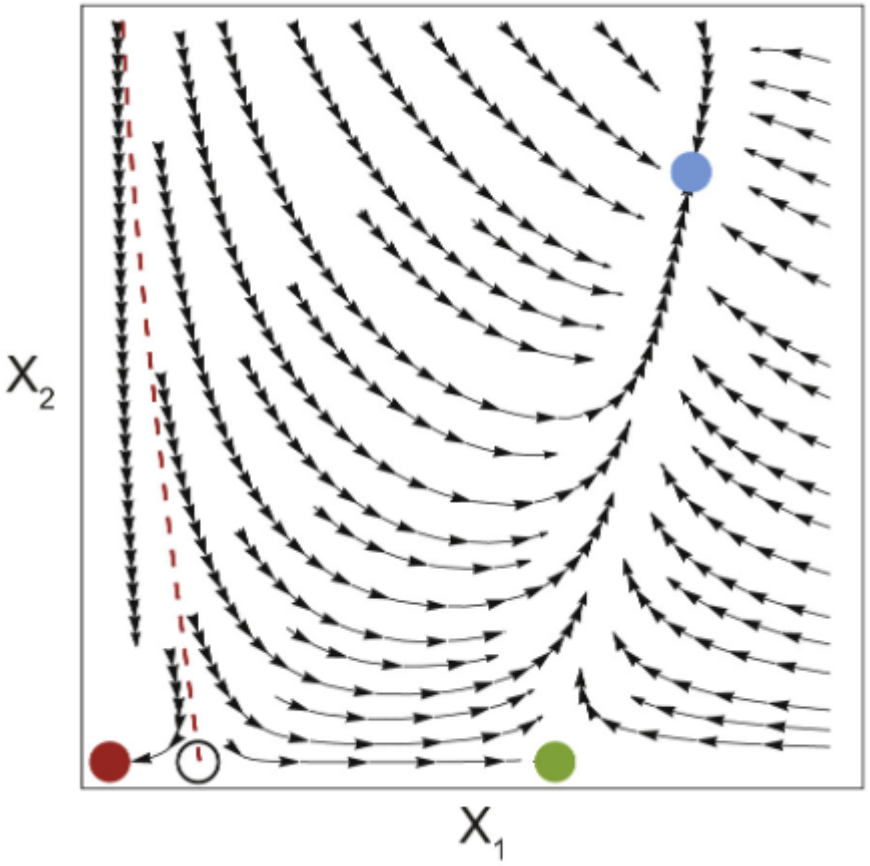
Fig. 3.24 Steps in repair by scar formation: healing of a large wound in the skin. This is an example of healing by second intention. (A) Hemostatic plug and inflammation. (B) Proliferation of epithelial cells; formation of granulation tissue by vessel growth and proliferating fibroblasts. (C) Remodeling to produce the fibrous scar.

Model: Macrophage Fibroblast Circuits



Severe Injury

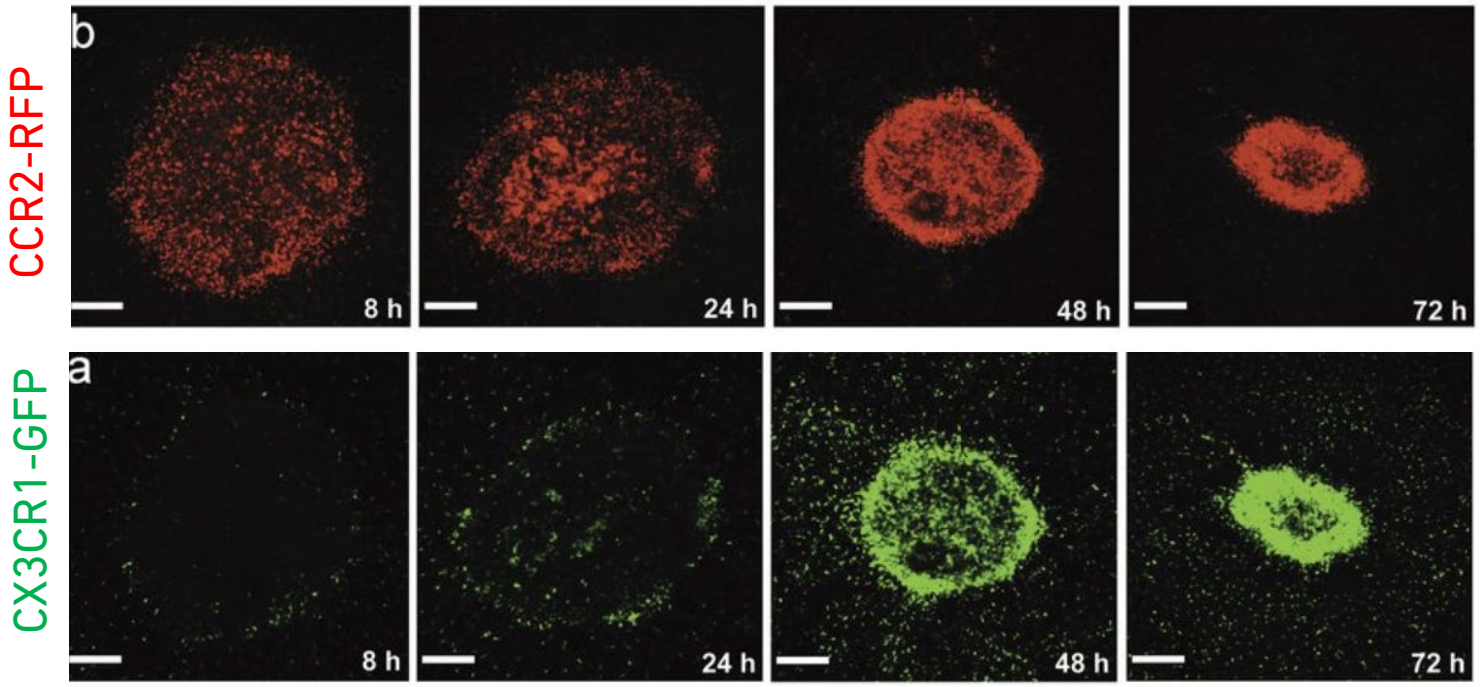
https://doi.org/10.1016/j.cell.2018.01.015

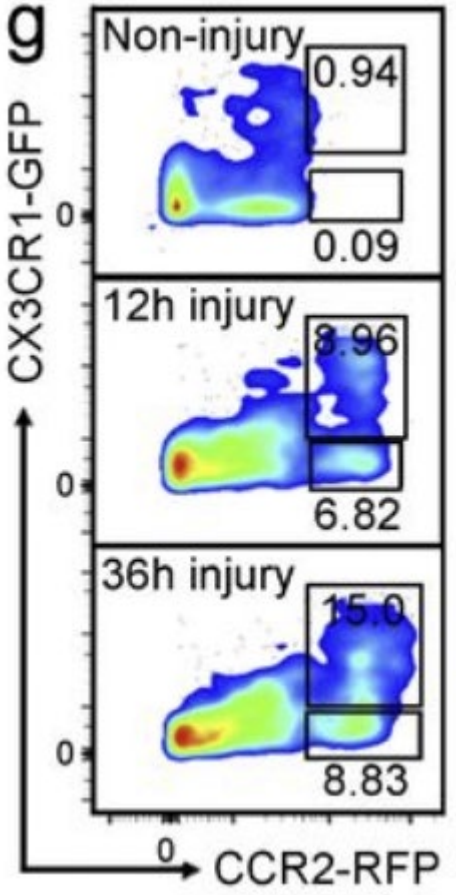


Teaching Note-link to Prof. Werner lecture: this is a classical double paracrine loop

