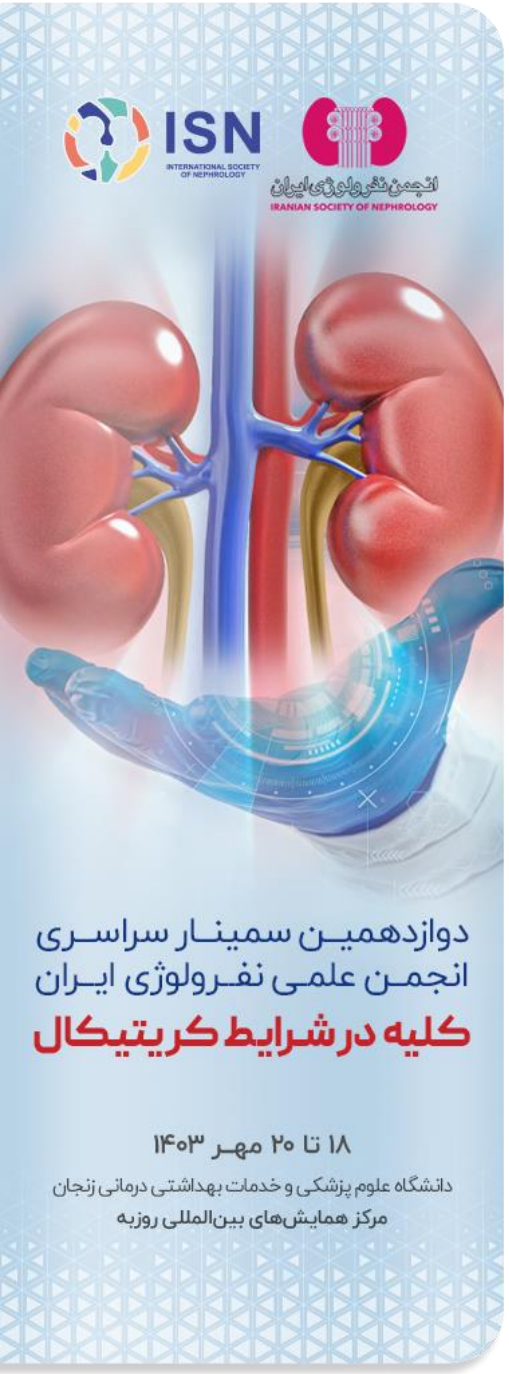

Renal Regeneration and Repair Post AKI

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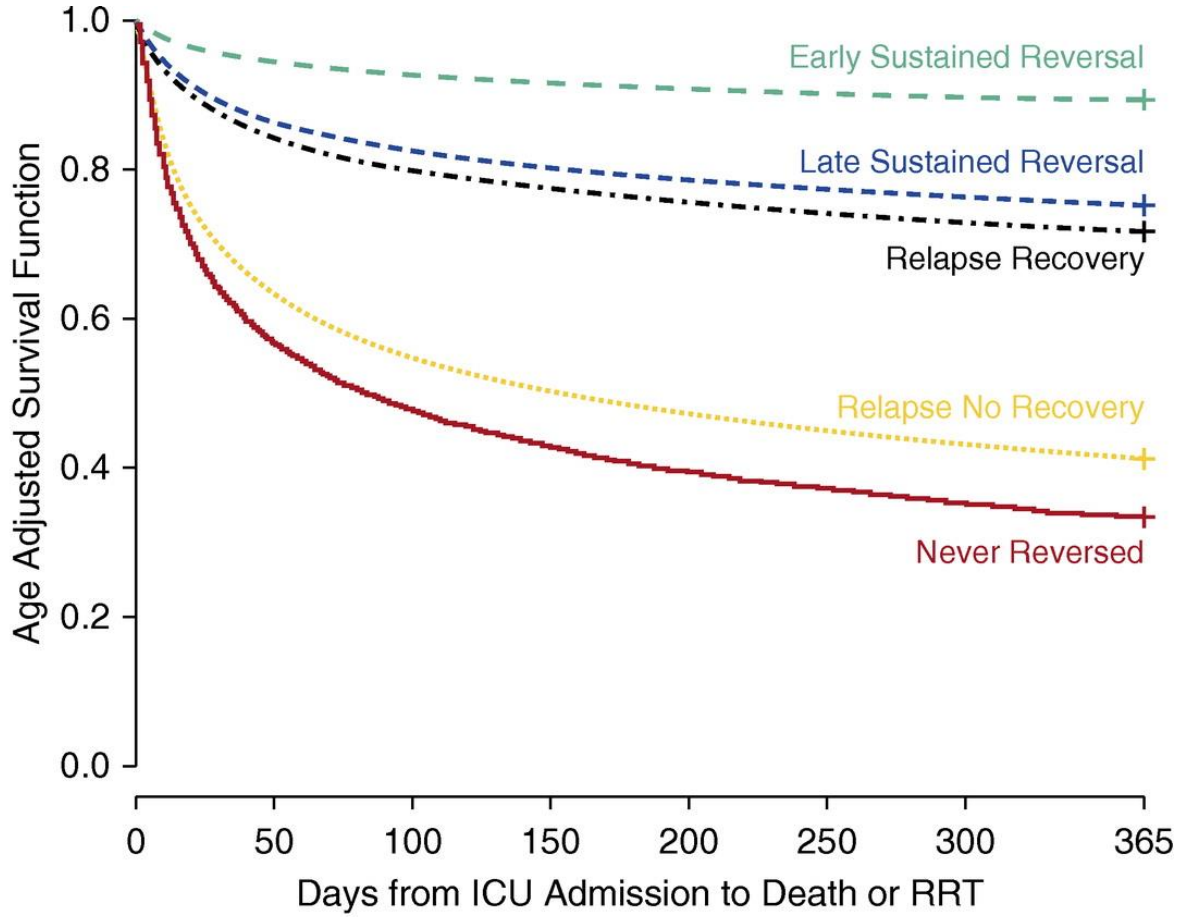
Introduction

- Acute kidney injury (AKI) remains an independent predictor of in-hospital mortality.
- In-hospital mortality rates can approach 50% to 70%.
- AKI survivors are at
  - 9-fold risk of progression to CKD
  - 3-fold risk of progression to ESKD
  - 2-fold increased risk of mortality.

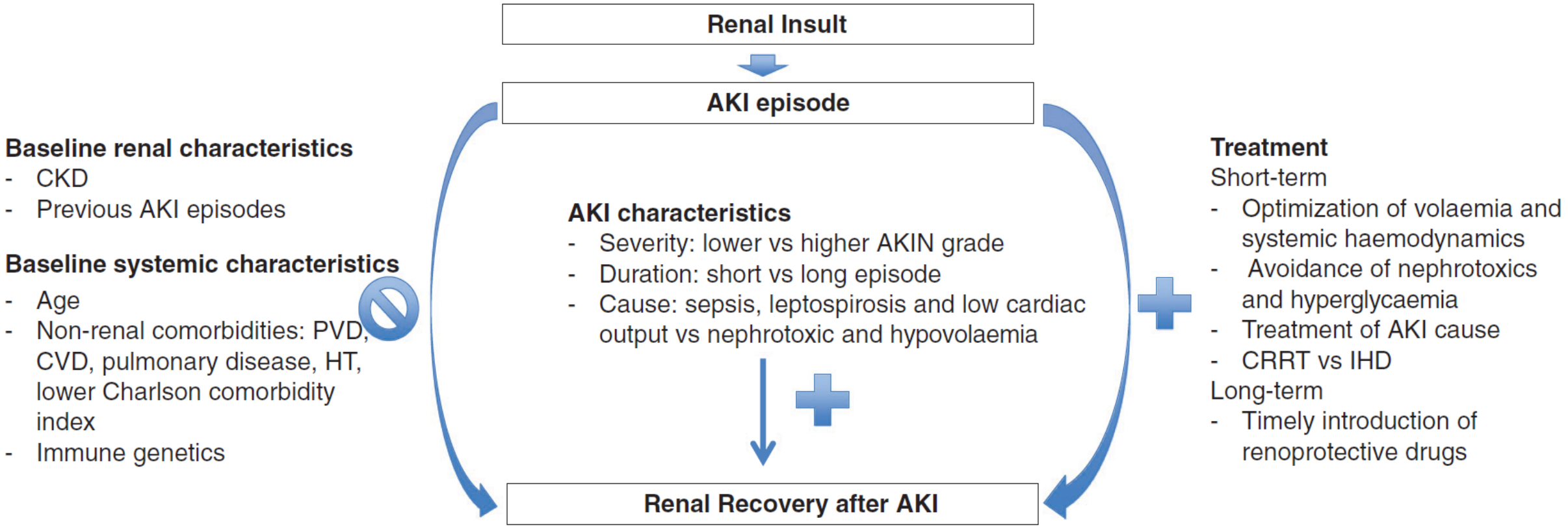
- KDIGO guidelines suggest patients be evaluated 3 months after an episode of AKI and an early nephrology follow-up of patients who recovered from severe AKI has been associated with lower all-cause mortality.
- Studies show that nephrologists see less than half of these patients at 90 days.

