ETH zürich

D-BIOL



Tissue Repair Part I: Injury

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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: Perspective or fun facts (slides with black background are from our own laboratory). Not to be committed to memory—although sometimes the most random facts stick best.

Resources:
- Zindel & Kubes 2020 Annu Rev Pathol 2020

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

- Model A: Macrophage-fibroblast circuits
- Model B: Stem cell compartments
- Fundamental repair processes

LECTURE 4

Remodelling

days – weeks – months

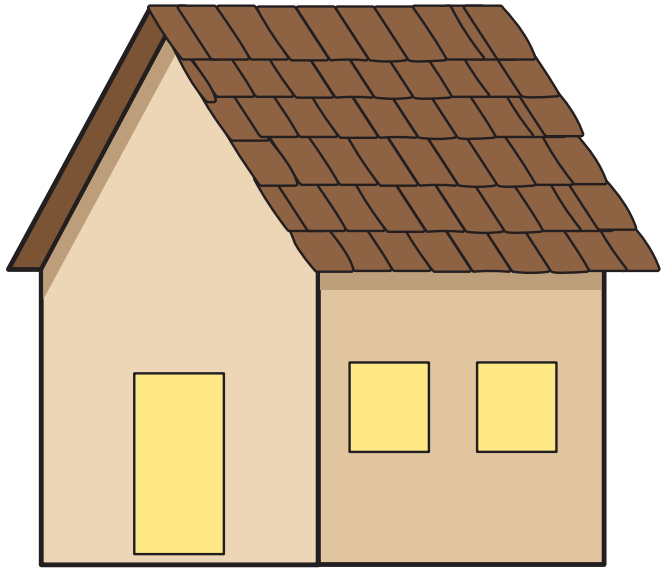
- MMP/TIMP balance, collagen I/III
- Myofibroblast resolution
- Fibrosis vs. regeneration

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

Learning Objectives — Lecture 1: Injury

- Students can **define homeostasis**, **injury**, **repair**, and **regeneration**, and distinguish the **failure modes** of insufficient repair (leakage/non-healing) and excessive repair (fibrosis/pathological scarring).
- Students can **explain** the conceptual basis of the **danger/damage model** — that the innate immune system detects molecular patterns rather than antigens, and responds to both foreign (PAMPs) and endogenous (DAMPs) danger signals.
- Students can **describe** the **compartmentalisation principle** underlying DAMP recognition — the "wrong neighbourhood principle" (**localisation**) and the "wrong shape principle" (**conformation/modification**) — and give one experimental example of each.
- Students can **distinguish** between **cDAMPs** and **iDAMPs** in terms of mechanism of release, cell state, and functional consequence, and explain why LAMPs do not fit the strict DAMP definition.
- Students can **name** representative **DAMPs** from major molecular categories (nucleic acids, proteins, lipids, metabolites) and describe their cognate receptors.

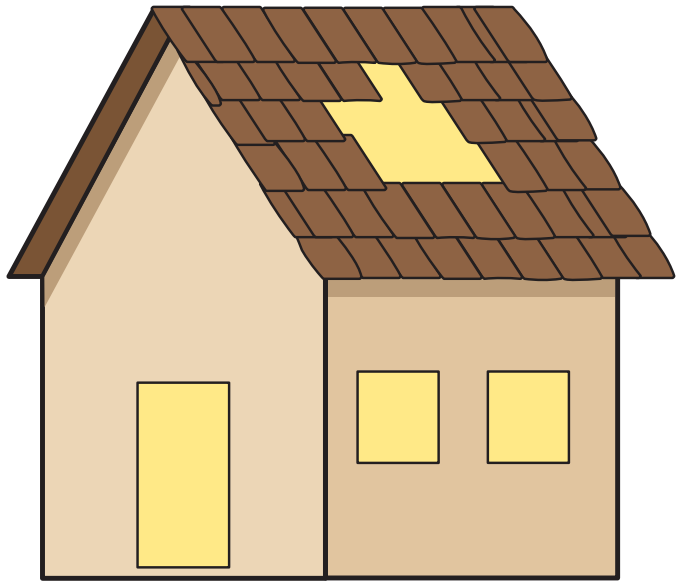
Definition: Tissue Homeostasis



Tissue Homeostasis *The active maintenance of tissue structure and function within a defined set point.*

- Requires continuous energy input — not a passive equilibrium.
- Defined by tissue-resident cells (tissue resident macrophages, fibroblasts, epithelium) sensing and correcting deviations.
- Parameters maintained: organ function, barrier integrity, cell number, ECM composition, metabolic state.
- **Small deviations are** corrected silently and consistently by local mechanisms (e.g. macrophage efferocytosis) and are a **part of homeostasis.**

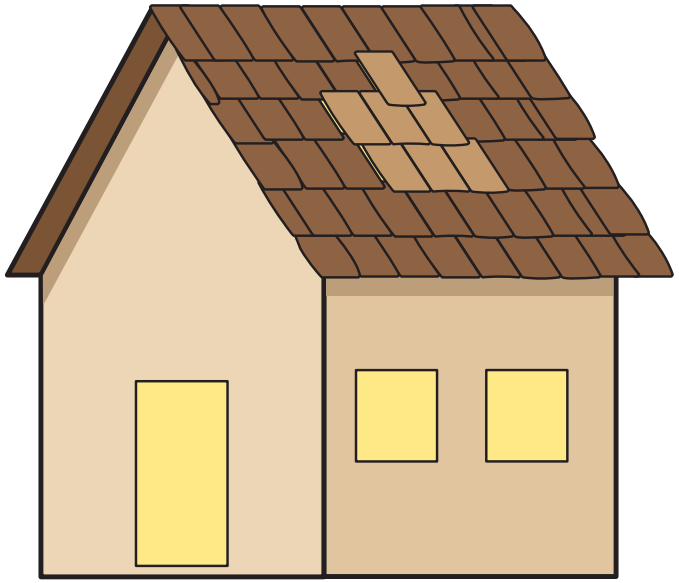
Definition: Injury



Tissue injury is a deviation from homeostatic set points that exceeds the capacity of local homeostatic mechanisms to correct. — Medzhitov, Nature 2008 & Cell 2010.

- **Causes:**
  - Physical
    - Trauma: e.g. surgery, accident
    - Radiation (UV, Gamma)
    - Thermal
    - Sterile particulate (crystals, implants, foreign body)
  - Biochemical
    - *Exogenous toxins*: drugs, venoms,
    - *Endogenous toxins*: autoimmune efforts, enzymes, ROS, bile acids)
    - Pathogen-driven cell death
    - Deprivation (lack of oxygen, nutrients, growth factors)
- **Consequences:** — Loss of structural integrity — Loss of tissue function — Loss of homeostatic regulation

Definition: Regeneration*



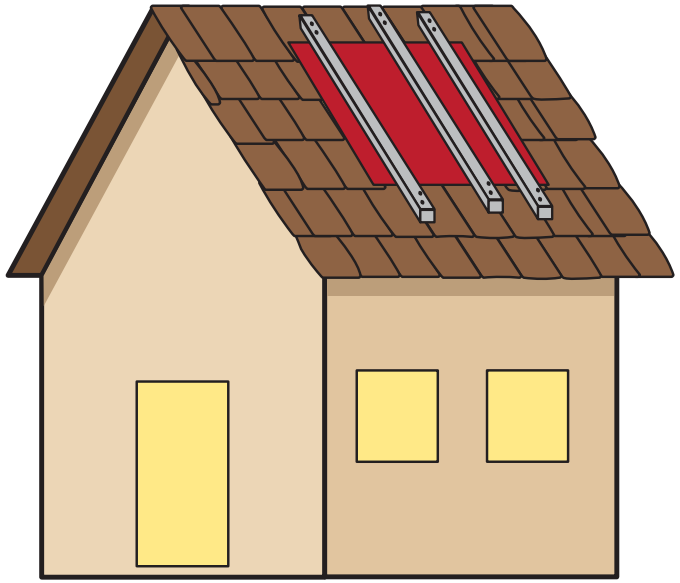
Regeneration is a heroic biological process that restores tissue architecture and function in the face of day-to-day cell loss or the aftershock of injury. Poss & Tanaka, *Cell Stem Cell* 2024.