Macrophage Switch: the phenomenon

Focal liver injury

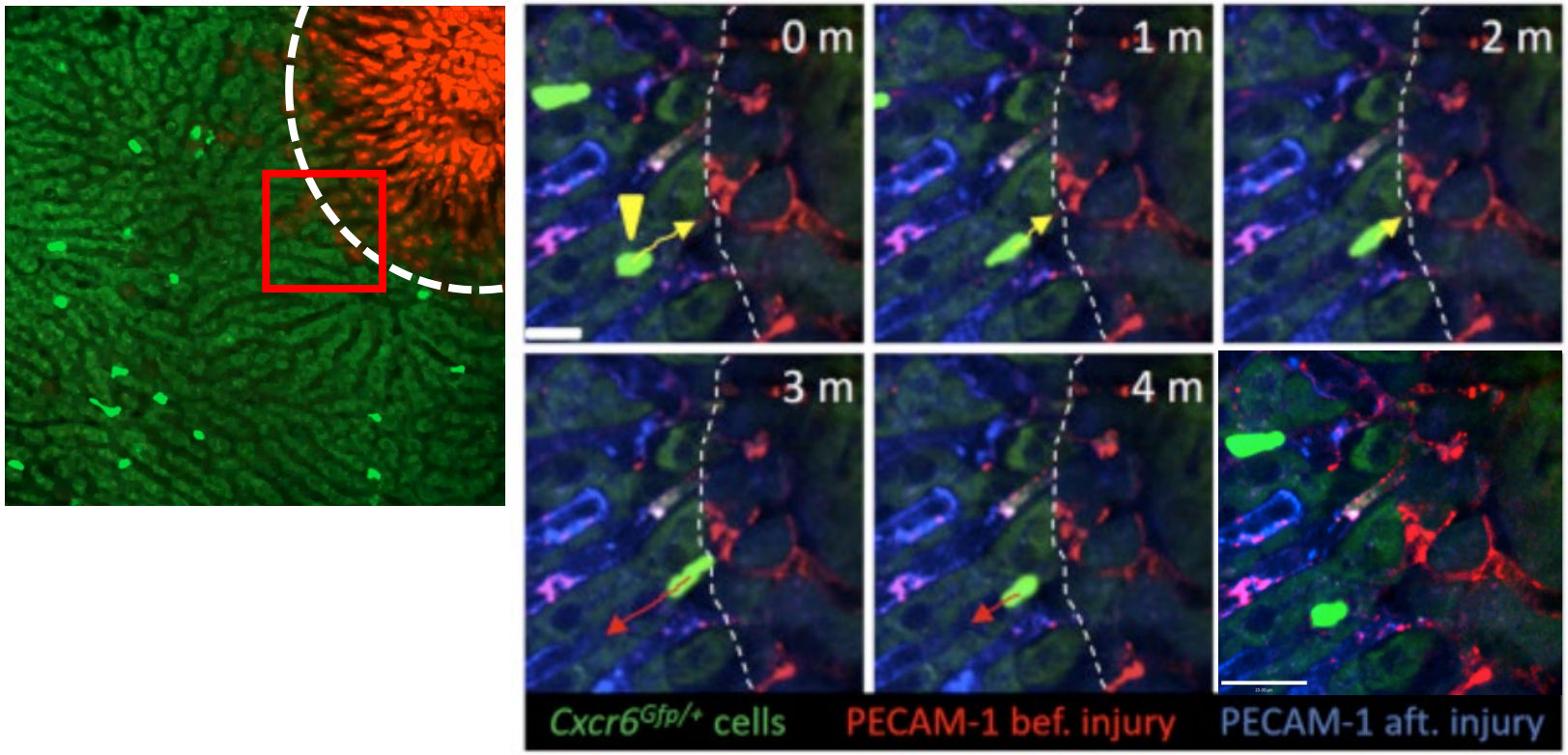


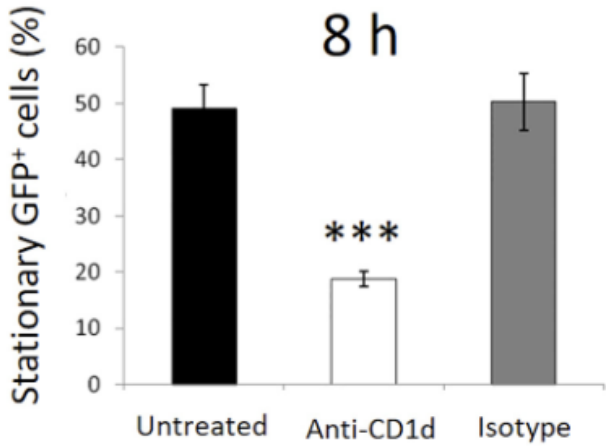


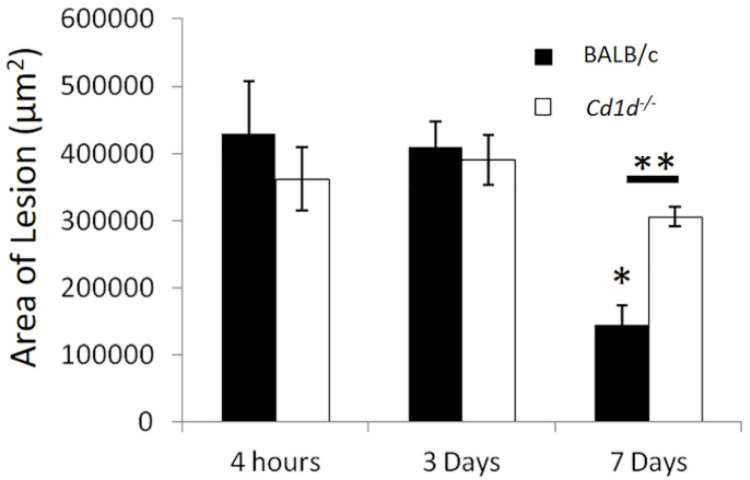
https://doi.org/10.1084/jem.20141539

Macrophage Switch: iNKT cells and glycolipid self-antigens

Focal liver injury

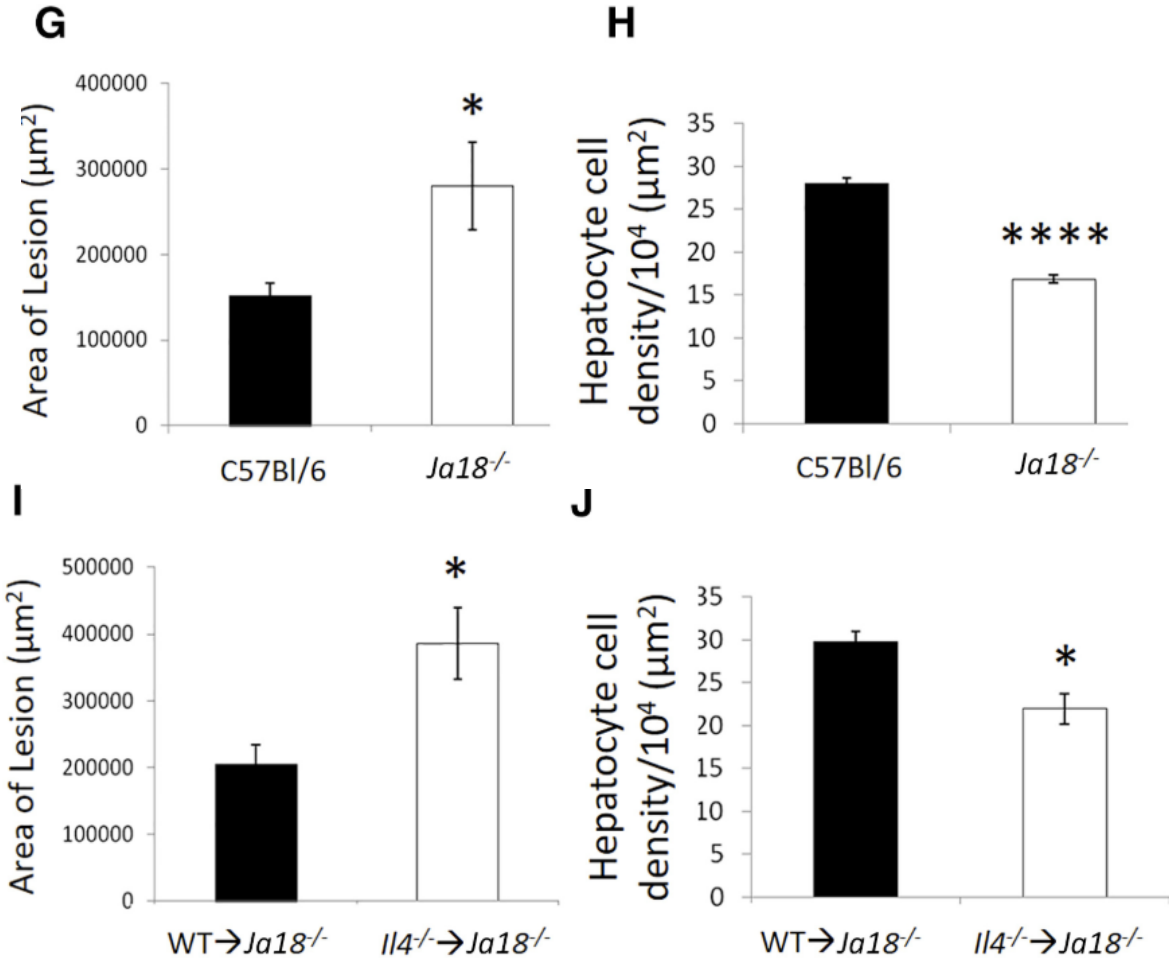


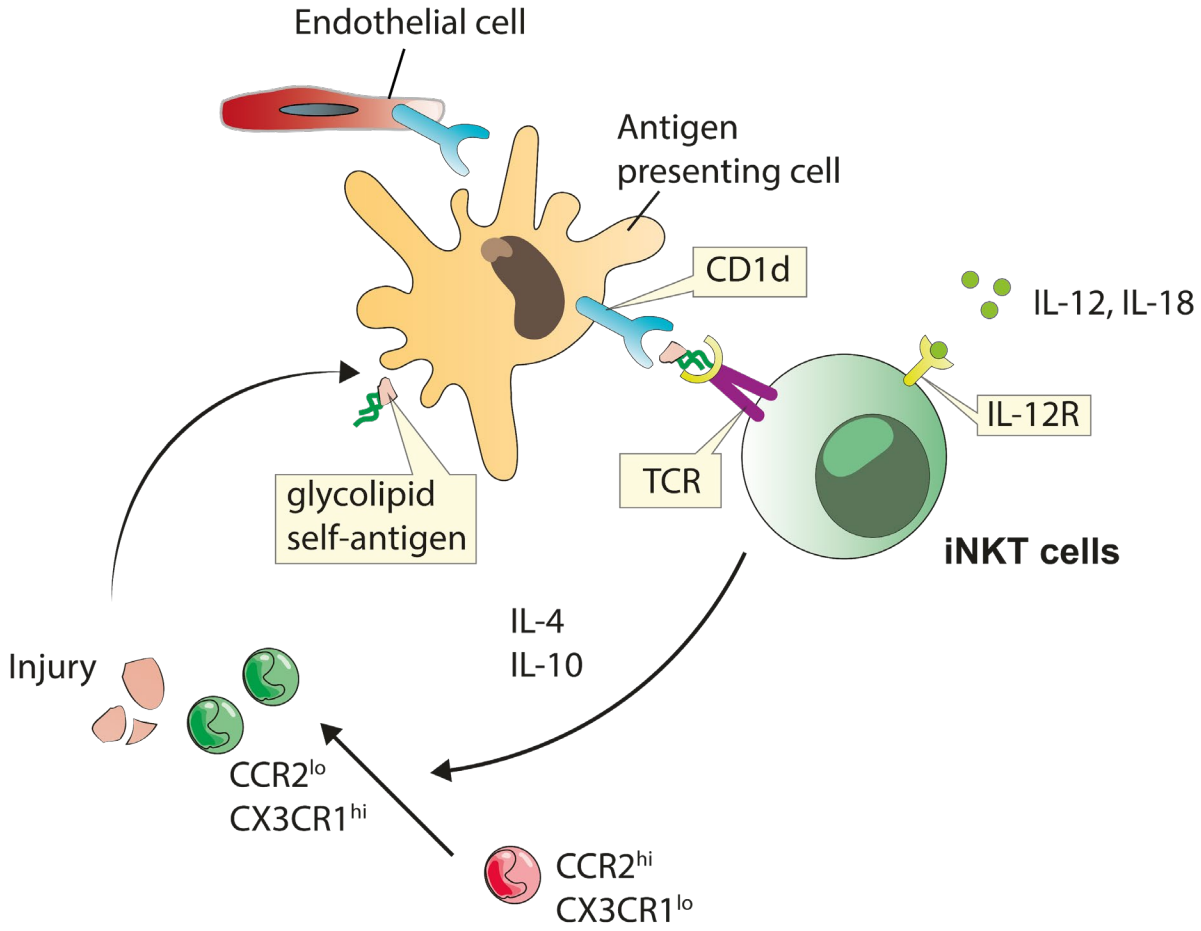




https://doi.org/10.1016/j.immuni.2017.09.016

Macrophage Switch: iNKT cells and glycolipid self-antigens





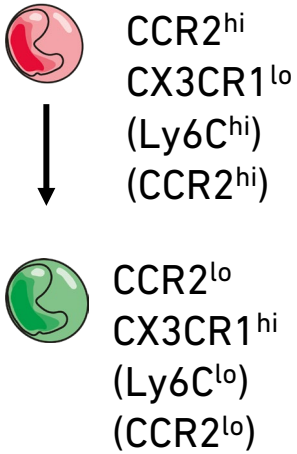
https://doi.org/10.1016/j.immuni.2017.09.016

Macrophage Switch: Overview of signals

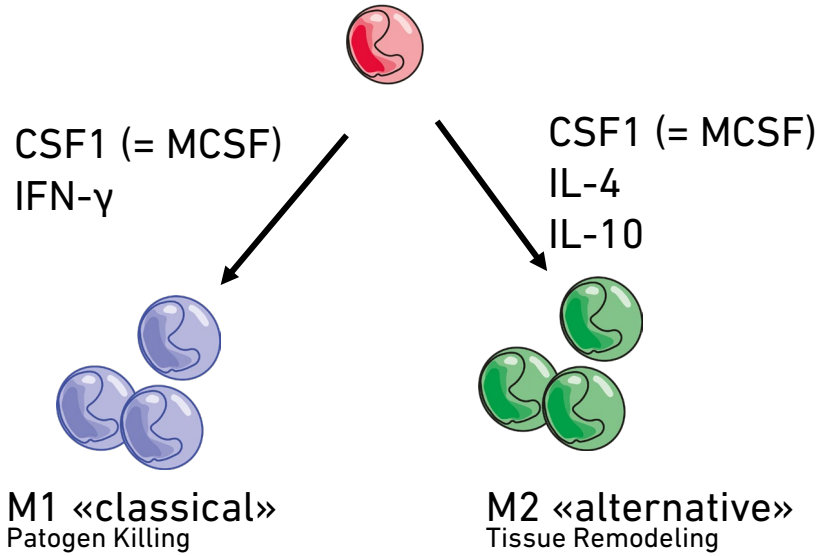
Signal	Source	Tissue context	Receptor on macrophage	Mechanism / output	Reference
Common logic: tissue-resident lymphocytes					
IL-4 / IL-13	iNKT cells	Liver	IL-4Rα / IL-13Rα1	STAT6 → CCR2→CX3CR1 conversion	Liew et al. Immunity 2017 doi:10.1016/j.immuni.2017.09.016
IL-4 / IL-13	ILC2s	Lung, gut, skin	IL-4Rα / IL-13Rα1	STAT6 → repair gene programme	Bosurgi et al. Science 2017 doi:10.1126/science.aai8132
Amphiregulin	Tregs	Muscle	EGFR (?)	Epithelial repair programme, macrophage reprogramming	Burzyn et al. Cell 2013 doi:10.1016/j.cell.2013.11.010
IGF-1 / Amphiregulin	γδ T cells (DETCs)	Skin	IGF-1R / EGFR (?)	Keratinocyte and macrophage activation	Jameson et al. Science 2002 doi:10.1126/science.1069639
Universal Signals independent of tissue context					
PS / efferocytosis	Apoptotic neutrophils	All tissues	TIM4, AXL, MERTK	TGFβ, IL-10, PGE2 → NF-κB suppression, anti-inflammatory reprogramming	Bosurgi et al. Science 2017 doi:10.1126/science.aai8132
SPMs	Neutrophils, macrophages	All tissues	ALX/FPR2, GPR32, ChemR23	Lipid mediator class switch → resolution	Serhan & Levy Nat Rev Immunol 2018 doi:10.1038/nri.2017.103