KDIGO. KI Suppl. 2012; 2: 1–138



No. at risk								
Early Sustained Reversal	4,507	4,404	4,317	4,235	4,176	4,122	4,070	4,026
Late Sustained Reversal	1,642	1,529	1,424	1,357	1,310	1,272	1,242	1,203
Relapse Recovery	3,823	3,535	3,245	3,061	2,910	2,818	2,719	2,625
Relapse No Recovery	2,496	1,386	1,190	1,114	1,075	1,052	1,027	1,008
Never Reversed	4,496	2,127	1,922	1,826	1,757	1,709	1,678	1,648

Am J Respir Crit Care Med, 2017



ESKD in >50% with eGFR <30 vs.
<15% with eGFR 45–69 &
<1% when eGFR >60

(Am J Kidney Dis. 2011;58(2):206-213)

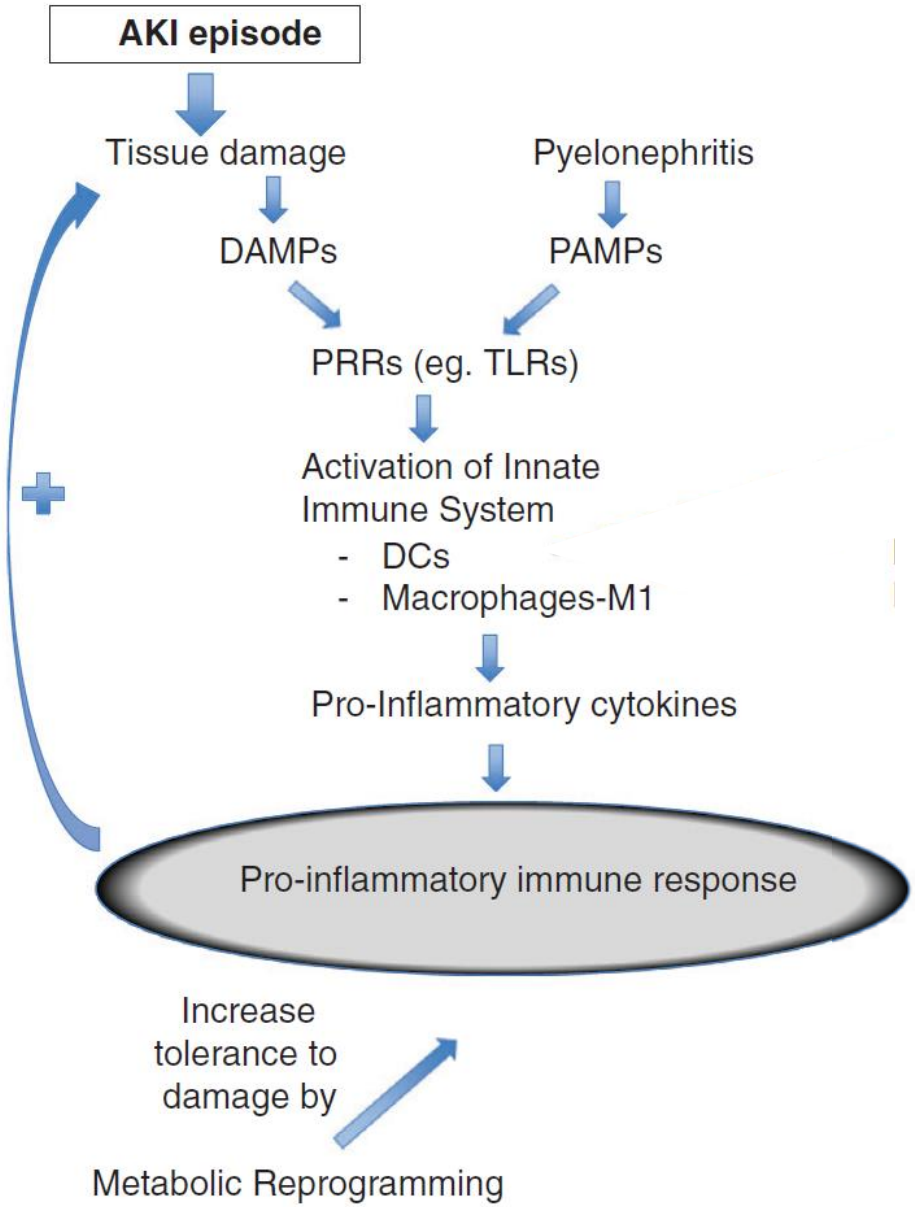
Coelho S. Nephrology 23 (2018)

CELLULAR AND MOLECULAR FACTORS ASSOCIATED WITH RENAL REGENERATION

- Ischemia reperfusion injury (IRI) in most animal models induces the most severe injury in the **S3** segment of the proximal tubule, whereas, in humans, a controversy exists whether the extent of injury is more severe in proximal or distal tubular epithelial cells.

- Growing evidence suggests that, in human AKI, both the **proximal** and **distal** tubular cells are injured with urinary increase of biomarkers for proximal tubular epithelial cells as kidney injury molecule-1 (**KIM1**) and distal tubule markers such as neutrophil gelatinase-associated lipocalin (**NGAL**).

Kermann et al. NDT (2015) 30: 903–910



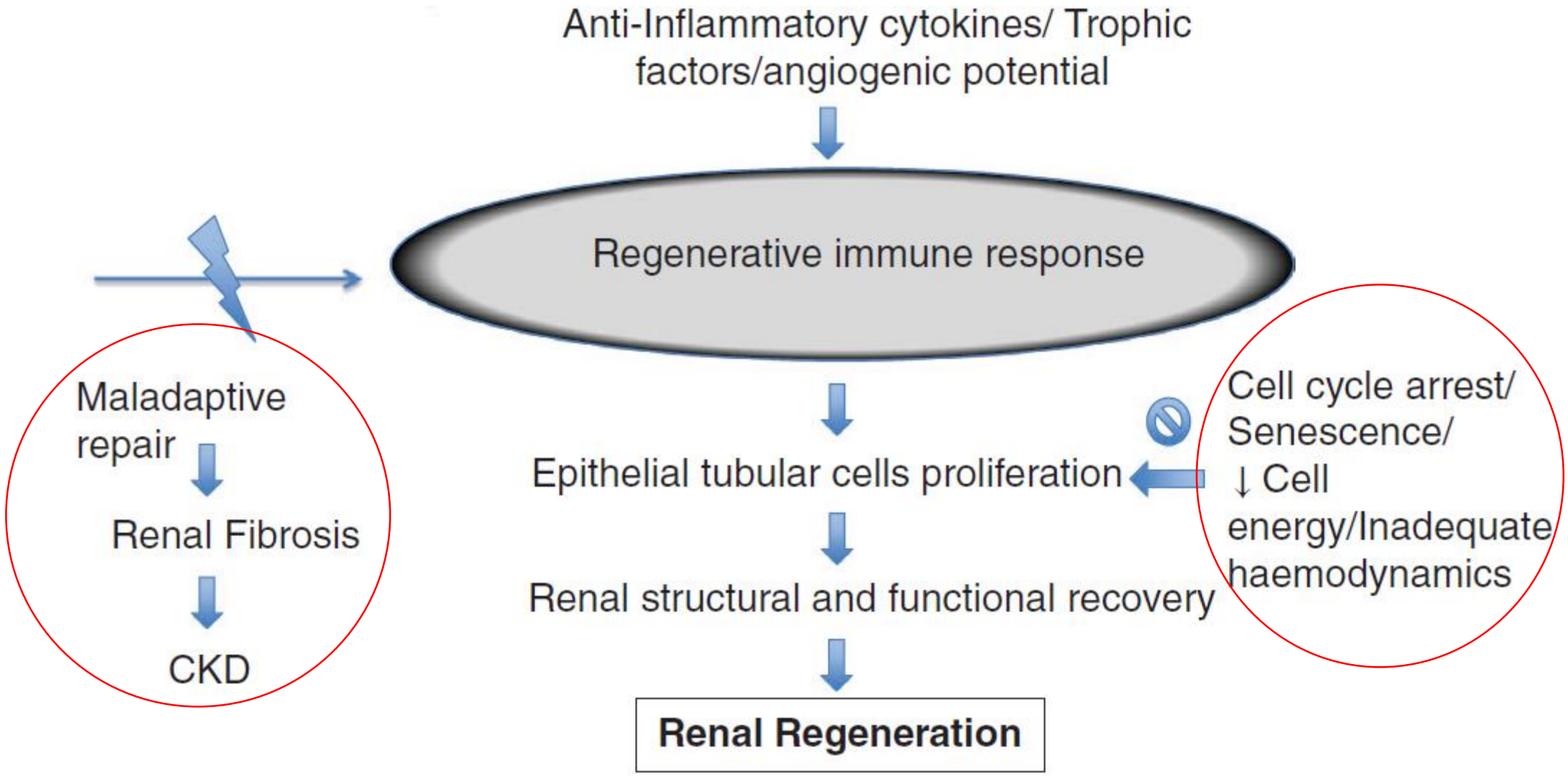
Able to protect the kidney from injury!