Characteristics:

- Restitutio ad integrum
- Restores both **function AND original architecture** — layer by layer, cell type by cell type
- Involves **morphogenetic programmes** — positional identity, tissue patterning, size control
- Slow — quality prioritised over speed
- **Rare in adult mammals** — default in: gut epithelium, liver (partial), haematopoietic system, skin epidermis, mesothelium
- Retained in lower vertebrates throughout adult life (zebrafish heart, salamander limb)

***Teaching note—Regeneration:** In clinical contexts the term regeneration is used to describe any successful healing, but in developmental biology and regenerative medicine this strict definition is the gold standard.

Definition: Repair

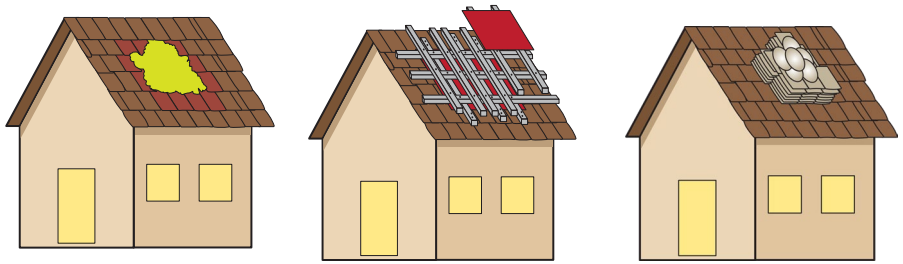


Tissue Repair is the restoration of tissue function and structural continuity following injury, typically resulting in a functional but architecturally imperfect scar. — Gurtner et al., Nature 2008

Characteristics:

- Restores **function** — barrier integrity, mechanical continuity, organ capacity.
- Does **not** fully restore original architecture — collagen scar replaces original ECM.
- Speed prioritized over perfection — evolutionary design for acute survival.
- Outcome determined by injury type, tissue context, and systemic factors (age, diabetes, nutrition).

Failure Modes of Repair



Chronic Wound | **Fibrosis** | **Cancer**

Failure modes of repair — *when the repair programme encounters what it was not designed for*

Chronic non-healing wound — repair stalled

- Inflammatory phase cannot resolve → DAMPs not cleared
- Impaired macrophage switch
- Biofilm, ischaemia, neuropathy prevent progression

Fibrosis — repair that never switches off

- Myofibroblasts persist → excess collagen deposition
- TGFβ loop not terminated → progressive ECM accumulation
- Macrophage-fibroblast circuit stuck in activation

Cancer — uncontrolled proliferation

- Not strictly a failure mode of repair, but cancer hijacks repair machinery and has been likened to *"wounds that do not heal"* — Dvorak, NEJM 1986

Recap: Pattern Recognition







- Innate pattern recognition is **germline-encoded** — fixed, conserved, present from birth
- Recognises **molecular patterns**, not specific antigens — no clonal selection, no memory*
- Original paradigm: immune system detects **foreignness** (non-self) — Burnet & Fenner
- Revised paradigm: immune system detects **danger / damage** — Matzinger 1994
- PRRs respond to both **PAMPs** (pathogen-derived) and **DAMPs** (host-derived) — same machinery
- This is why sterile injury triggers inflammation — no pathogen required

***Nerd factor—Trained Immunity:** We now know that innate cells (monocytes, NK cells) can undergo epigenetic reprogramming after exposure to certain PAMPs (like β-glucan), leading to a "heightened" response to secondary infections. It isn't "memory" in the V(D)J recombination sense, but it functions similarly.

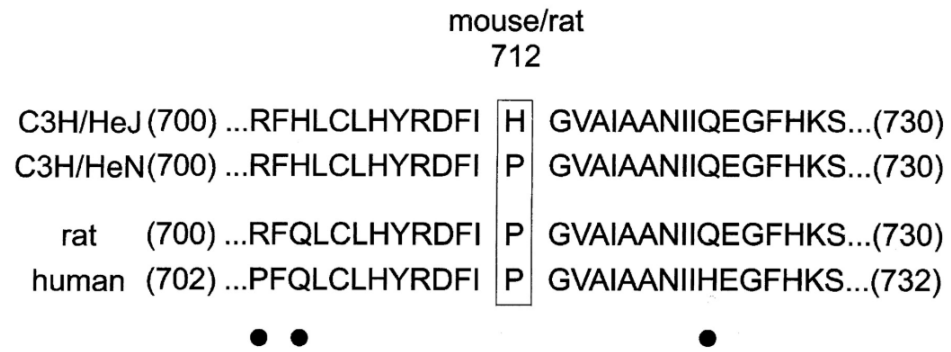
Recap: Pattern Recognition Receptors (PRR)

TABLE 1. *Susceptibility of inbred strains of mice and their hybrids to the lethal effect of endotoxin*

Male mice	LD_{50} (μg)[a]
A/HeJ	60
C_3H/HeJ	2,240
F1 (A/HeJ × C_3H/HeJ)	900
Backcross (F1 × A/HeJ)	672
Backcross (F1 × C_3H/HeJ)	1,350

[a] Mortality at 72 hr after intraperitoneal injection of *E. coli* 0127:B8 endotoxin.

B. Sultzer, Nature 1968, Infect Immun. 1972



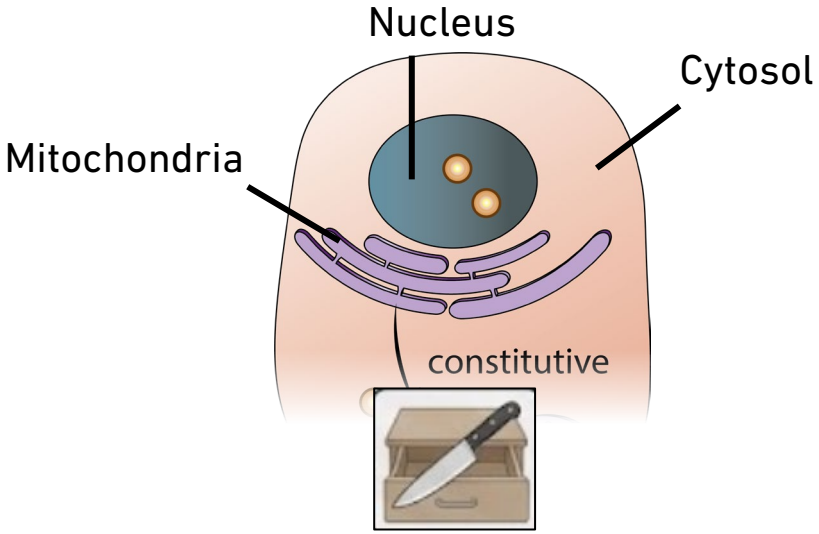
Poltorak, ..., Beutler, Science 1998

- Lipopolysaccharide (LPS) is a strong inducer in gram-negative sepsis.
- (**Sultzer 1968**) **C3H/HeJ** mice are **resistant to LPS.**
- C3H/HeN controls, humans, and rats are LPS susceptible.
- (**Beutler et al 1998**) Positional cloning identified position 712 P -> H (Pro712His) in TLR4 gene.
  - Proline: LPS-susceptible, very conserved
  - Histidine: LPS-resistant
- TLR4 = the paradigmatic PAMP receptor