Link to Immunology III: Macrophage Polarization Models

Class Switch Literature

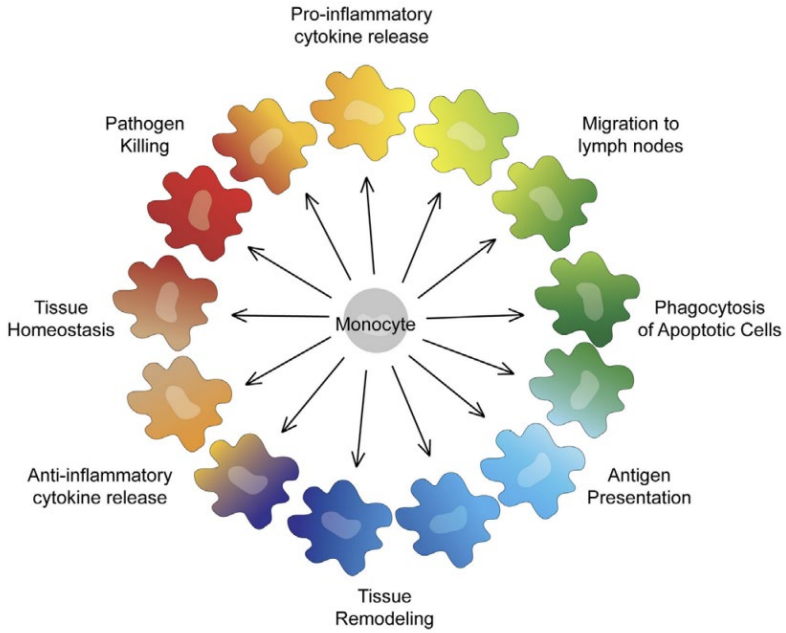


Historic Binary Polarization Model

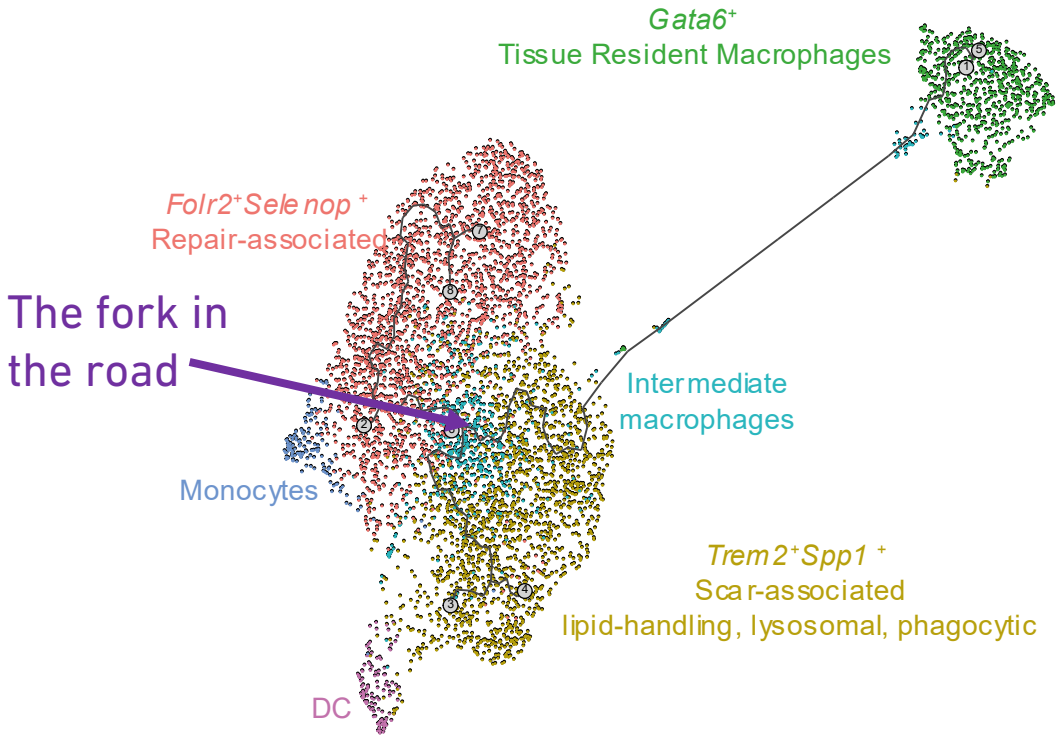


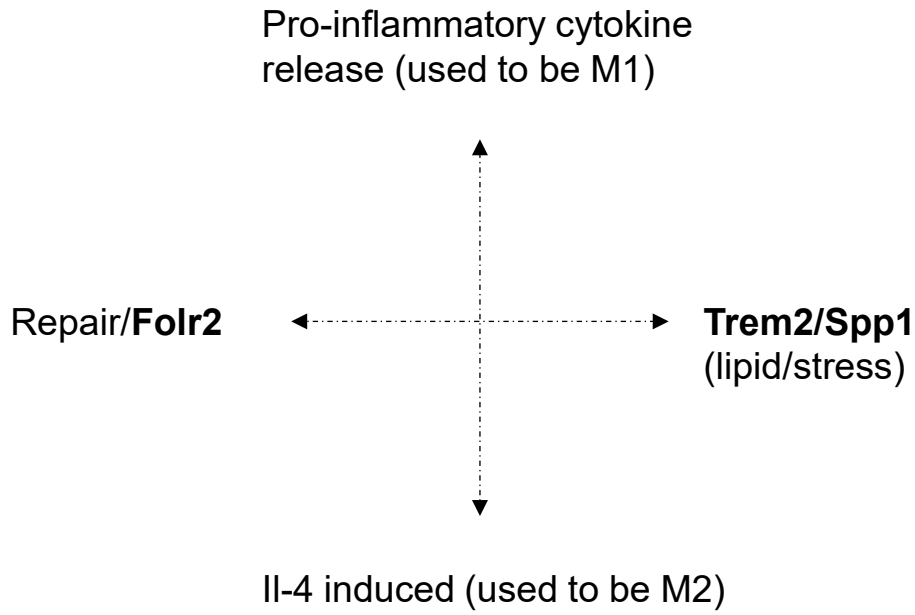
How you should think about it nowadays

CX3CR1^{hi} = mature macrophage, to know what that macrophage is doing:



Link to Immunology III Class Switch





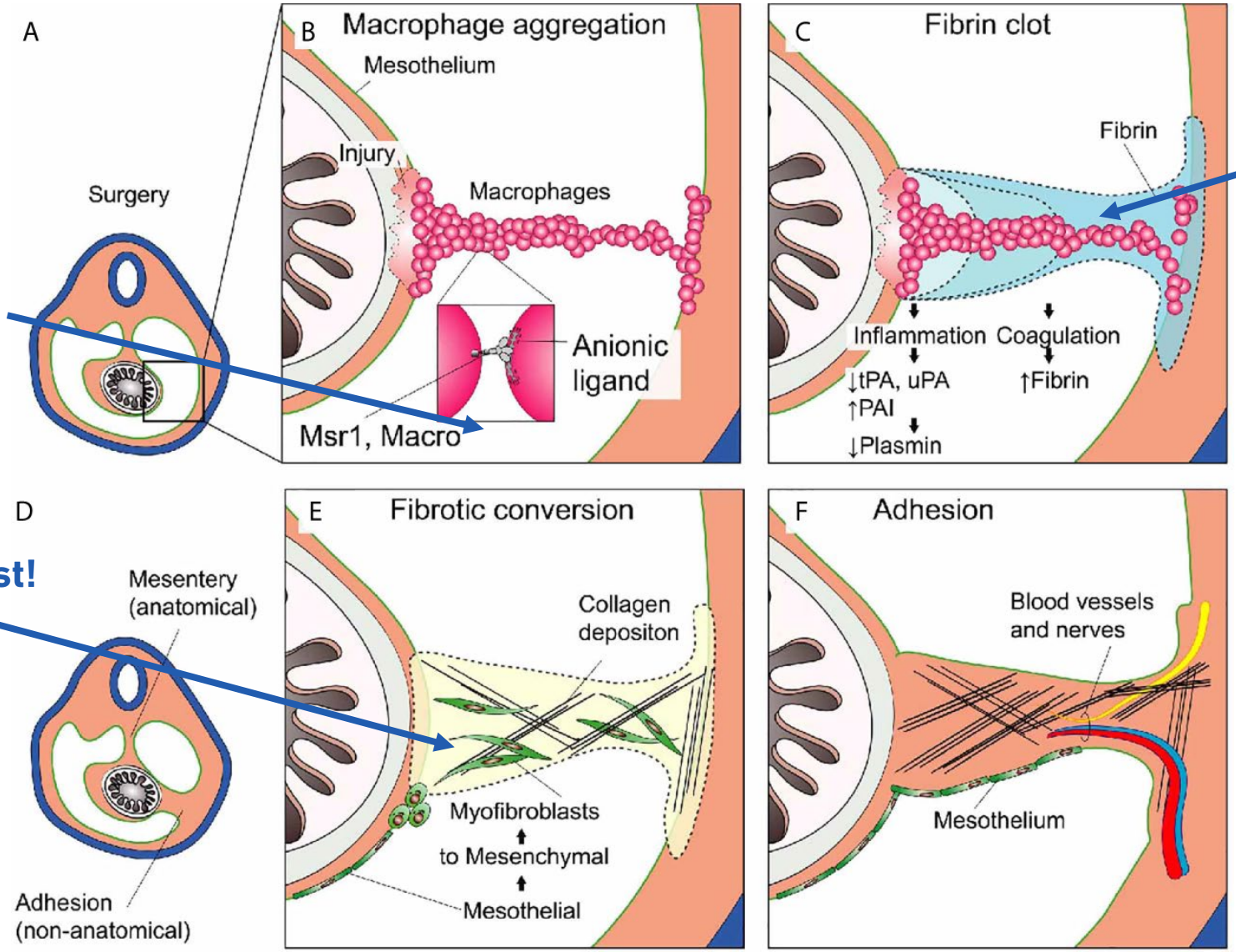
Feature	TREM2 SPP1+ "Fibrotic Cleaner"	FOLR2 SELENOP+ "Repair Cleaner"
Phagocytic Cargo	Necrotic debris, oxidized lipids.	Apoptotic cells (efferocytosis).
Core Signature	TREM2, GPNMB, CD9, SPP1.	FOLR2, SELENOP, MRC1, CD163.
Tissue Outcome	**Scarring (Fibrosis).**	**Functional Repair.**
Vascular Effect?	Spp1-driven angiogenesis (tumour context)	Perivascular localisation (function unclear)
Emerging in the field?	Spp1/OPN signaling hub	Antioxidant protection, survive in «hot» injury zone.