Healing Phenotype!

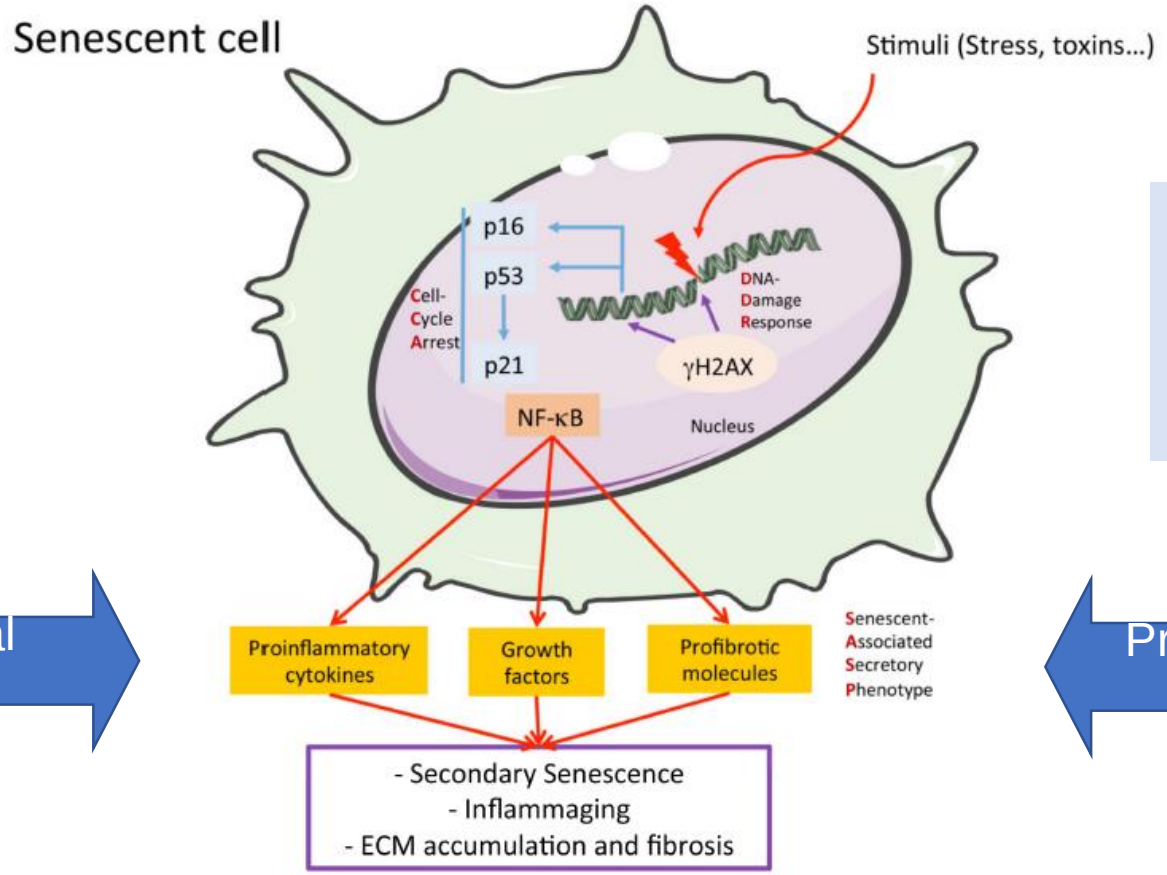
- **IL-22**
- **Wnt pathway ligand Wnt7b**
- **IL1 Receptor Antagonist**

Macrophage CSF-1

Coelho S. Nephrology 23 (2018)



Coelho S. Nephrology 23 (2018)



After DNA repair, cells abandon this growth arrest state and re-enter the cell cycle.
However, in pathological conditions, DDR and CCA are permanent, thus provoking cellular senescence

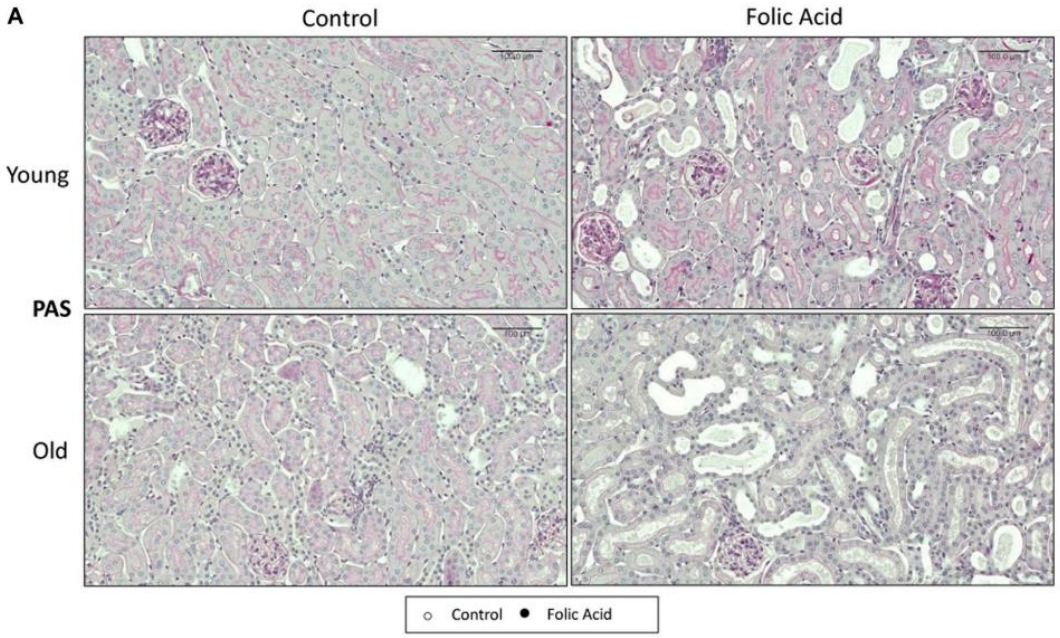
Podocytes & endothelial cells

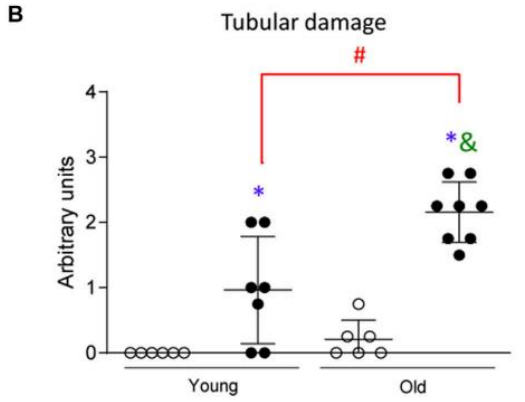
Immune system cells

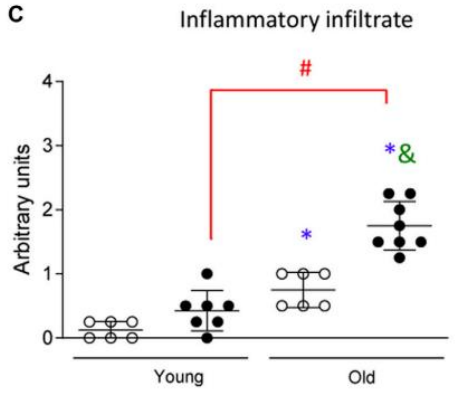
Proximal tubular cells

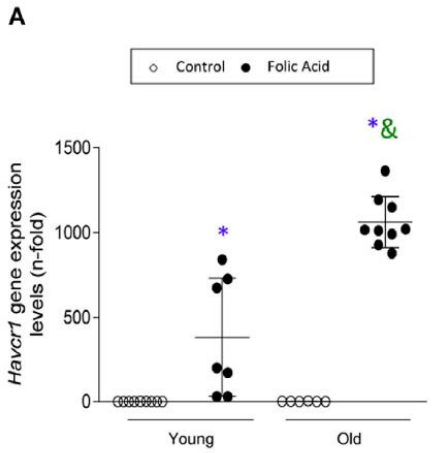
Figure 2. Principal hallmarks of senescent cells. Many different stimuli may cause a DNA damage in the cell and activate the DNA-Damage Response (DDR), which may produce the expression of the Cell-Cycle Arrest (CCA) molecules. Prolonged activation of DDR and CCA proteins produce cellular senescence and the release of the Senescent-Associated Secretory Phenotype (SASP), enriched in different proinflammatory, profibrotic and growth factors that are regulated by NF-κB pathway activation and may cause activation of cellular senescence in a paracrine manner, inflammaging and fibrosis in the kidney, and other tissues.