Damage **A**ssociated **M**olecular **P**atterns **DAMPS**

The **compartmentalization** principle

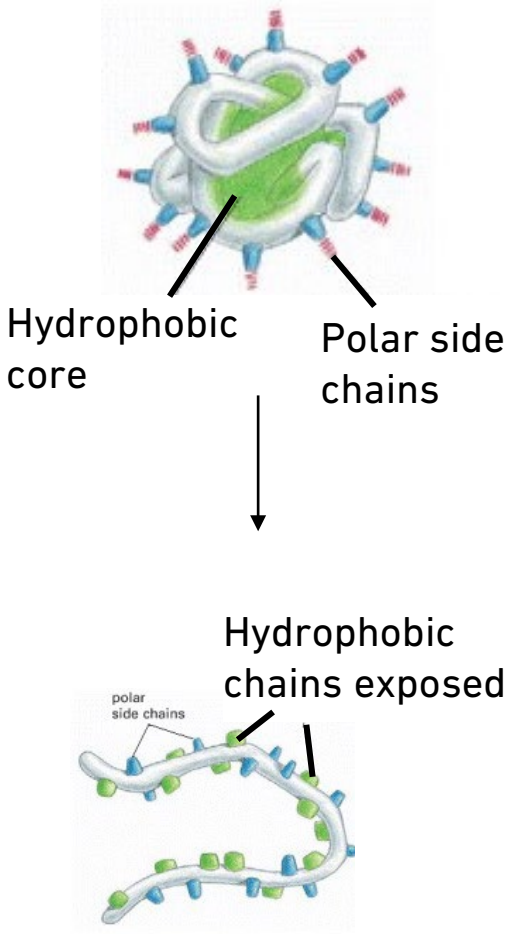
Localization («wrong neighborhood» principle)



Ubiquitous tool

Danger signal

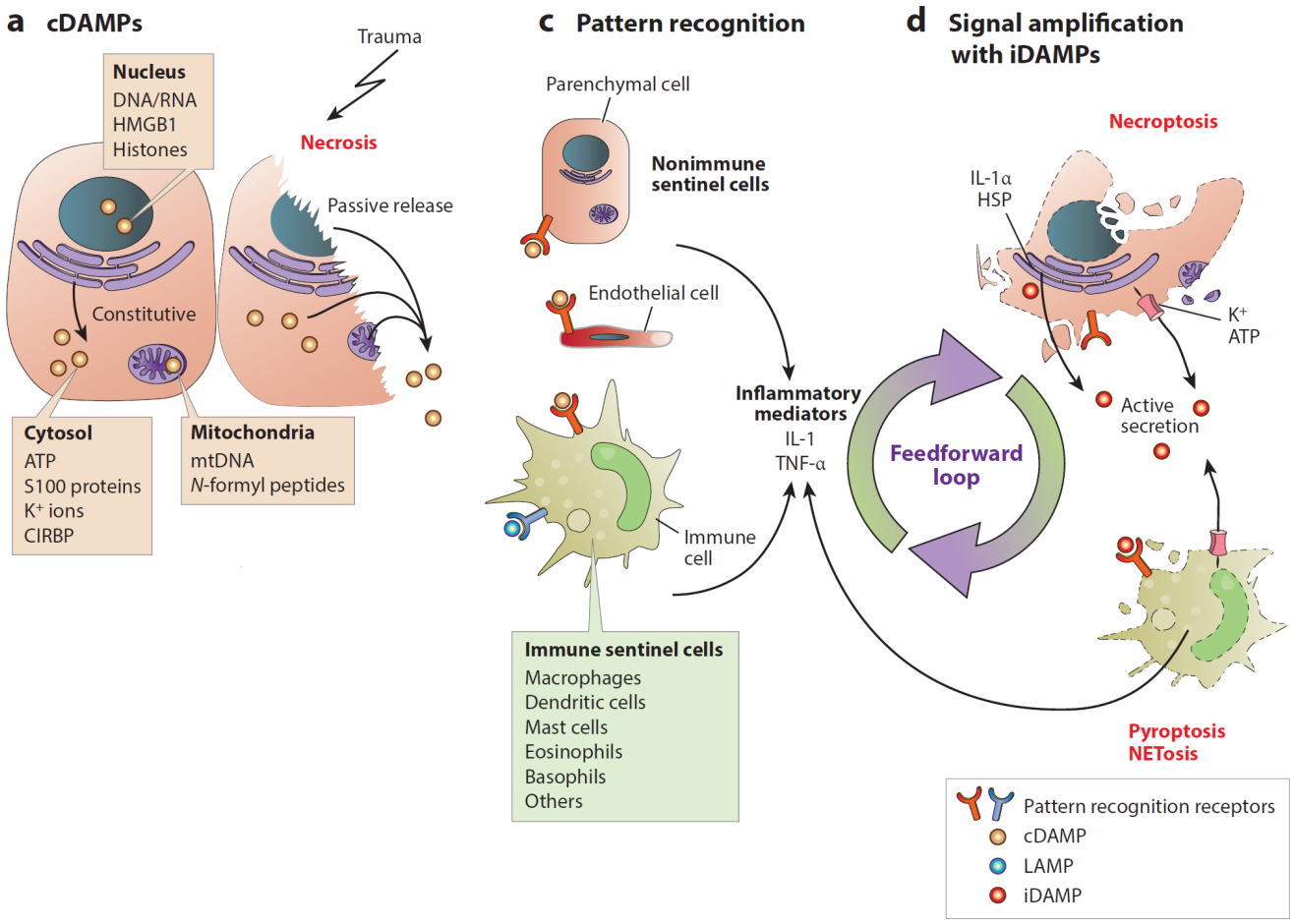
Conformation («wrong shape» principle)



- **Covalent modifications (Oxidation, Acetylation, Phosphorylation)**
- **Proteolytic cleavage**
- **Crystallisation**
- **Protein misfolding/ Aggregation**

www.britannica.com, Molecular Biology of the Cell, Chapter 3.