Overshooting Tissue Repair in the Adominal Cavity (Adhesion Formation)

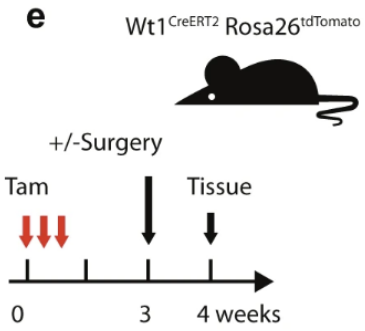
1. DAMP Detection, Inflammation

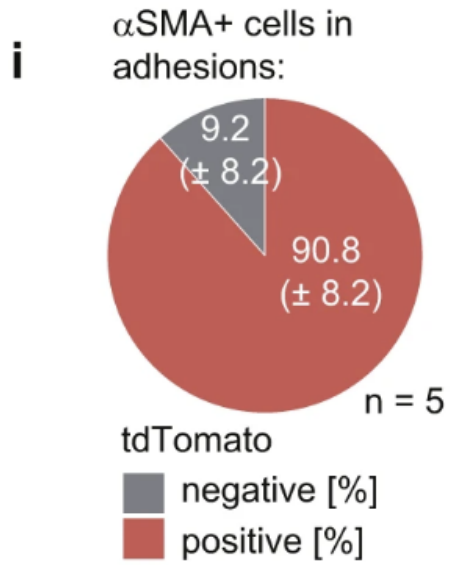
2. Fibrin Clot

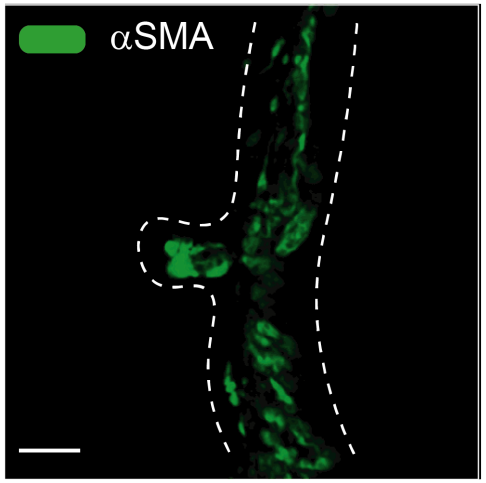
3. Myofibroblast!



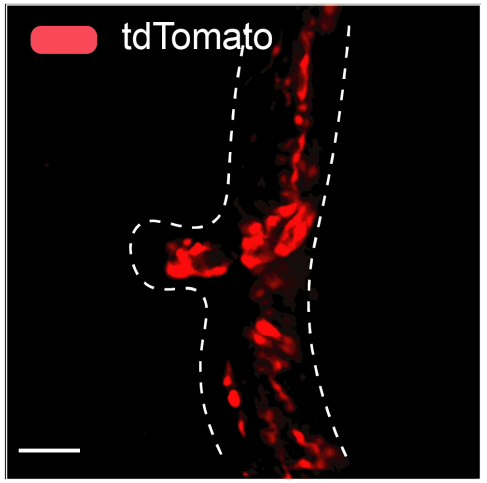
Myofibroblasts in adhesions are Mesothelium-derived



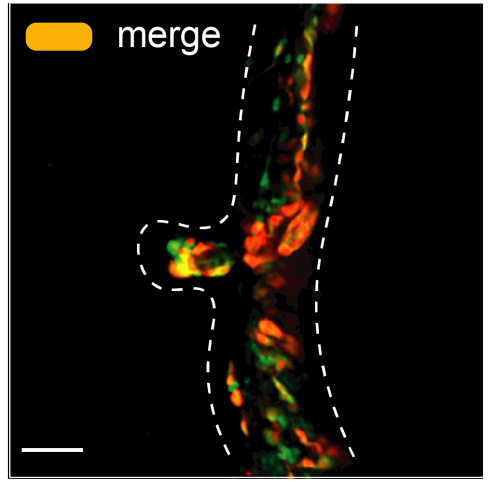




Green = Myofibroblasts

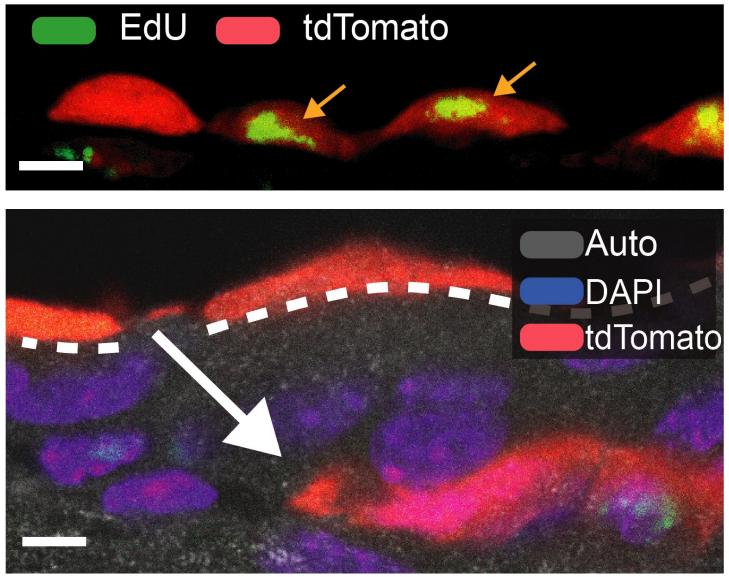


Red = Mesothelium Derived



Yellow = Mesothelium Derived Myofibroblasts

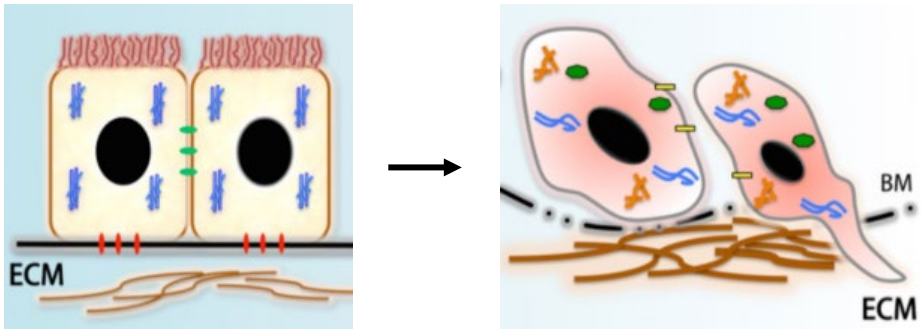
Mesothelial to mesenchymal transition (**MMT**)