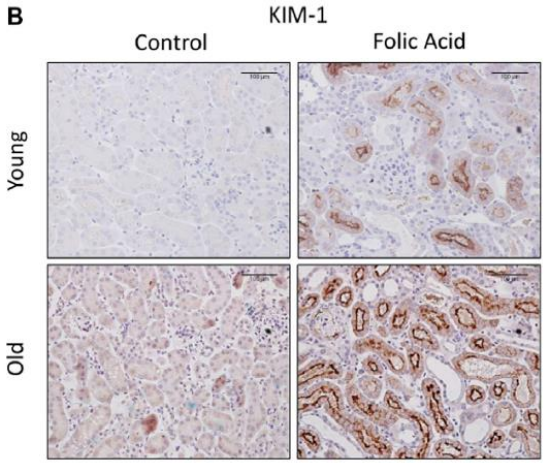
Rayego Mateos. S.Int.J Mol. Sci. 2022, 23, 1542

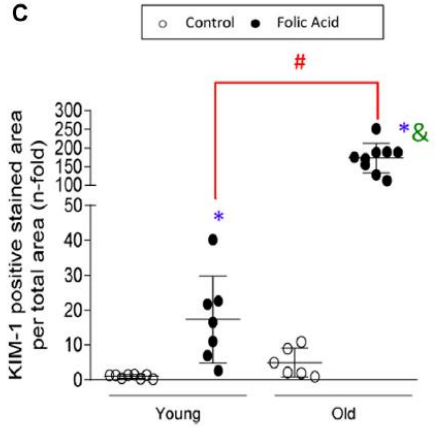












Marquez-Exposito L,Front Pharmacol. 2021; 12: 662020.

Regulated Cell Death

- Apoptosis
- Regulated necrosis:
  - Necroptosis
  - Ferroptosis
  - Pyroptosis
- Unlike cells dying from apoptosis, which display cell surface "eat-me" signals and are rapidly engulfed by macrophages or adjacent healthy cells, cells dying from regulated necrosis release **DAMPs** and **alarmins** that amplify tissue injury, in a process termed **necroinflammation** that interferes with kidney repair.

Rayego Mateos. S.Int.J Mol. Sci. 2022, 23, 1542

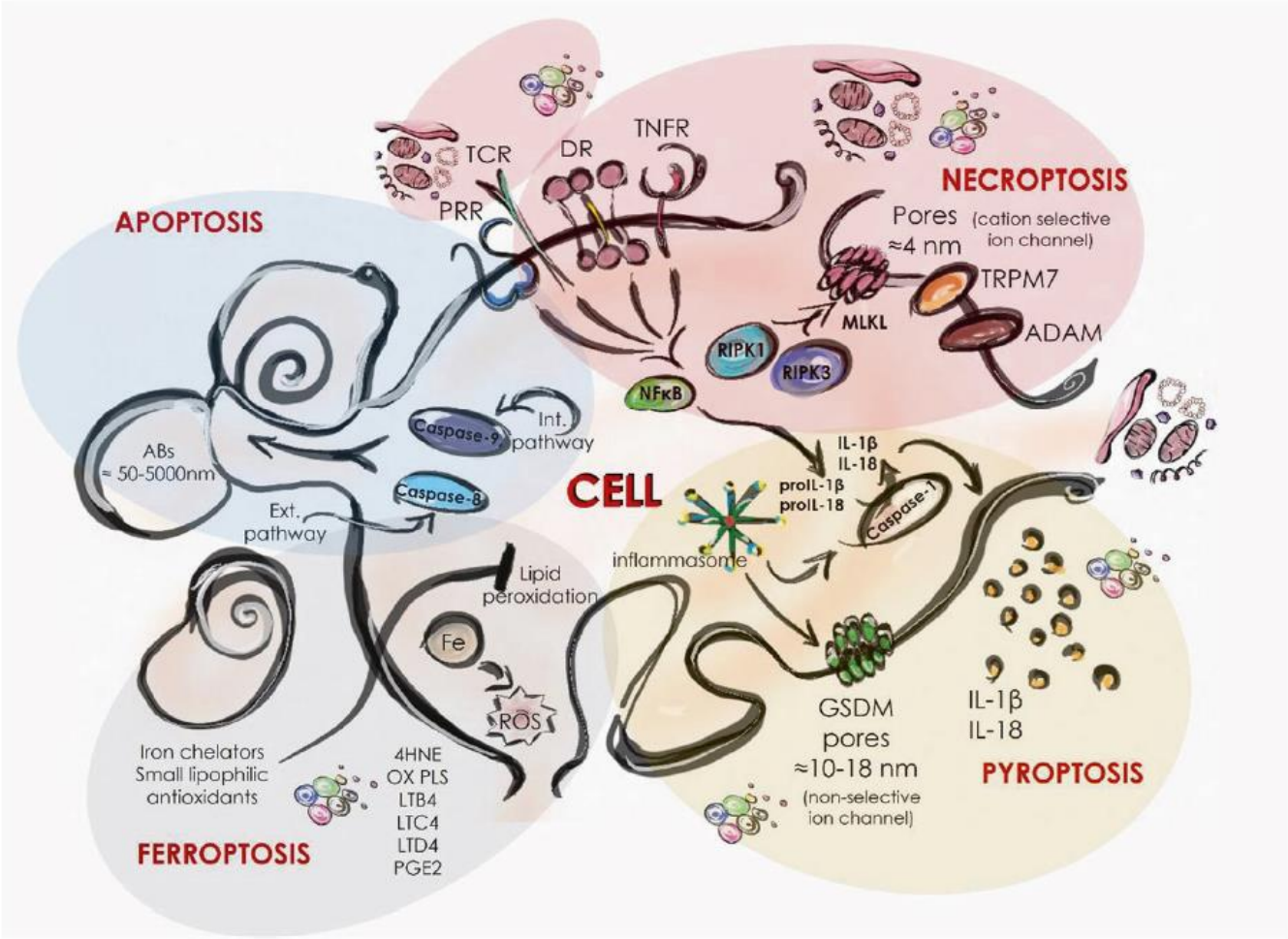


Fig. 2 Comparison of the main processes leading to DAMP release in apoptosis, necroptosis, pyroptosis and ferroptosis. During apoptosis, caspase-regulated events lead to the wrapping of intracellular components into apoptotic bodies. Subsequent efferocytosis prevents the release of DAMPs into the extracellular space. Necrosome induction results in the activation of cation-selective ion channels, leading to cell lysis due to osmotic shock. Pyroptosis is characterized by the secretion of IL-1 and IL-18 cytokines by inflammasome activation and the formation of voluminous non-selective pores formed by GSDMs. In ferroptosis, oxidative perturbations accumulate toxic lipid peroxides that ultimately cause the DAMP release. PRR Pattern Recognition Receptor DR death receptor, GSDM gasdermin, ADAM a disintegrin and metalloproteinase, TRPM7 Transient receptor potential cation channel, subfamily M, member 7, 4HNE 4-Hydroxynonenal, PGE2 Prostaglandin E_2, OX PLS oxidized glycerophospholipids, LTB4 Leukotriene B4, LTC4 Leukotriene C4, LTD4 Leukotriene D4, RIPK1 Receptor-interacting serine/threonine-protein kinase, MLKL Mixed lineage kinase domain-like pseudokinase.