cDAMPs and **iDAMPs**

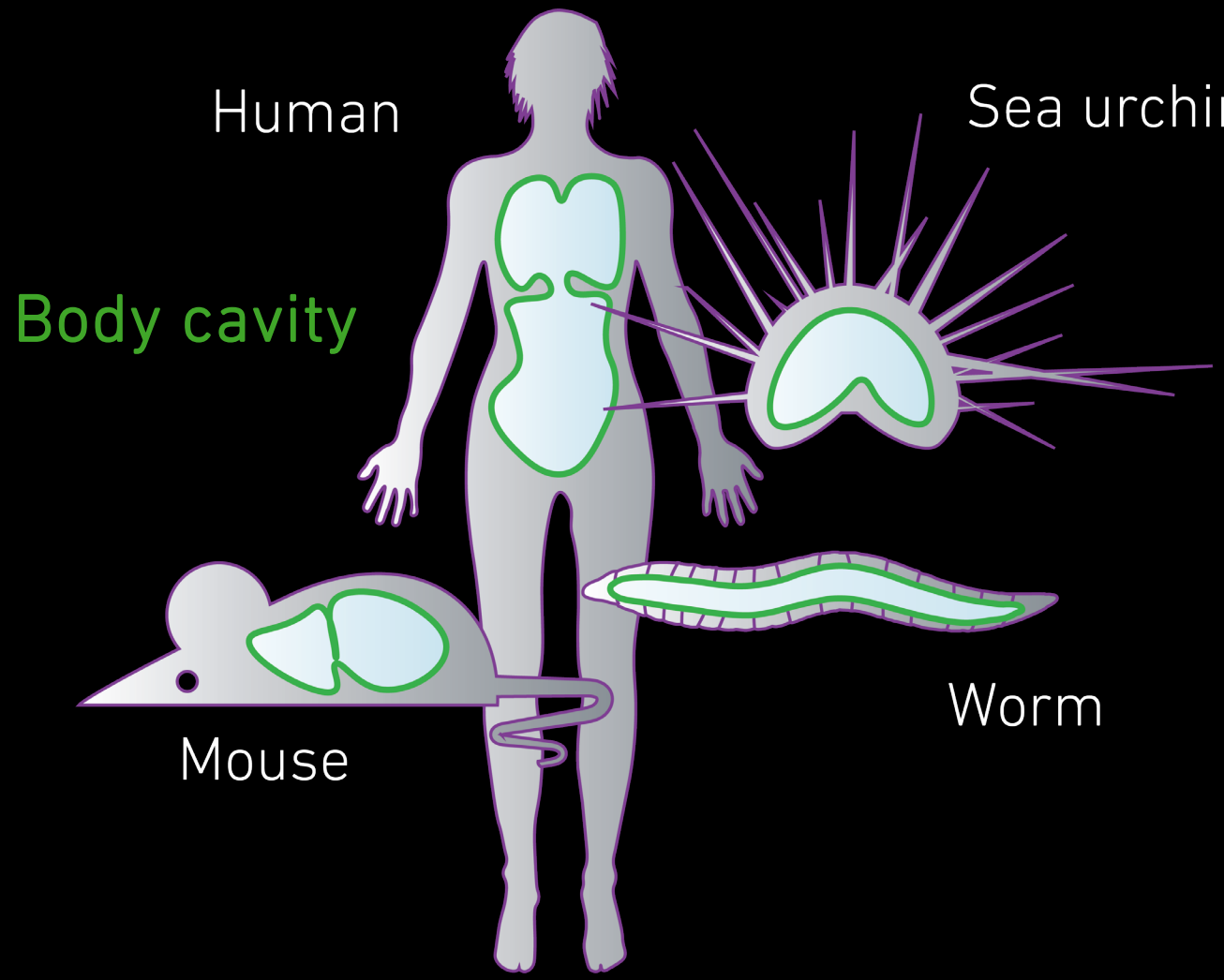


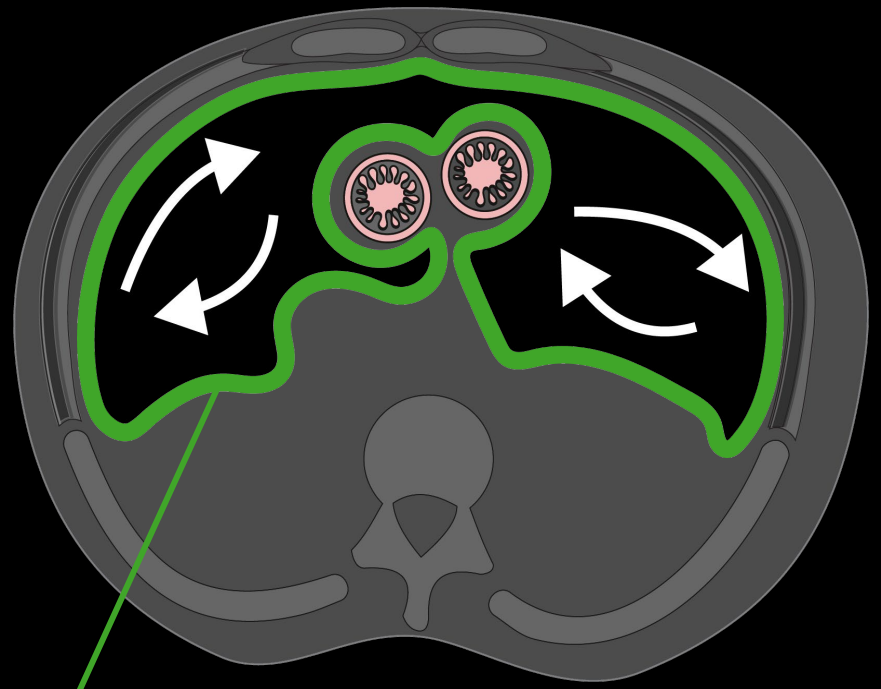
Adapted from Zindel & Kubes 2020 Annu Rev Pathol 2020

- (**a**) Injury => release of constitutively expressed DAMPS (**cDAMPs**)
- (**b**) Proposition of lifestyle associated molecular patterns (LAMPs) as alternative initiation event see teaching comment next slide
- (**c**) Immunostimulatory patterns are recognized by PRRs on both nonimmune cells and specialized immune sentinels. Ligation of PRRs leads to the secretion of proinflammatory cytokines (e.g., TNF-α and IL-1) as well as other inflammatory mediators.
- (**d**) Proinflammatory signals, such as IL-1 and TNF-α, induce programmed **nonapoptotic cell death** in parenchymal cells (necroptosis) as well as in leukocytes (referred to as pyroptosis, or NETosis in neutrophils). This leads to the induction and active (noncanonical) secretion of inducible DAMPs (**iDAMPs**).

Abbreviations: CIRBP, cold-inducible RNA binding protein; CPPD, calcium pyrophosphate dihydrate; HSP, heat shock protein; HMGB1, high mobility group box 1; IL, interleukin; MSU, monosodium urate; mtDNA, mitochondrial DNA; NET, neutrophil extracellular trap; PRR, pattern recognition receptor; TNF, tumor necrosis factor.