Green = proliferating

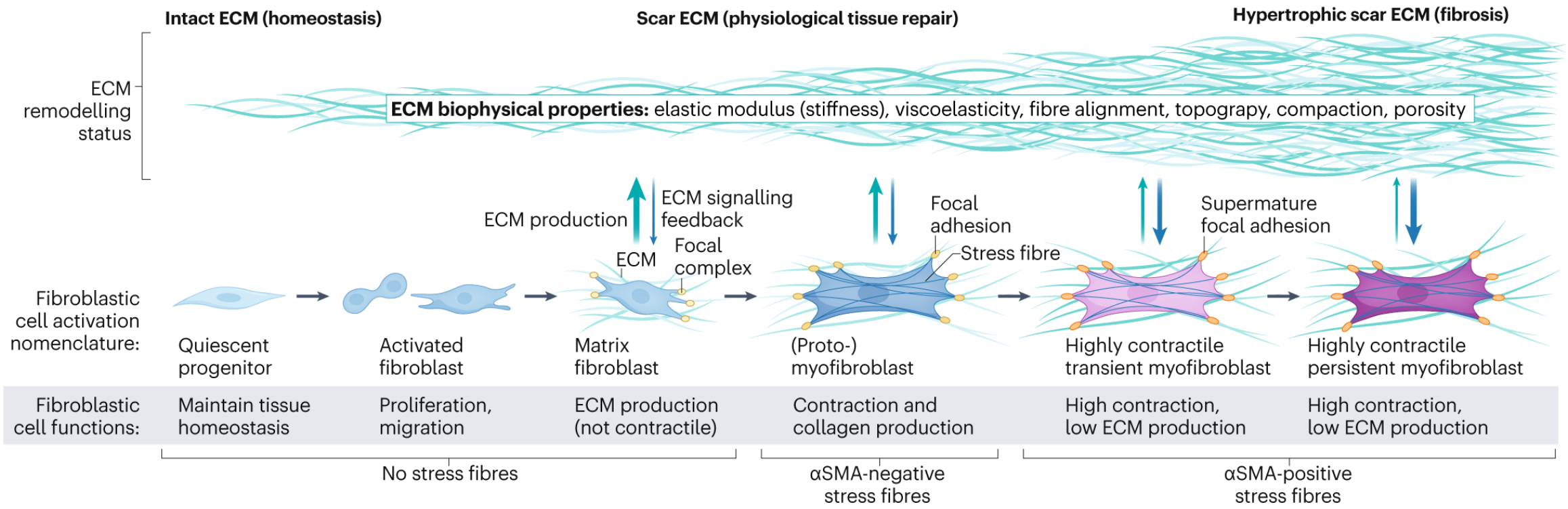
Red = Mesothelium Derived

MMT



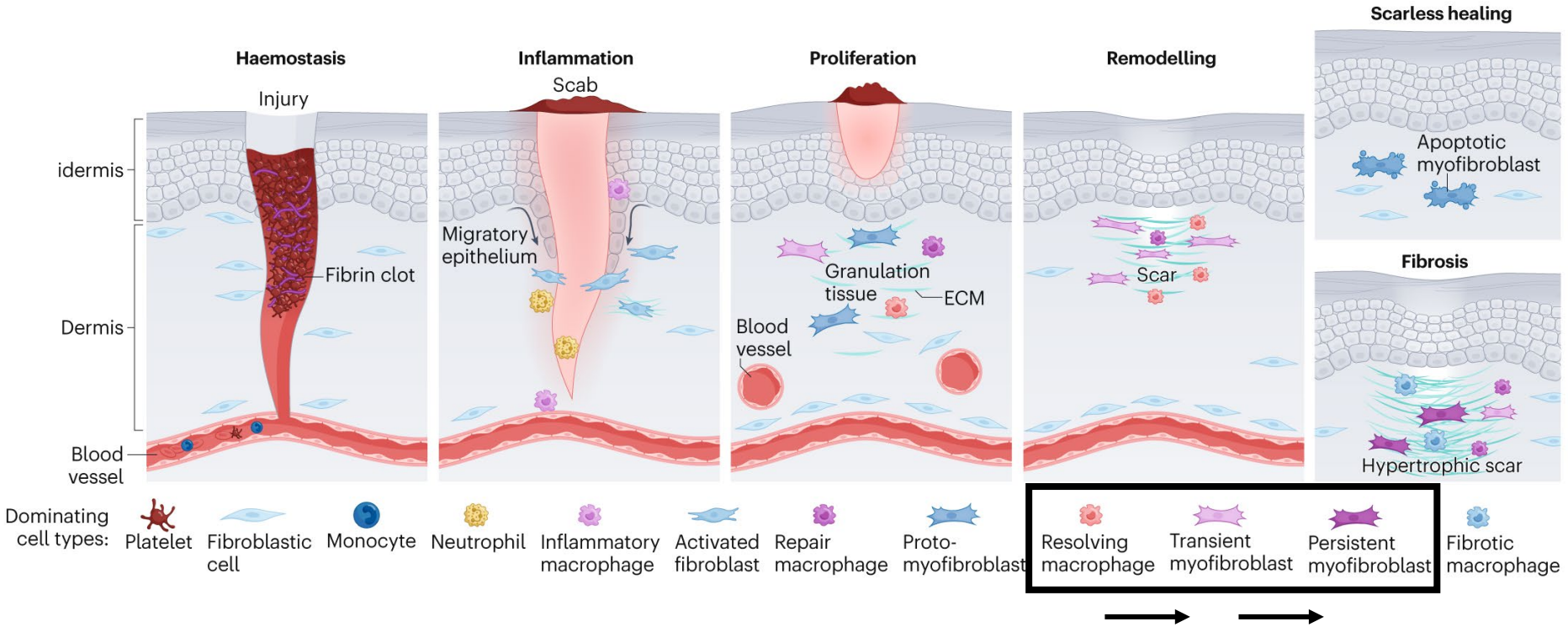
↑α-SMA
↑Proliferation
↑ Migration via disrupted BM
↑ Mobility

Myofibroblasts



https://doi.org/10.1038/s41580-024-00716-0

Myofibroblast resolution



https://doi.org/10.1038/s41580-024-00716-0

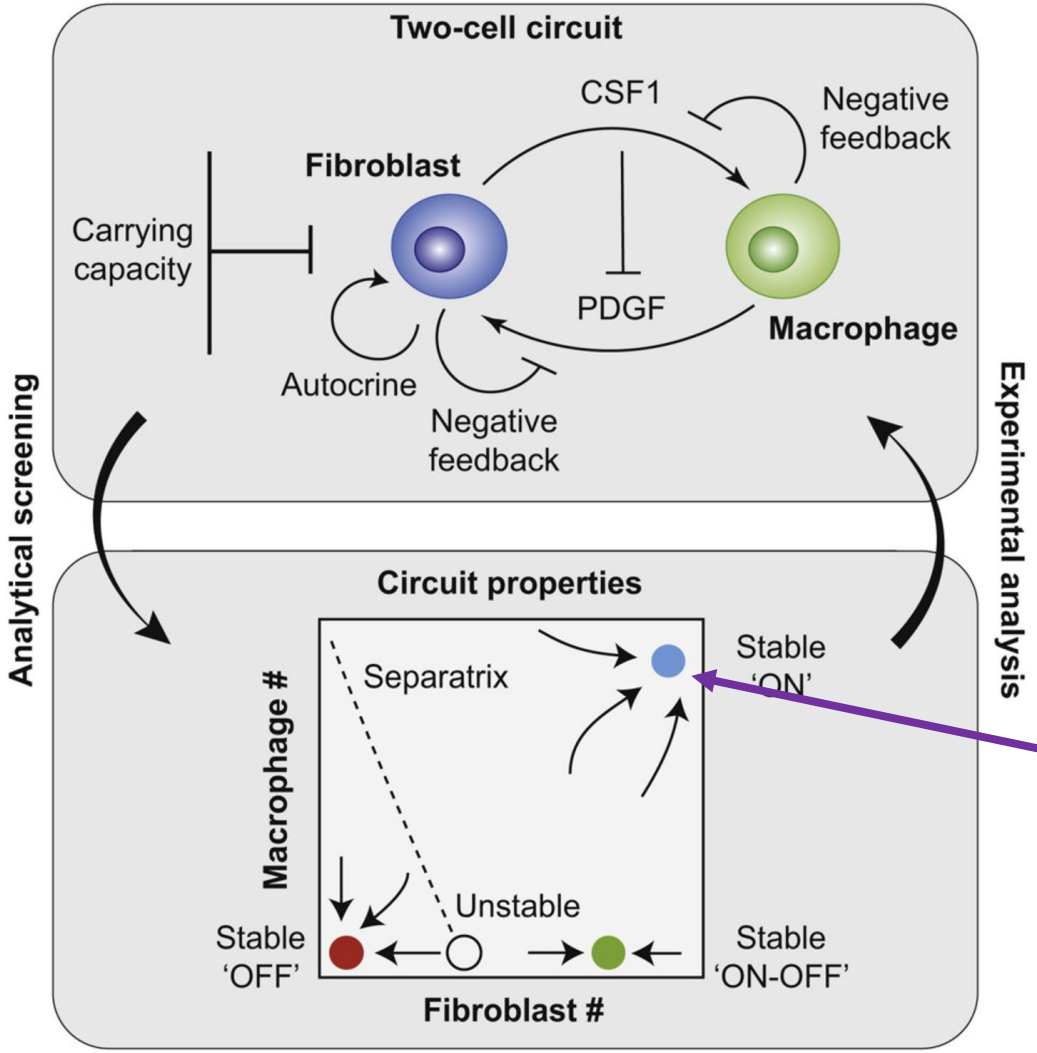
Physiological resolution	Pathological persistence
TGF-β signal drops	Persistent TGF-β / stiff ECM
Mechanical tension reduces	Fibrotic ECM maintains tension
Myofibroblast apoptosis	Resistance to apoptosis
→ Scar matures, cellularity drops	→ Fibrosis