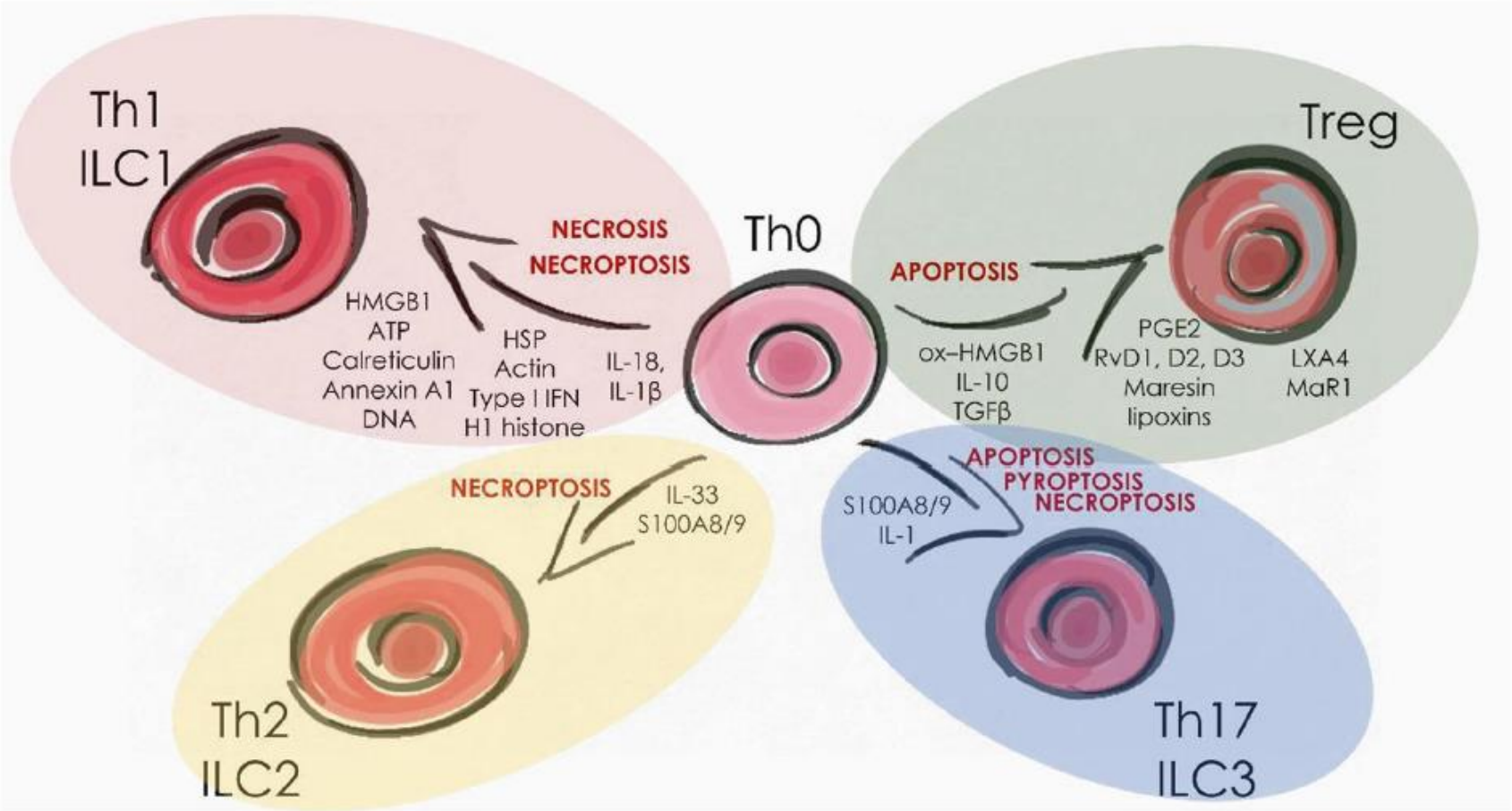


Fig. 3 DAMP and SAMP molecules regulating Th cell differentiation. Types of cell death, DAMP and SAMP molecules directly associated with T helper cell subpopulations based on literature data. HMGB1 High mobility group box 1, PGE2 Prostaglandin E_2, TGFβ Transforming growth factor-beta.

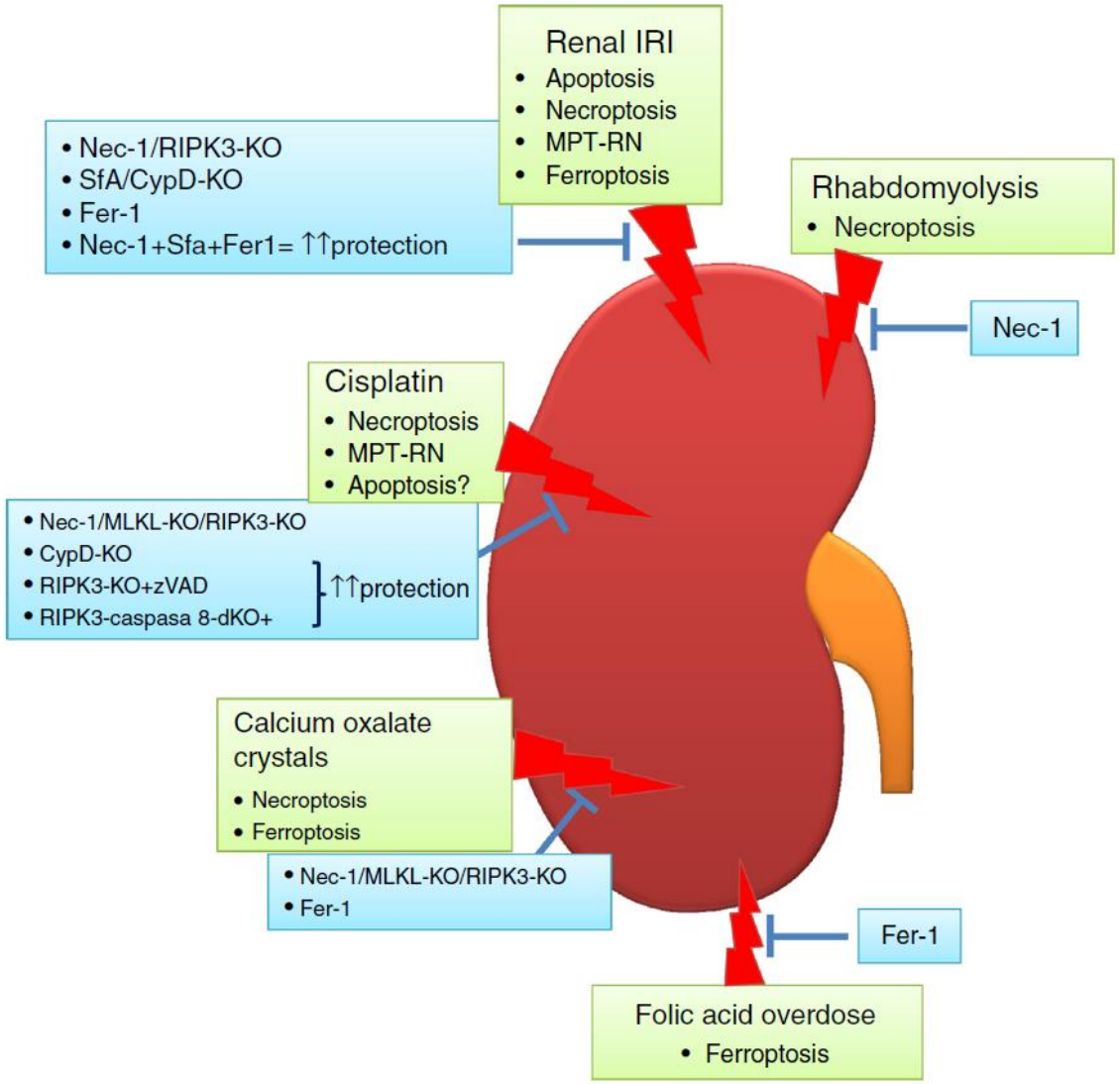


Fig. 2 – Regulated necrosis in kidney disease. Different pathways of cell death are activated and contribute to kidney injury, based on intervention studies in vivo in preclinical models of AKI. Ferroptosis and necroptosis are the forms of cell death involved in most specific etiologies of AKI. IRI: ischemia-reperfusion injury.

The Cell Source for Regeneration

- **Surviving renal epithelium cells** now prevail as the most relevant source for the regenerating tissue
- The renal ECs seem to possess poor regenerative capacity: Angiogenesis ?
- ~~Bone marrow derived cells~~
- Scattered tubular cells with stem cell properties?

Coelho S. Nephrology 23 (2018) 805

Localization of Proliferating Cell Nuclear Antigen, Vimentin, c-Fos, and Clusterin in the Postischemic Kidney

Evidence for a Heterogenous Genetic Response among Nephron Segments, and a Large Pool of Mitotically Active and Dedifferentiated Cells

Ralph Witzgall, Dennis Brown, Cordula Schwarz, and Joseph V. Bonventre

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Abstract

The mechanisms leading to the recovery of the kidney after ischemic acute renal failure are poorly understood. To explore the role played by mitogenesis and dedifferentiation in this repair process and to identify whether the genetic response of the nephron segments reflects the level of susceptibility to injury, the temporal and nephron segment expressions of various proteins implicated in mitogenesis, differentiation, and injury were determined. Proliferating cell nuclear antigen (PCNA), a marker for the G_1-S transition in the cell cycle and hence mitogenesis, was detected primarily in the S3 segment of the proximal tubule, with maximal expression at 2 d postischemia. Vimentin, normally present in mesenchymal cells but not epithelial cells, and hence a marker for the state of differentiation, was prominently expressed in the S3 segment 2–5 d postischemia. In the S3 segments in the outer stripe of the medulla cells that stained positively for PCNA also stained positively for vimentin. Clusterin, a marker for cell injury, was expressed primarily in the S3 segment and in the distal tubule with distinct staining patterns in each segment. None of the cells that stained with clusterin antibodies were positively stained with PCNA or vimentin antibodies. Likewise, none of the PCNA or vimentin-positive cells expressed clusterin at detectable levels. Thus, in the S3 segment, where there is significant ischemic injury, surviving cells express markers indicating that they undergo mitogenesis and dedifferentiate in the postischemic period. While there is some expression of c-Fos in the S3 segment, c-Fos was expressed predominantly, at 1 and 3 h postischemia, in the nuclei of the distal nephron, particularly in the thick ascending limb. The data support the view that the mature renal S3 segment epithelial cell can be a progenitor cell. (*J. Clin. Invest.* 1994. 93:2175–2188.) Key words: acute renal failure • gene expression • ischemia • kidney • tissue repair

remain poorly understood (1, 2). Even less is known about the factors that are important for recovery of kidney function. In contrast to the heart and brain, where ischemia results in permanent cell loss, the postischemic kidney has the ability to restore structure and function completely. Yet in many cases the recovery is delayed or does not occur at all, and the persistence of the renal failure contributes to a high mortality rate (~ 40%) which has not changed significantly over the last 40 years (3). In order to develop strategies to hasten recovery, a more complete understanding of the cellular mechanisms involved in kidney repair is necessary.