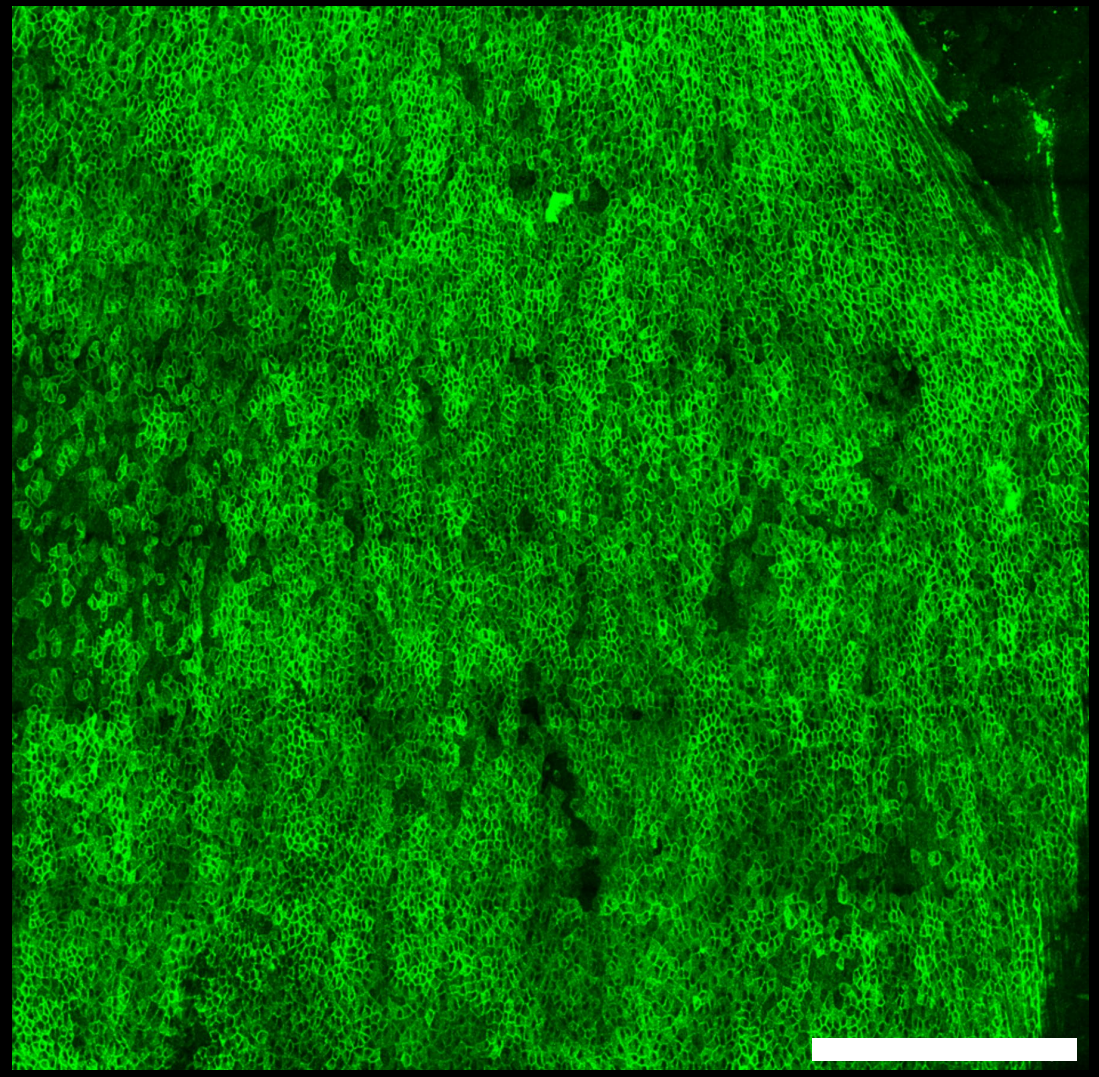
Universal Building Plan





Mesothelium ~ Serosa ~ Peritoneum

Slippery Surface



Anti-Podoplanin

500u
m



Mesothelium ~ Serosa ~
Peritoneum

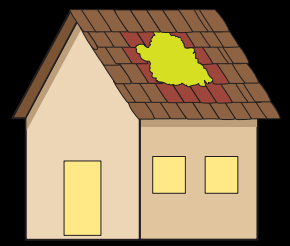
A Look Inside





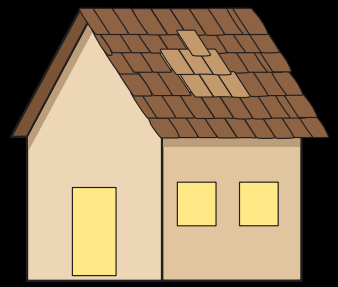
Fair Warning

Failure modes



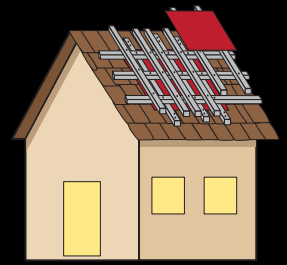
Leakage

«Not enough repair»



Regeneration

«just right»



Scar (Adhesion)

«too much repair»