Myofibroblast Activation – chemical vs mechanical signalling view

	Chemical signalling view	Mechanical signalling view
Primary driver	Macrophage-derived TGFβ, IL-4, PDGF	ECM stiffness sensed via **integrins**
Key initiating event	Cytokine release from inflammatory cells	Loss of ECM structural integrity / fibrin clot mechanics
Persistence mechanism	Sustained macrophage activation / **TGFβ loop**	Self-amplifying stiffness-contraction feedback
Key transcription factors	**SMAD2/3, NF-κB**	**YAP/TAZ, MRTFA**
Therapeutic target	Anti-TGFβ, anti-IL-4Rα, macrophage re-polarization	Anti-integrins, ROCK inhibitors, matrix softening
Main evidence base	In vivo macrophage depletion, cytokine KO models	Tunable hydrogel stiffness, atomic force microscopy
Failure mode explained	Chronic inflammation → persistent macrophage activation	Stiff fibrotic ECM → irreversible mechanical memory
Weakness	Cytokine blockade rarely reverses established fibrosis	Stiffness alone insufficient without initial cytokine trigger

B. Hinz: «mechanical stress and TGFβ1 are actually two sides of the myofibroblast differentiation coin» check this for more on mechanical signaling: https://doi.org/10.1038/s41580-024-00716-0