There is controversy regarding the degree to which the pathophysiology of acute renal failure is related to loss of tubular cell polarity (4, 5), cell loss with tubular obstruction, loss of epithelial barrier function and backleak of filtrate (6), enhanced tubular pressures (7, 8), and vasoconstriction of preglomerular vasculature (9). It is our hypothesis that, although a functional defect in epithelial polarity may play a role in mild ischemic injury, cell death is an important component of acute ischemic renal failure, and therefore cellular proliferation and repair are necessary for restoration of the functional characteristics of the epithelium. If tubular cells divide, then another important question is whether all surviving cells have the potential to dedifferentiate, divide, and then redifferentiate into mature tubular cells or whether the replacement of the tubular epithelium is due to the action of only a few undifferentiated stem cells.

Experiments were designed to determine whether mitogenesis and dedifferentiation play important roles in the kidney response to ischemia and to determine whether only a few cells or many of the remaining viable cells are involved in the response. The postischemic kidney was evaluated for the appearance of histochemical markers of cell cycle progression, state of differentiation, and cell injury. We also evaluated the temporal

Cellular plasticity in kidney injury and repair

Monica Chang-Panesso and Benjamin D. Humphreys

Abstract | Terminally differentiated cells can be reprogrammed to pluripotency or directly to another differentiated cell type *in vitro*, a capacity termed cellular plasticity. Plasticity is not limited to *in vitro* manipulations but rather represents an important aspect of the regenerative response to injury in organs. Differentiated adult cells retain the capacity to dedifferentiate, adopting a progenitor-like phenotype after injury or, alternatively, to transdifferentiate, directly converting to a different mature cell type. Emerging concepts on cellular plasticity have relevance to our understanding of repair after kidney injury, including epithelial regeneration. Here we discuss work published in the past 5 years on the cellular hierarchies and mechanisms underlying kidney injury and repair, with a particular focus on potential roles for cellular plasticity in this response.

Key points

- The ability of a mature cell to convert into a different cell type is called cell plasticity
- Originally described in cultured cells, cell plasticity is now a recognized feature of organisms, particularly in response to injury
- Epithelial dedifferentiation occurs after kidney injury, and can be considered as a limited form of cellular plasticity
- No evidence exists to support the notion that epithelial dedifferentiation confers multipotency, or the ability of a cell from one tubule segment to differentiate into a cell from another segment
- The potential existence of a fixed population of epithelial progenitors versus the existence of cells with universal dedifferentiation capacity is still controversial
- The molecular pathways underlying epithelial cell plasticity are likely to be different from developmental pathways, and must be understood in order to identify novel therapeutic targets

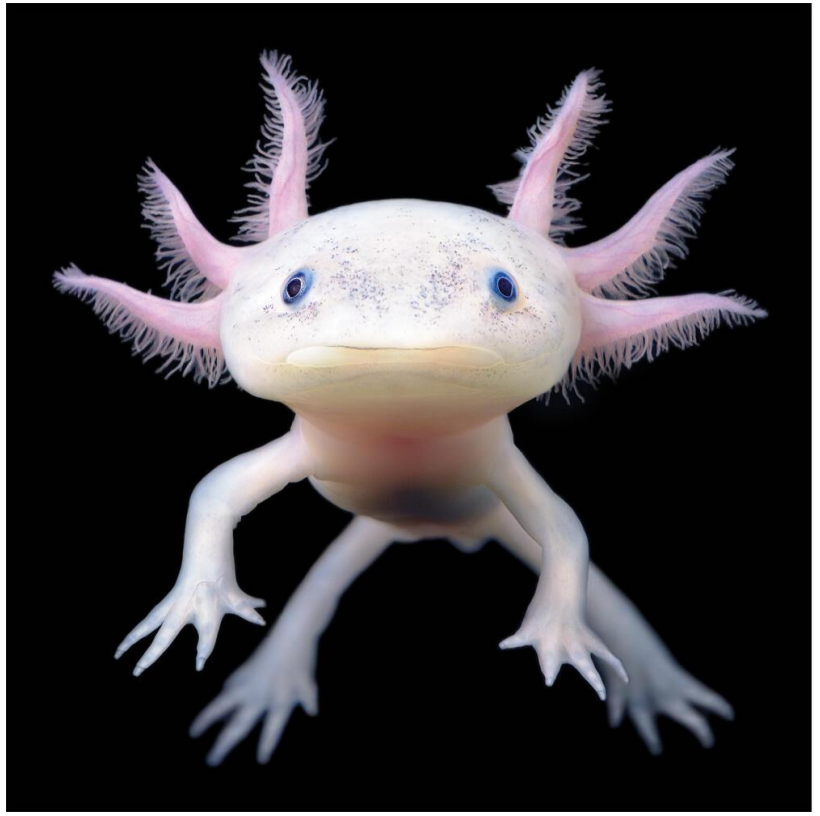
Chang-Panesso, M., Nat.Rev.Neph,2016;13:39–46.

Cellular Plasticity

1. Dedifferentiation: reversion of a differentiated cell to a more primitive form encountered within that lineage during development (with progenitor characteristics).
2. Transdifferentiation: direct conversion of one differentiated cell type into another differentiated cell type without the need for an intermediary progenitor-like step.

- Both also occur ***in vivo*** as part of the injury response.
- The amphibian axolotl, for example, has been studied for decades owing to its ability to fully regenerate amputated limbs

Chang-Panesso, M., Nat.Rev.Neph,2016;13:39–46.



- **Axolotl:** Has the ability to fully regenerate amputated limbs.
- During repair, differentiated cells near the site of amputation dedifferentiate to form a cluster of stem cells called the **blastema**.
- This group of proliferating progenitor cells ultimately redifferentiates into all of the cell types required to form a new limb.

Chang-Panesso, M., Nat.Rev.Neph,2016;13:39–46.

nature Vol 460|2 July 2009|doi:10.1038/nature08152

ARTICLES

Cells keep a memory of their tissue origin during axolotl limb regeneration

Martin Kragl[1,3]*†, Dunja Knapp[1,3]*, Eugen Nacu[1,3], Shahryar Khattak[1,3], Malcolm Maden[4], Hans Henning Epperlein[2] & Elly M. Tanaka[1,3]

During limb regeneration adult tissue is converted into a zone of undifferentiated progenitors called the blastema that reforms the diverse tissues of the limb. Previous experiments have led to wide acceptance that limb tissues dedifferentiate to form pluripotent cells. Here we have reexamined this question using an integrated GFP transgene to track the major limb tissues during limb regeneration in the salamander *Ambystoma mexicanum* (the axolotl). Surprisingly, we find that each tissue produces progenitor cells with restricted potential. Therefore, the blastema is a heterogeneous collection of restricted progenitor cells. On the basis of these findings, we further demonstrate that positional identity is a cell-type-specific property of blastema cells, in which cartilage-derived blastema cells harbour positional identity but Schwann-derived cells do not. Our results show that the complex phenomenon of limb regeneration can be achieved without complete dedifferentiation to a pluripotent state, a conclusion with important implications for regenerative medicine.

The salamander is a powerful regeneration model because it can reconstitute a fully functional limb after injury. Amputation anywhere between the shoulder and the hand triggers the formation of a progenitor cell zone called the blastema that regenerates the missing portion. The mature limb consists of multiple tissues, including the epidermis, dermis, muscle, nerve, blood vessels and skeletal elements that potentially contribute to the blastema, and these tissues must regenerate coordinately to restore functionality. In addition, the limb is structured into three major segments—upper arm, lower arm and hand, generically termed the proximo-distal axis—that must be properly patterned. Remarkably, the fundamental questions of which tissues contribute to the blastema, and whether blastema cells are a multipotent or pluripotent cell type have remained largely unanswered, owing to the complexity of the adult limb as an experimental starting point and the lack of tools with which to follow different cell types precisely over the course of regeneration.

Histologically, the blastema appears to be a homogeneous group of cells and has been commonly viewed as a single cell type. Considering progenitor[9]. Complementarily, BrdU was used to track cultured newt muscle satellite cells *in vivo*, where labelled cells populated cartilage, muscle and even epidermis[10]. Such apparent plasticity could, however, have been acquired during culturing, through BrdU incorporation into DNA or through label transfer to the host[11]. These experiments pointed out the need to mark the different limb cell types indelibly with high resolution, specificity and minimal perturbation.

Here, by comprehensively tracking limb tissues marked by an integrated green fluorescent protein (GFP)–transgene in the salamander *Ambystoma mexicanum* (the axolotl), we show that cells do not become pluripotent during limb regeneration and retain a strong memory of their tissue or embryonic origin. This leads to the important conclusion that the blastema is a heterogeneous pool of restricted progenitor cells from its outset. Using this information, we further show that proximo-distal positional identity is a tissue-specific property of blastema cells: blastema cells deriving from cartilage harbour positional identity but Schwann cells do not. This means that tissue-specific origin must be considered when studying any aspect of the limb blastema.