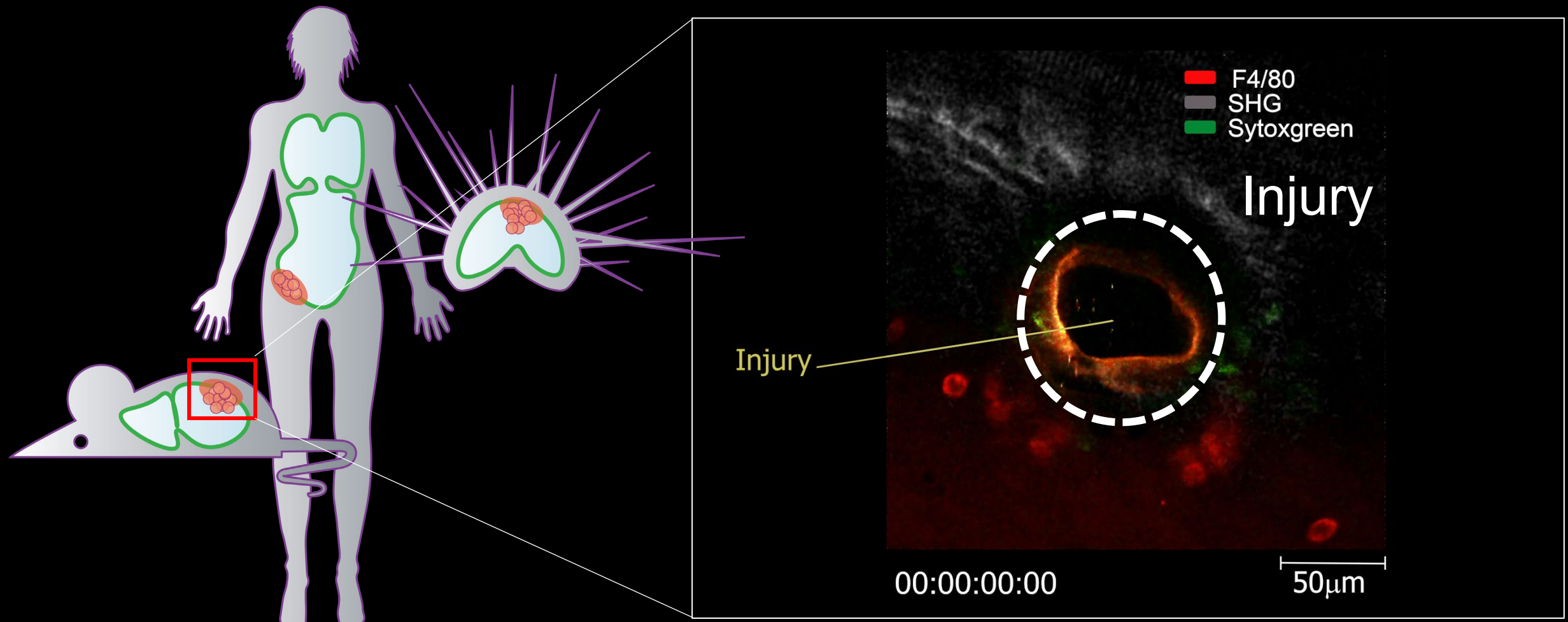


Repair Spectrum

$$ Health Burden

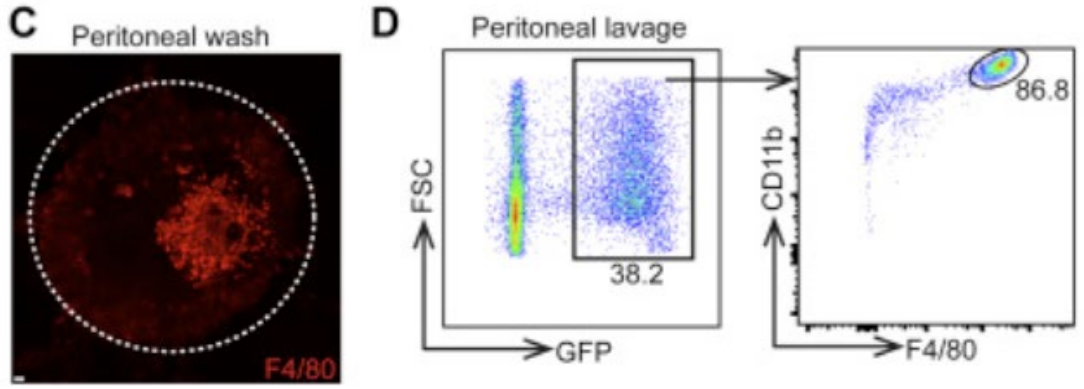
$$ Health Burden

Macrophage Activation

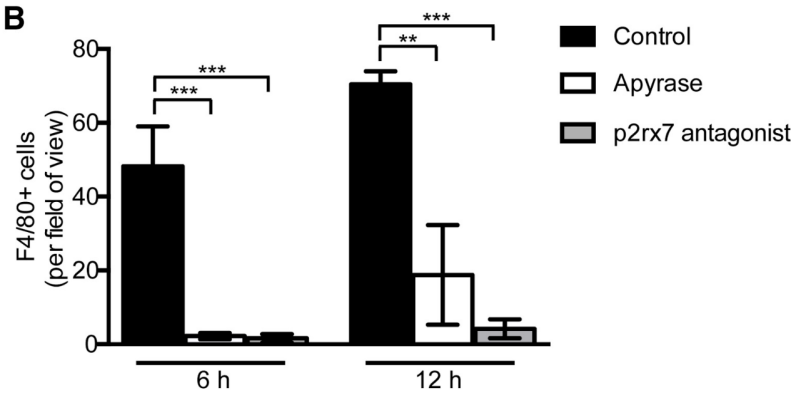


Example «wrong neighborhood»: ATP as cDAMP and iDAMP (II)

cDAMP

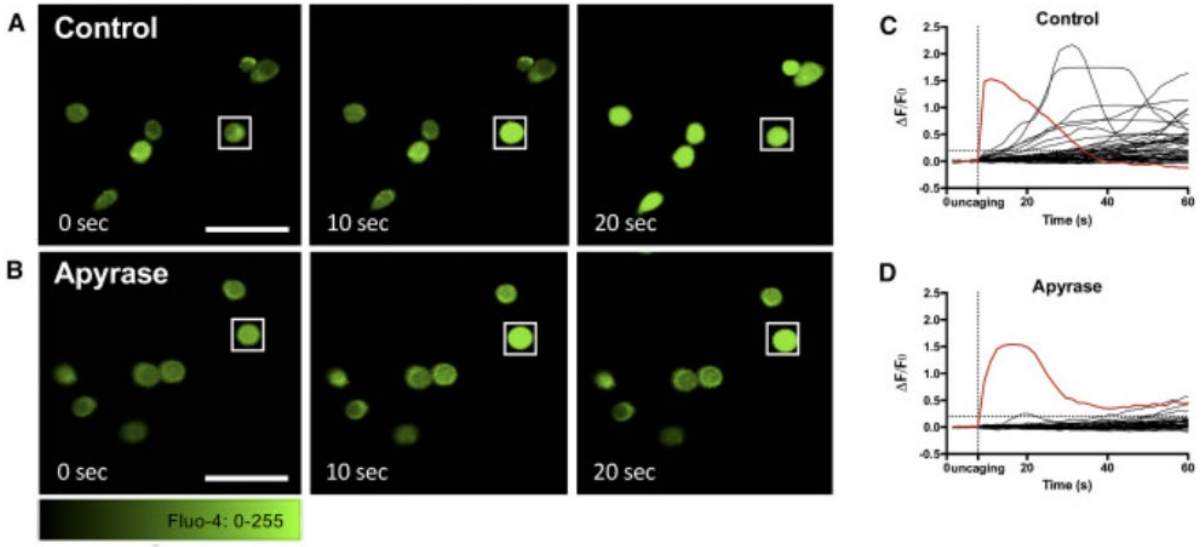


Wang and Kubes, Cell 2016 Figure S2



Wang and Kubes, Cell 2016 Figure 3

iDAMP

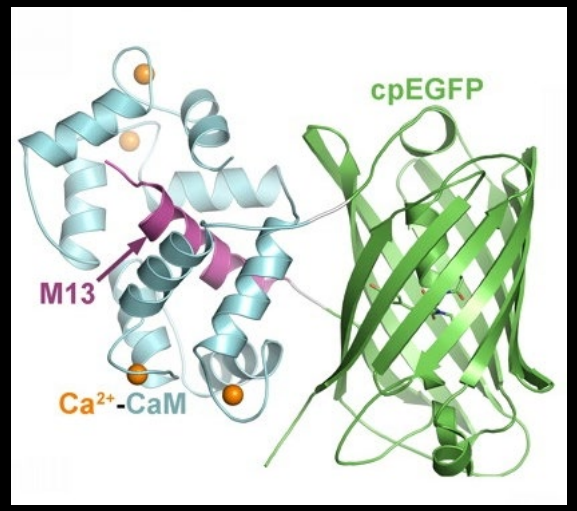


Zumerle et al. Cell Reports 2019 Figure 1

- (**Fig. S2 C and D**) Peritoneal macrophages (F4/80hi CD11b+ cells) are recruited to injuries.
- (**Fig 3 B**) This recruitment can be inhibited with Apyrase and ATP-receptor antagonists.
- (**Fig 1**) Calcium signaling can be induced in macrophages in culture using photo-uncaging of caged IP3 (white box in A and B, red curve in C and D). This induces a Calcium wave in the neighboring cells (black curves in C and D) in an ATP-dependent manner.