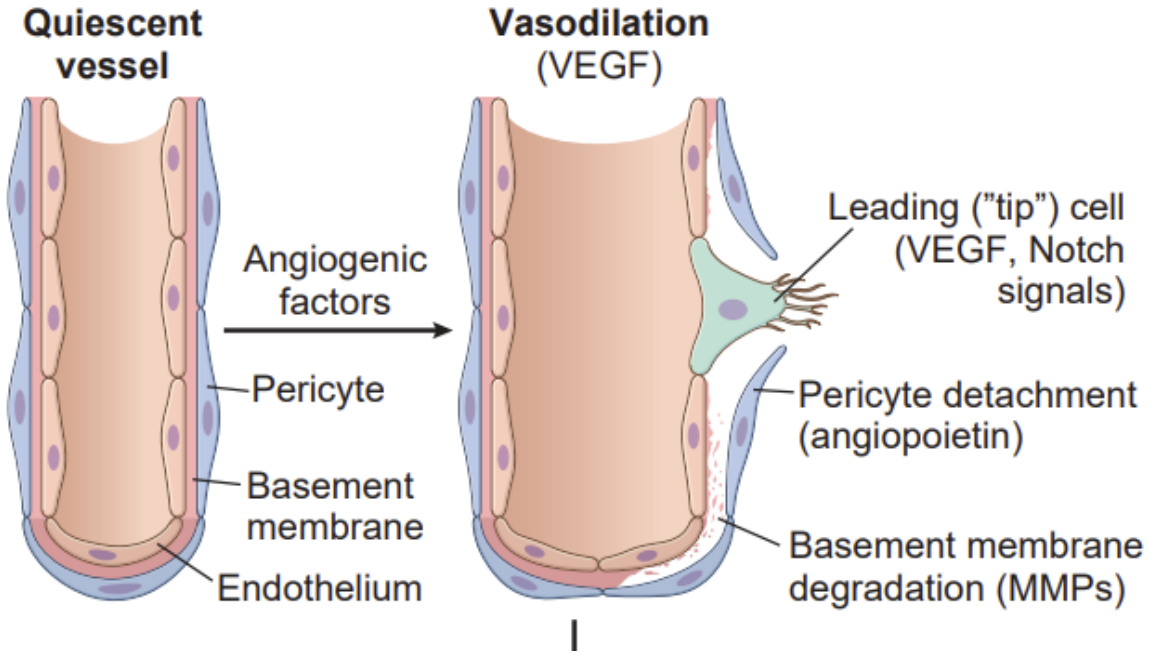
Model: Macrophage Fibroblast Circuits



Return to stable ON

https://doi.org/10.1016/j.cell.2018.01.015

Angiogenesis



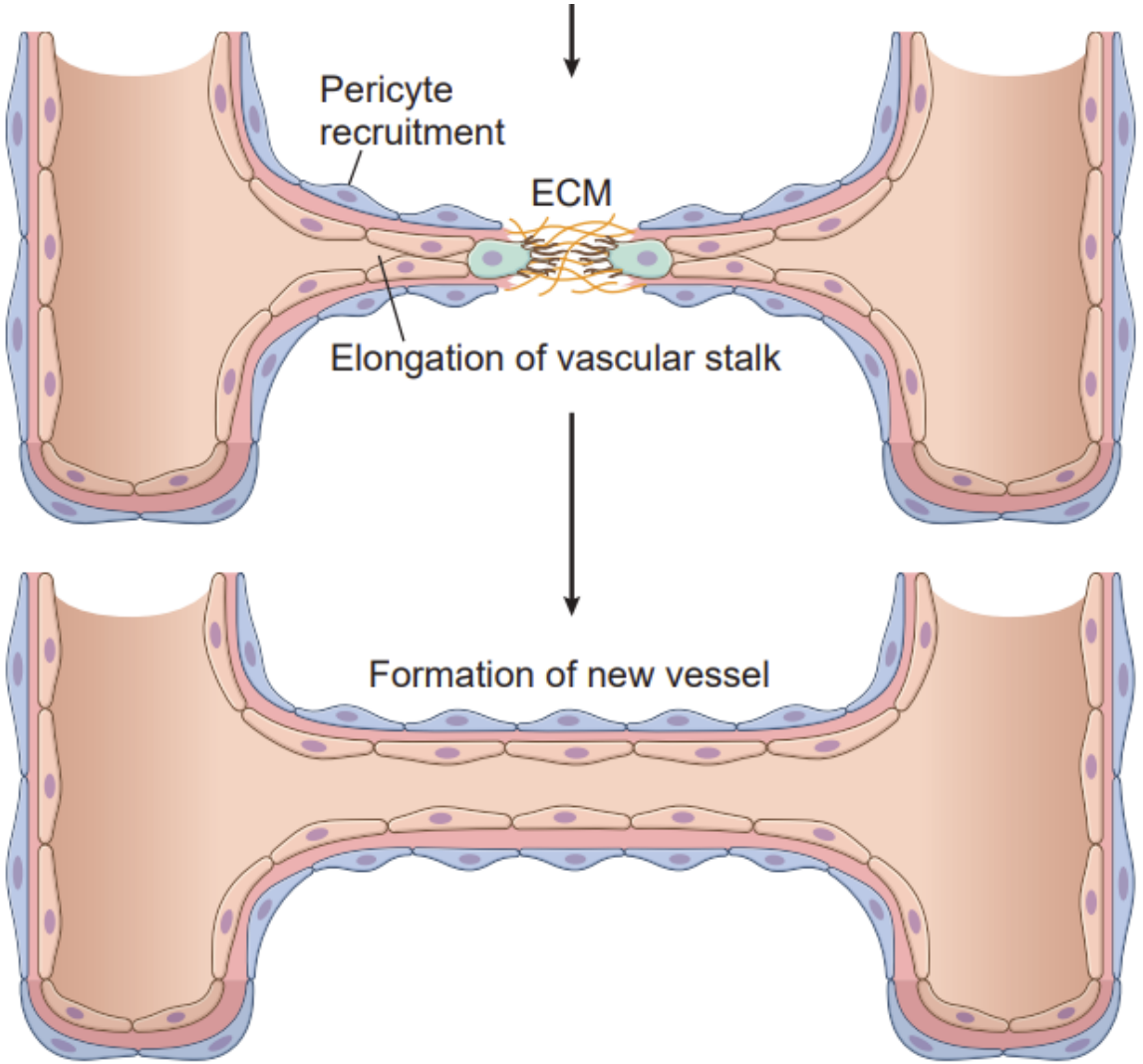
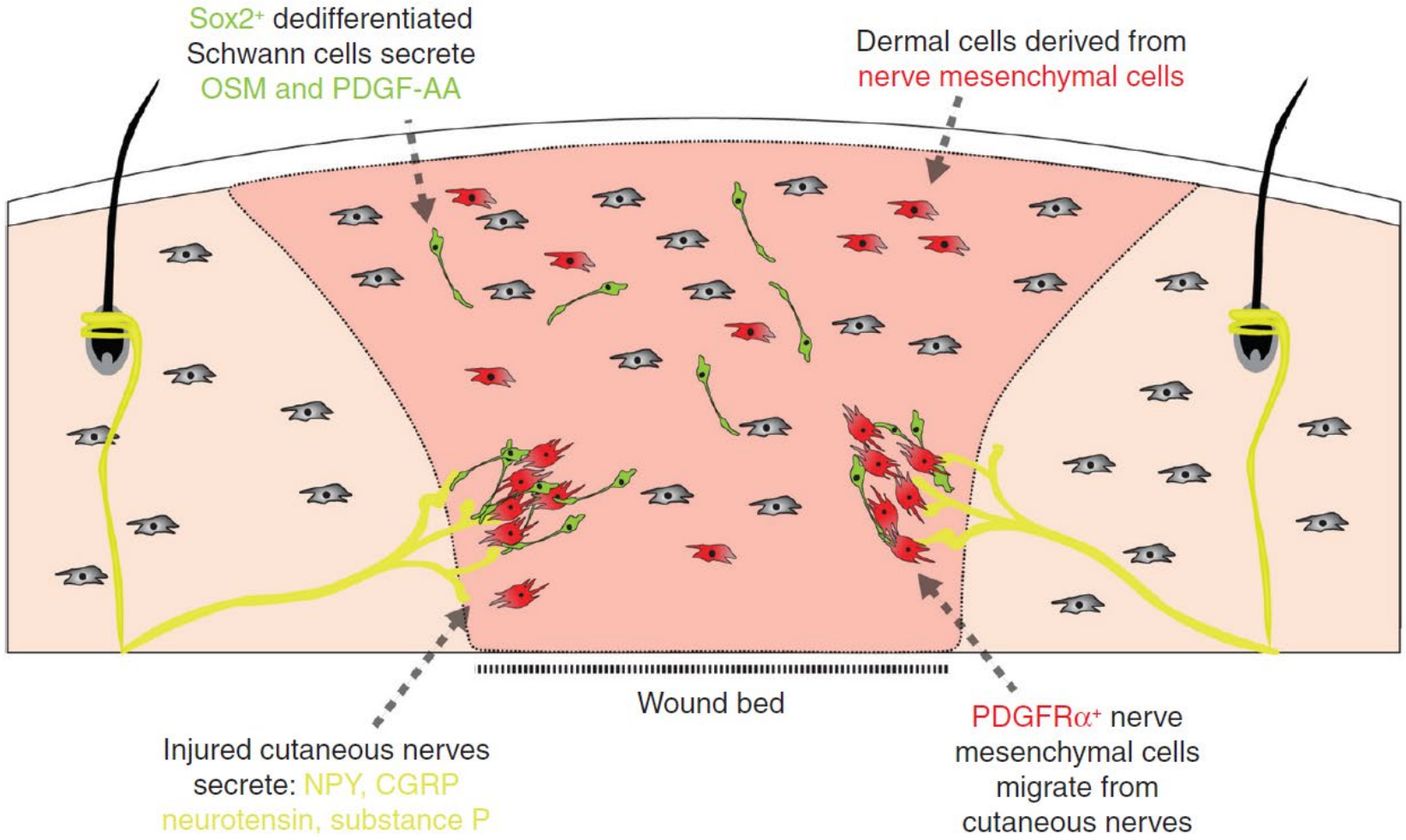


Fig. 3.25 Angiogenesis. In tissue repair, angiogenesis occurs mainly by the sprouting of new vessels. The steps in the process, and the major signals involved, are illustrated. The newly formed vessel joins up with other vessels (not shown) to form the new vascular bed.

Neural Regulation of Repair



10.1101/cshperspect.a041233

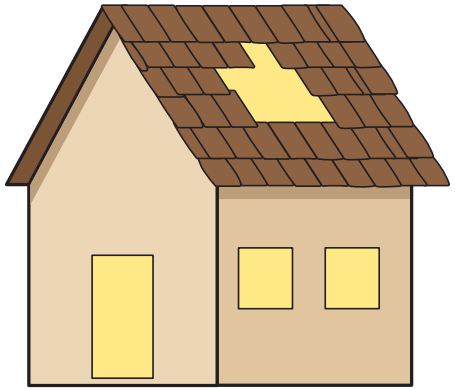
Growth Factors in Repair (Link Lecture Prof. Werner)

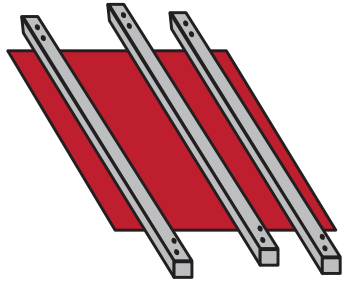
Table 1.1 Growth Factors Involved in Regeneration and Repair

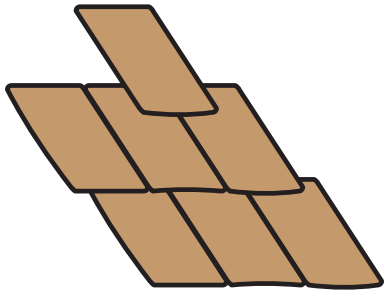
Growth Factor	Sources	Functions
Epidermal growth factor (EGF)	Activated macrophages, salivary glands, keratinocytes, and many other cells	Mitogenic for keratinocytes and fibroblasts; stimulates keratinocyte migration; stimulates formation of granulation tissue
Transforming growth factor-α (TGF-α)	Activated macrophages, keratinocytes, many other cell types	Stimulates proliferation of hepatocytes and many other epithelial cells
Hepatocyte growth factor (HGF) (scatter factor)	Fibroblasts, stromal cells in the liver, endothelial cells	Enhances proliferation of hepatocytes and other epithelial cells; increases cell motility
Vascular endothelial growth factor (VEGF)	Mesenchymal cells	Stimulates proliferation of endothelial cells; increases vascular permeability
Platelet-derived growth factor (PDGF)	Platelets, macrophages, endothelial cells, smooth muscle cells, keratinocytes	Chemotactic for neutrophils, macrophages, fibroblasts, and smooth muscle cells; activates and stimulates proliferation of fibroblasts, endothelial, and other cells; stimulates ECM protein synthesis
Fibroblast growth factors (FGFs), including acidic (FGF-1) and basic (FGF-2)	Macrophages, mast cells, endothelial cells, many other cell types	Chemotactic and mitogenic for fibroblasts; stimulates angiogenesis and ECM protein synthesis
Transforming growth factor-β (TGF-β)	Platelets, T lymphocytes, macrophages, endothelial cells, keratinocytes, smooth muscle cells, fibroblasts	Chemotactic for leukocytes and fibroblasts; stimulates ECM protein synthesis; suppresses acute inflammation
Keratinocyte growth factor (KGF) (i.e., FGF-7)	Fibroblasts	Stimulates keratinocyte migration, proliferation, and differentiation

ECM, Extracellular membrane.

Regeneration and Stem Cells (Link Lecture Prof. Gehart)







Macrophage fibroblast circuit (Model A)

- Rapid
- Robust function
- Low architectural fidelity

Regeneration (Model B)

- Slow, costly
- High architectural fidelity
- Requires **stem cells**

Learning Objectives — Lecture 3: Granulation Tissue

- Students can **describe** the **macrophage-fibroblast two-cell circuit** — key signals, three stable states, separatrix — and explain why injury requires circuit reconstruction from scratch.
- Students can **explain** the **monocyte-to-macrophage class switch**, clarify that CX3CR1 is a maturation not a polarisation marker, and describe the iNKT/CD1d/IL-4 mechanism with its tissue-specific generalisations.
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- Students can **distinguish Model A (functional repair) from Model B (regeneration)** in terms of speed, fidelity, and cellular requirements

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