M. Kragl. Nature, 2009; 460(7251),60–65.

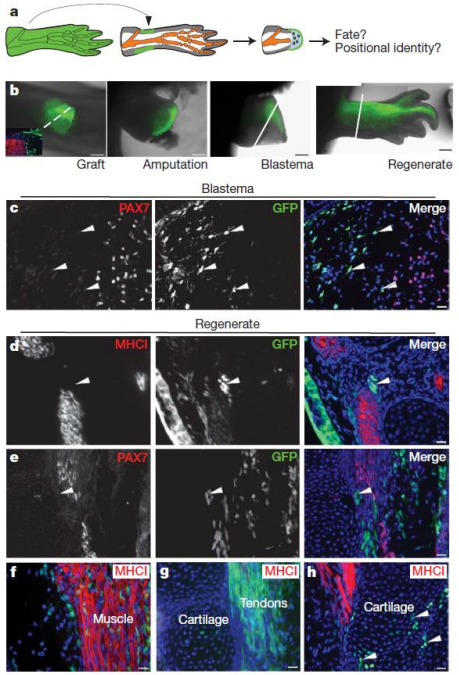


Figure 1 | Dermis does not make muscle but makes cartilage and tendons. **a**, Schematic of experiment. **b**, Representative time course. Inset shows cross-section at dashed line immunostained for MHCI (see Supplementary Fig. 4a, b). **c**, Longitudinal section of 12-day blastema. GFP$^+$ (arrowhead) and PAX7$^+$ signals did not overlap. **d**, **e**, Cross-sections through regenerated limbs. GFP$^+$ cells (arrowheads) were negative for the indicated muscle markers (red). **f**–**h**, Longitudinal sections immunostained for anti-MHCI. Fluorescent cells contributed to connective tissue (**f**), tendons (**g**) and cartilage (**h**, arrowheads). Blue shows DAPI in merge panels (**d**–**h**). Scale bars: **b**, 0.5 mm; **c**–**h**, 50 µm.

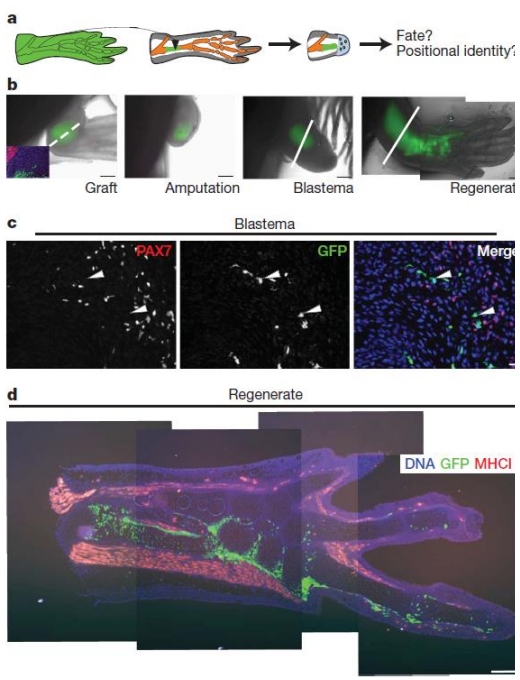


Figure 2 | Cartilage cells do not make muscle. **a**, Schematic of experimen
b, Time course through regeneration. Inset shows cross-section at dashed line immunostained for MHCI (see Supplementary Fig. 4c, d).
c, Longitudinal section of a 12-day blastema. GFP$^+$ cells (arrowheads) we negative for PAX7$^+$ signals. **d**, Longitudinal section of a regenerated limb 30 days post-amputation immunostained for MHCI (red). The majority fluorescent cells were found located in the regenerated skeleton; no signa was found in muscle. Blue shows DAPI in merge panels (**b**–**d**). Scale bars **b**, 0.5 mm; **c**, 50 µm; **d**, 100 µm.

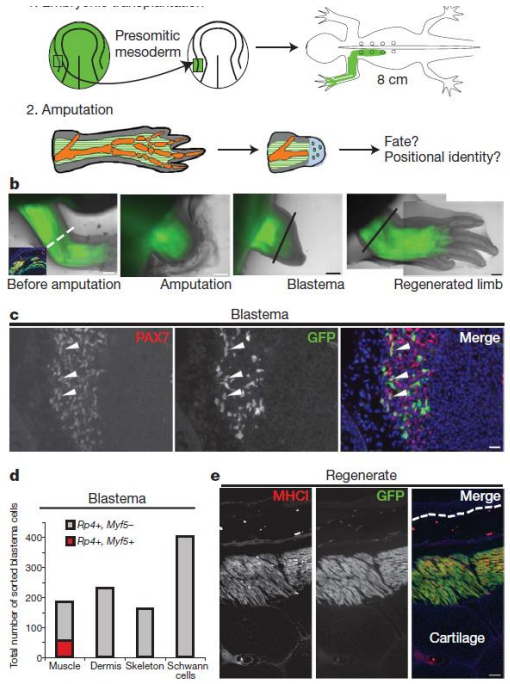


Figure 3 | Muscle does not make cartilage or epidermis. **a**, Schematic of labelling. **b**, Time course. Inset shows cross-section at dashed line (see Supplementary Fig. 4e). **c**, Section of 12-day blastema. GFP$^+$ cells (arrowheads) were positive for PAX7. **d**, Single-cell PCR showed that GFP$^+$ muscle-derived blastema cells expressed *Myf5* (see also Supplementary Fig. 9a) but GFP$^+$ cells from other tissues did not. RP4 acted as quality control. Numbers of cells/blastemas/animals/experiments analysed were as follows for each tissue. Skeleton: 152/8/8/4, Schwann cells: 402/6/6/6, dermis: 230/12/12/6, muscle: 184/6/6/3. **e**, Longitudinal section through regenerated limb. No GFP$^+$ cells were found in cartilage or epidermis (above dotted line). Scale bars: **b**, 0.5 mm; **c**, 50 µm; **e**, 100 µm.

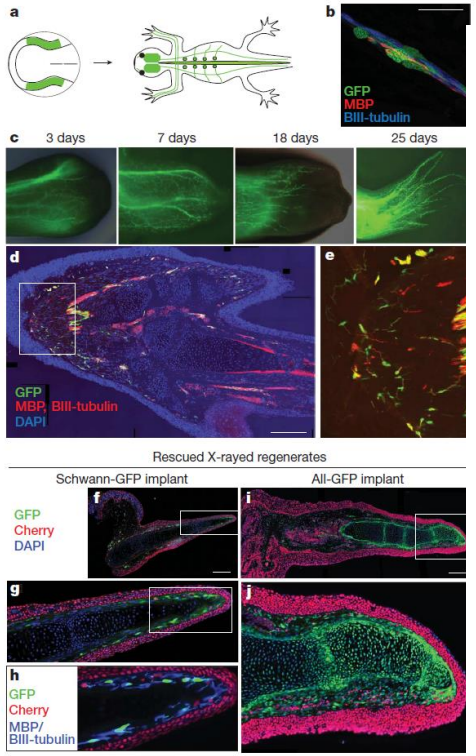


Figure 4 | Schwann cells give rise to Schwann cells and do not form cartilage even during nerve-rescue of irradiated limbs. **a**, Schematic of labelling. **b**, Confocal fluorescence image of GFP$^+$ Schwann cells in the han **c**, Time course of regeneration. Note that Schwann cells did not enter the distal tip until 25 days post amputation. **d**, Longitudinal section through a regenerated hand. GFP$^+$ Schwann cells were closely associated to MBP and BIII-tubulin staining. **e**, Enlarged part of **d** shown without DAPI.
f–**j**, Sections of regenerating limbs that had been X-rayed and rescued by a non-irradiated nerve implant. **f**–**h**, A regenerate rescued by nerve with GFP-labelled Schwann cells. Cartilage was negative for both GFP and nuclear Cherry. **i**, **j**, A regenerate rescued by nerve tissue in which all cells expressed GFP. Cartilage cells were GFP$^+$, indicating that they derived from non-Schwann cells in the nerve. **g**, **j**, Higher magnification of the regions framed in **f** and **i** respectively. **h**, Higher magnification of the frame in **g** showing MBP and BIII-tubulin staining. Scale bars: **b**, 50 µm, **d**, **f**, **i**, 0.5 mm.

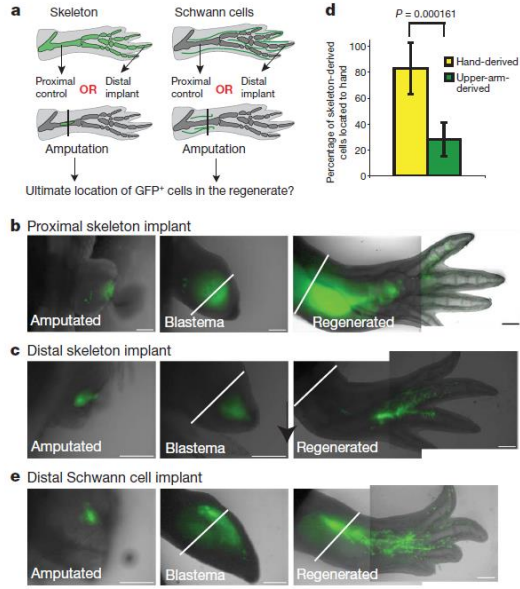


Figure 5 | Schwann cell-derived blastema cells do not possess proximo-distal positional identity but cartilage-derived cells do. **a**, Schematic to show the experimental design. **b**, **c**, **e**, Time course through regeneration of the indicated graft type. Progeny of distal skeletal cells localize distally while Schwann-cell-derived cells show no positional preference. $n = 14$ (**b**), 20 (**c**) and 15 (**e**) limbs. Scale bars: 0.5 mm. **d**, Percentage of cartilage-derived progeny originating from upper arm (six limbs) or hand transplants (seven limbs) that contribute to hand skeleton after regeneration. Error bars are standard deviations; P value is from Student's t-test (Welch; unpaired).