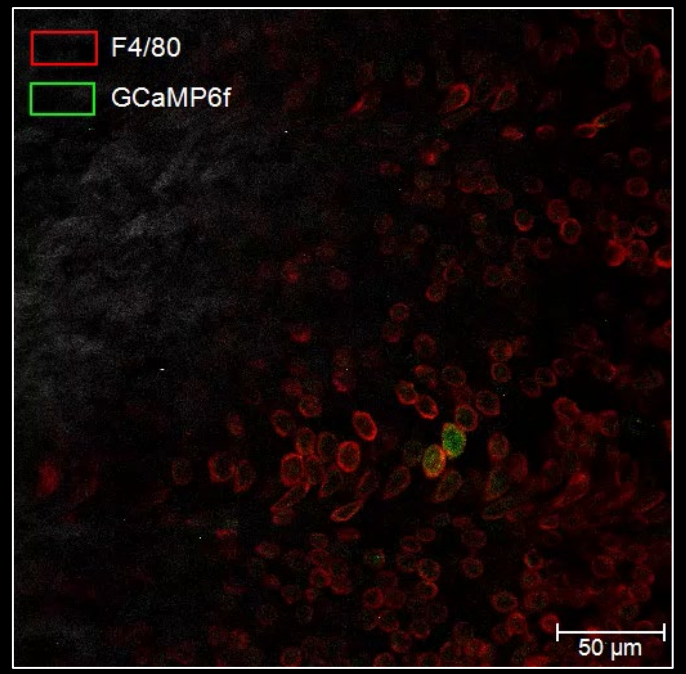
Calcium signaling

GCaMP: Calmodulin GFP Fusion Protein



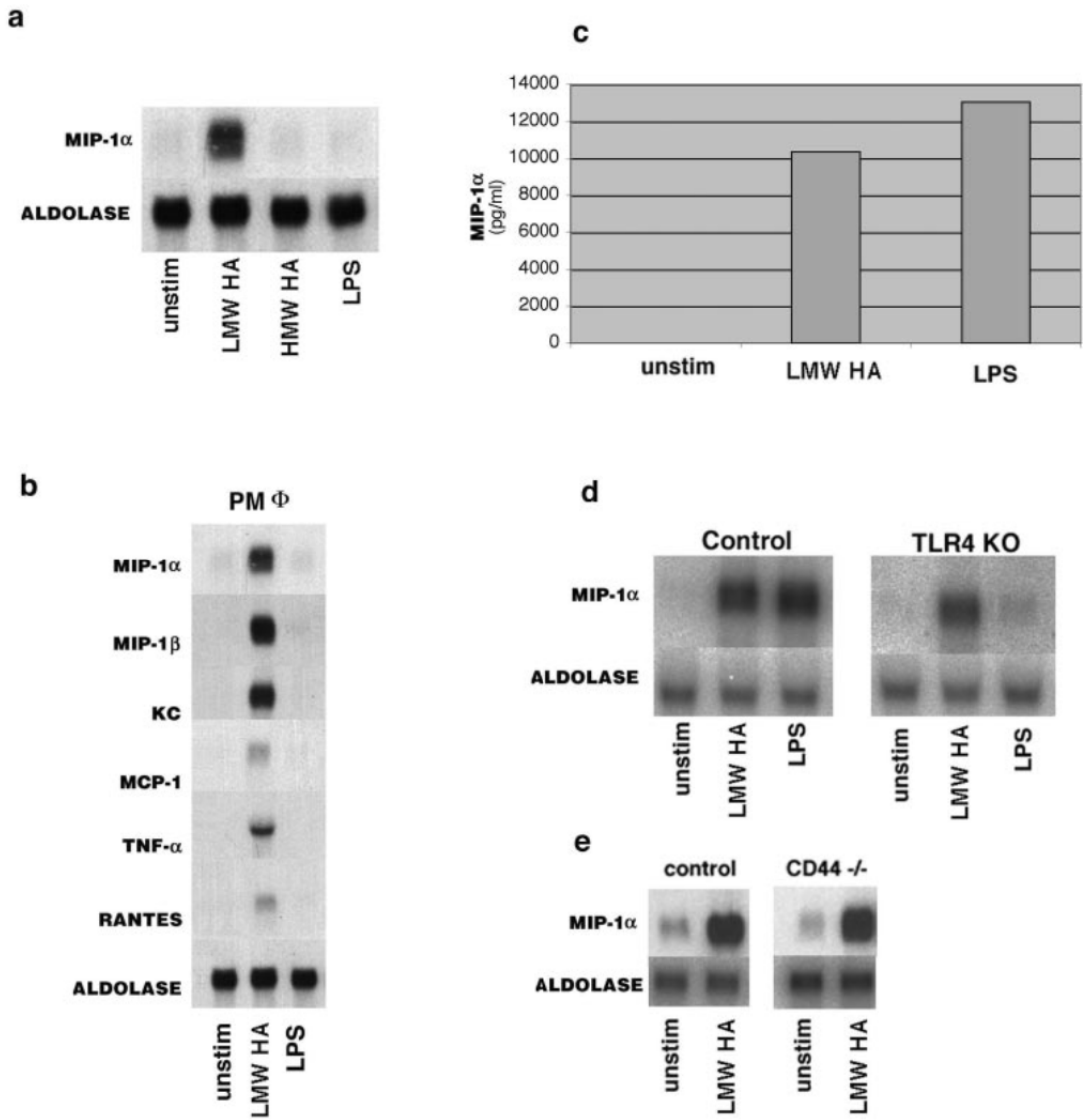
Green: GCaMP6f (Ca^{2+} wave)





Red: F4/80 Macrophages, Blue: SHG Collagen

Example «wrong shape»: Hyaluronan



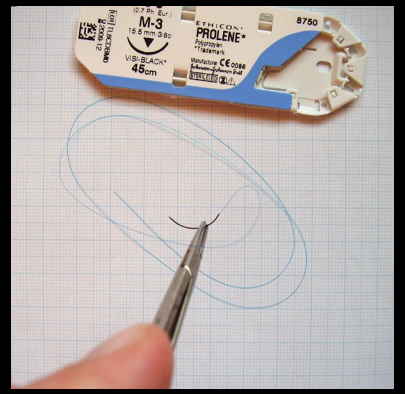
Scheibner et al., J. Immunol. 2006

- **Hyaluronan (HA),** a ubiquitously distributed ECM component, is broken down into lower m.w. fragments (LMW HA) upon injury.
- LMW HA activates innate immune response (MIP-1α = CCL3 = pro-inflammatory chemoattractant).
- (**a and b**) Peritoneal Excudate Cells (PEC) from LPS-insensitive ($TLR4^{-/-}$) mice* show pro-inflammatory response to LMW HA but not to uncleaved HA.
- (**c**) The response in wild-type dendritic cells (from C57Bl/6 mice) to LMW HA is substantial, almost as high as LPS.
- (d and e) The response does not depend on TLR4 (**d**) and does not depend on CD44 (**e**).
- In the other figures they show that LMW HA activates the innate immune response via TLR-2 in a MyD88 NF-κB-dependent pathway

*role of TLR4 contested for different HA fragment sizes

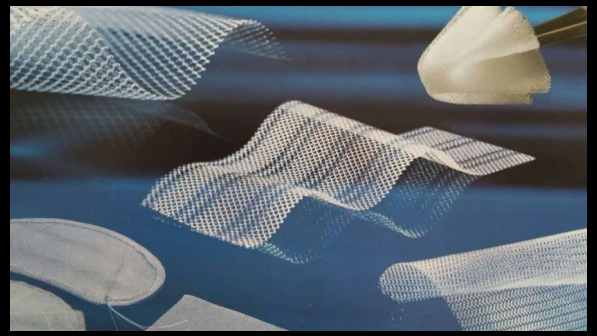
Example: Lifestyle Associated Molecular Patterns **LAMPs**

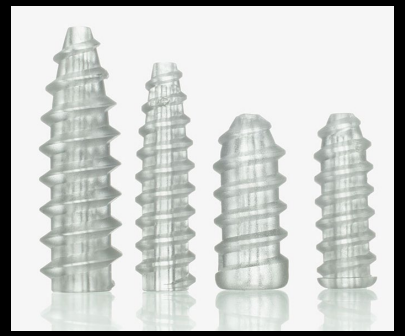


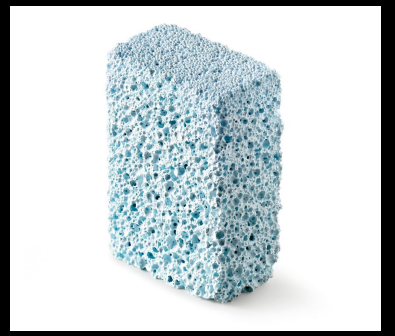


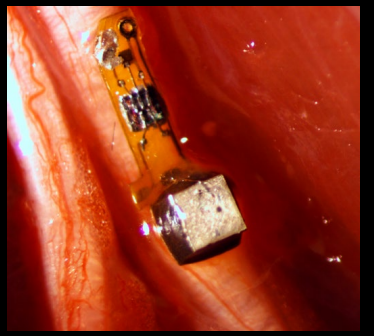














These materials were not present during evolution

DAMPS Overview (I)

Intracellular DAMPs (cDAMPs)			
Nucleus			
Double-stranded DNA	TLR9, AIM2, cGAS → STING	Damage surveillance	TLR antagonists, DNases; STING inhibitors (clinical trials)
HMGB1	TLR2, TLR4, TLR9, RAGE, CD24	Damage surveillance	Neutralising antibodies, TLR4 antagonists
Histones	TLR2, TLR4	Damage surveillance	TLR antagonists; role in sepsis-DIC
SAP130	CLEC4E (Mincle)	Damage surveillance	—
Self RNA (mRNA, miRNA, Z-RNA)	MDA5, RIG-I, ZBP1, TLR7, TLR8	Shielded from immune recognition under homeostasis by RNA-binding proteins and modification	Aicardi-Goutières syndrome (ADAR1 deficiency); neurodegeneration; tumour progression
Mitochondria			
Mitochondrial DNA (mtDNA)	TLR9, NLRP3, cGAS → STING	Damage surveillance	TLR antagonists, DNases; STING inhibitors; monocyte tolerance in MI
Mitochondrial N-formyl peptides	FPR1	DAMP gradient, necrotaxis	Antibodies, honokiol
Cytochrome c	Unknown	Damage signal	Potential marker; γ-tocotrienol
Cardiolipin	NLRP3	Mitochondrial membrane integrity signal	Barth syndrome; cancer; obesity; Alzheimer's disease
Cytosol			
ATP	P2 receptors (P2X7, P2Y)	Damage surveillance, DAMP gradient	P2X receptor inhibitors
S100 calcium-binding proteins	RAGE	Secondary messenger	Antibodies
K^+ ions	K^+ channels → NLRP3	Secondary messenger	Inflammasome activation
CIRBP	TLR4–MD2 complex	Stress signal	Inflammatory response in shock and sepsis
Thioredoxin	Many	Redox signal	Cancer, viral diseases, aging

Adapted from Zindel & Kubes 2020 Annu Rev Pathol 2020. Abbreviations: cDAMP, constitutively expressed DAMP; iDAMP, inducible DAMP; HMGB1, high-mobility group box-1; CIRBP, cold-inducible RNA-binding protein; cGAS, cyclic GMP-AMP synthase; STING, stimulator of interferon genes; FPR1, formyl peptide receptor 1; ECM, extracellular matrix; SHAP, serum-derived hyaluronan-associated protein; ARDS, acute respiratory distress syndrome; FPP, farnesyl pyrophosphate; GGPP, geranylgeranyl pyrophosphate; SR-A, scavenger receptor A; TCA, tricarboxylic acid cycle; LAMP, lifestyle-associated molecular pattern.

DAMPS Overview (II)

Molecular pattern	Receptor	Physiological purpose	Role in disease / treatment
Inducible DAMPs (iDAMPs) — secreted upon stress			
Heat shock proteins (hsp60, hsp70, hsp90, gp96, calreticulin)	TLR2, TLR4, CD91, CD14, CD40, CD24	Signal amplification, DAMP gradient	Antibodies; anti-cancer immune response
Defensins	CCR6, TLR4	DAMP gradient	Antagonists, antibodies
Galectins	CD2	Signal amplification	Cancer, fibrosis, chronic inflammation
IL-1α	IL-1R	Feedforward amplification	Sepsis; anakinra
Lysophosphatidylserine (LysoPS)	GPR34	Released by apoptotic cells — promotes tissue repair	Colitis; skin wound repair
Extracellular DAMPs — matrix-derived			
Short-fragment hyaluronan	CD44–TLR4–MD2, TLR2	Damage surveillance, DAMP gradient	TLR antagonists, hyaluronidase
Biglycan	TLR2, TLR4	Damage surveillance	—
Versican	TLR2	Damage surveillance	Enhances tumour metastasis
Heparan sulfate	TLR4	Damage surveillance	Alzheimer's disease
ECM fragments / matricryptins (collagen, elastin, laminin)	CD14, TLR4, SHAP	Damage surveillance, DAMP gradient	Autoimmune diseases; potential anti-tumour properties

Adapted from Zindel & Kubes 2020 Annu Rev Pathol 2020. Abbreviations: cDAMP, constitutively expressed DAMP; iDAMP, inducible DAMP; HMGB1, high-mobility group box-1; CIRBP, cold-inducible RNA-binding protein; cGAS, cyclic GMP-AMP synthase; STING, stimulator of interferon genes; FPR1, formyl peptide receptor 1; ECM, extracellular matrix; SHAP, serum-derived hyaluronan-associated protein; ARDS, acute respiratory distress syndrome; FPP, farnesyl pyrophosphate; GGPP, geranylgeranyl pyrophosphate; SR-A, scavenger receptor A; TCA, tricarboxylic acid cycle; LAMP, lifestyle-associated molecular pattern.

DAMPS Overview (III)

Molecular pattern	Receptor	Physiological purpose	Role in disease / treatment
Inter-organ DAMPs			
DAMPs from distal tissues / organs (e.g. circulating mtDNA, HMGB1)	Same PRRs as local DAMPs (TLR9, RAGE, TLR4)	Trans-organ danger broadcast — physiological purpose debated	Multi-organ failure, remote ischaemic injury, ARDS after pancreatitis; therapeutic window being defined
Endogenous LAMPs — accumulate with lifestyle / metabolic disease			
Cholesterol crystals	NLRP3, CD36	Unclear	Atherosclerosis, cardiovascular disease
Uric acid / monosodium urate crystals	NLRP3	May physiologically act as a cDAMP	Gout; colchicine, IL-1 blockade (anakinra, canakinumab)
Calcium pyrophosphate dihydrate crystals	NLRP3	Unclear	Pseudogout
Oxidized lipoproteins (oxLDL)	TLR, SR-A, CD36, active component oxPAPC activates non-canonical NLRP3 via CD14	Unclear	Atherosclerosis; statins
Prions / prion-like signals (e.g. β-amyloid)	NLRP3, CD36, RAGE, NF-κB (extracellular)	Physiological iDAMP?	Alzheimer's disease, Creutzfeldt-Jakob disease
Metabolite-derived DAMPs: FPP, GGPP (mevalonate pathway); succinate, fumarate, citrate (TCA cycle), UPD-glucose	NLRP3, mTOR / HIF-1α axis	Unclear — possibly metabolic stress sensing; may drive trained immunity	Inflammaging, trained immunity, atherosclerosis; statins (block FPP/GGPP), mTOR inhibitors, LPS-induced lung injury, airway inflammation, sepsis.
Exogenous LAMPs — environmental / iatrogenic exposures			
Silica particles, asbestos particles	NLRP3	None (no evolutionary design)	Frustrated phagocytosis, granuloma, silicosis, asbestosis
Biomaterials / implants	Plasma proteins → complement receptors, TLR	None (no evolutionary design)	Foreign-body reaction, fibrous capsule; biomaterial surface engineering

Teaching note — LAMP: The term 'LAMP' was proposed in Zindel & Kubes 2020 to distinguish molecules that accumulate due to modern lifestyle or iatrogenic exposure from classical DAMPs released by acute cell death. The key distinction: LAMPs cannot be cleared, so they drive chronic sterile inflammation. The term has been cited in ~15–20 papers (Exp Mol Med 2025; Front Immunol 2021) but is NOT yet standard nomenclature. Students should understand the concept — not memorise the acronym as settled fact. This is a live example of how scientific vocabulary is proposed and debated.

Teaching note — Inter-organ DAMPs: The concept that circulating DAMPs from a distal organ can drive sterile inflammation elsewhere is well-supported (Zhou et al. 2024) but the physiological purpose remains debated. Is this an evolved systemic alarm, or pathological spillover?

Learning Objectives — Lecture 1: Injury

- Students can **define homeostasis**, **injury**, **repair**, and **regeneration**, and distinguish the **failure modes** of insufficient repair (leakage/non-healing) and excessive repair (fibrosis/pathological scarring).
- Students can **explain** the conceptual basis of the **danger/damage model** — that the innate immune system detects molecular patterns rather than antigens, and responds to both foreign (PAMPs) and endogenous (DAMPs) danger signals.
- Students can **describe** the **compartmentalisation principle** underlying DAMP recognition — the "wrong neighbourhood principle" (**localisation**) and the "wrong shape principle" (**conformation/modification**) — and give one experimental example of each.
- Students can **distinguish** between **cDAMPs** and **iDAMPs** in terms of mechanism of release, cell state, and functional consequence, and explain why LAMPs do not fit the strict DAMP definition.
- Students can **name** representative **DAMPs** from major molecular categories (nucleic acids, proteins, lipids, metabolites) and describe their cognate receptors.

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