M. Kragl. Nature, 2009; 460(7251),60–65.

Dedifferentiation and tubular repair

- The potent regenerative response of the kidney to acute injury has been known for decades, and historically, dedifferentiation was proposed as a central mechanism for proximal tubule repair.

- Proliferating cell nuclear antigen (**PCNA**), **c-Fos** and **the intermediate filament vimentin** were expressed *de novo* in the S3 segment of the proximal tubule after ischaemic injury in rodents.

- These findings were interpreted to reflect dedifferentiation of mature cells that re-entered the cell cycle to proliferate, redifferentiate and repair the nephron, as vimentin is normally expressed in mesenchymal cells.

Chang-Panesso, M., Nat.Rev.Neph,2016;13:39–46.

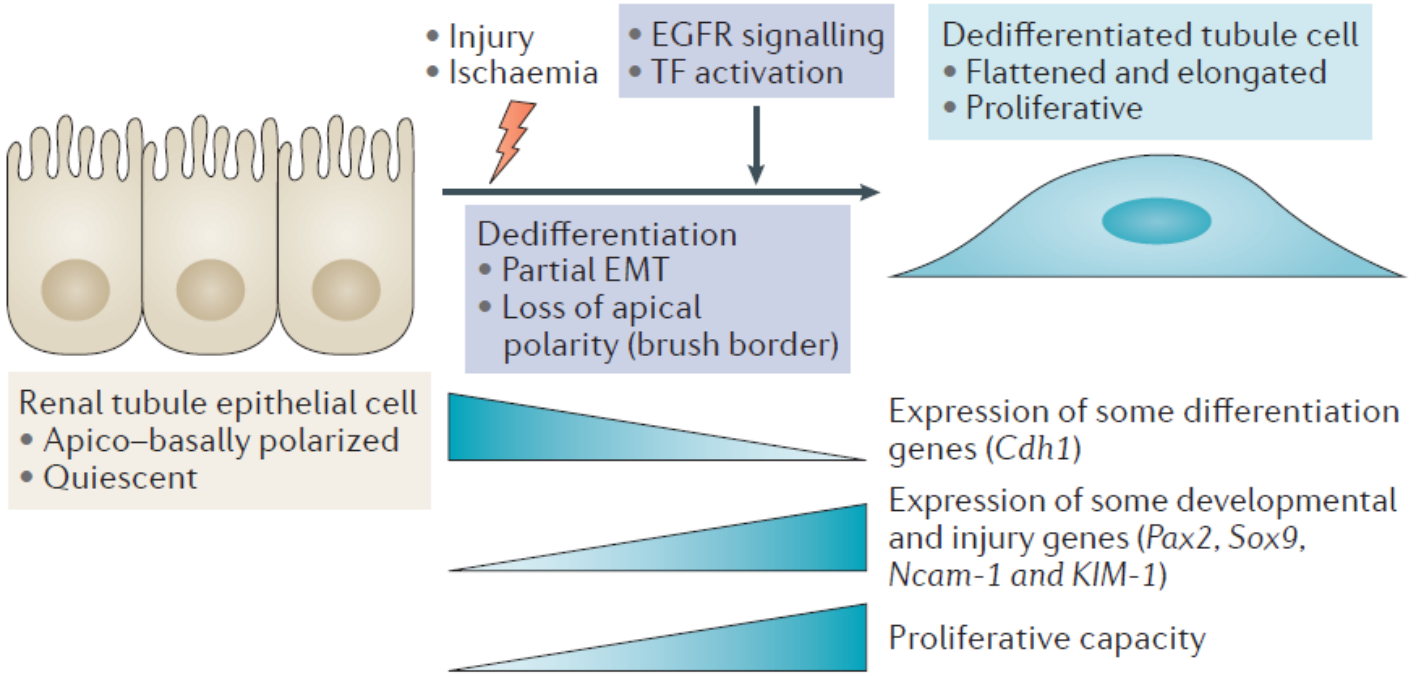


Figure 1 | **Dedifferentiation: a regenerative response to kidney injury.** After injury (such as toxic or ischaemic insults), epithelial tubular cells dedifferentiate. This process involves the activation of transcription factors (TFs) and the epithelial growth factor receptor (EGFR) signalling pathway. Dedifferentiated cells lose their polarity and expression of certain differentiation genes, and undergo partial epithelial-to-mesenchymal transition (EMT). The dedifferentiated cells acquired a flattened morphology, proliferative capacity and re-express some developmental and injury-related genes such as *Pax2*, *Sox9*, *Ncam-1* and *KIM-1*.

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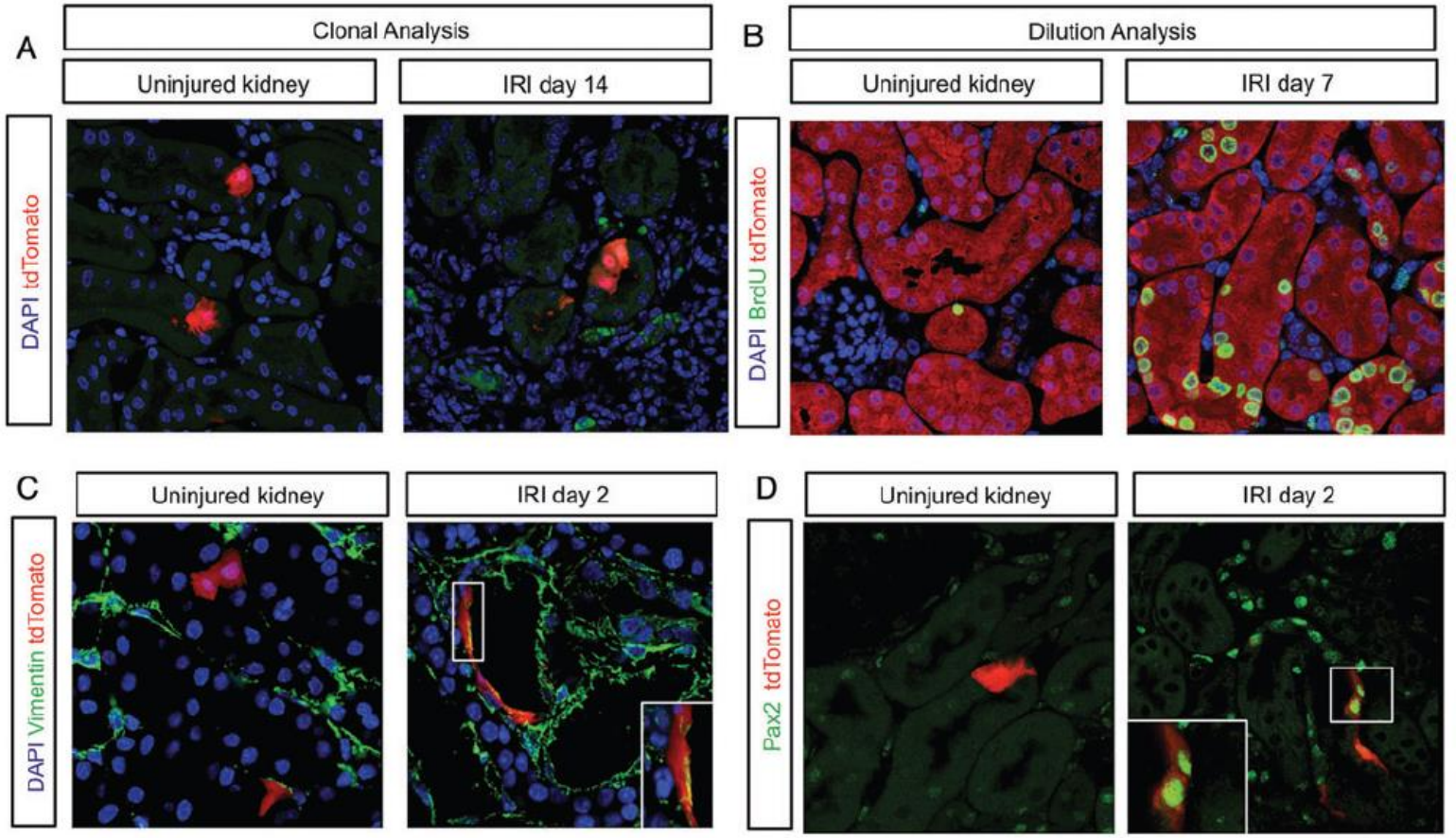

FIGURE 2: Clonal and dilution analysis of SLC34a1$^{GCE/+}$, Rosa26$^{tomato/+}$ mice. (**A**) In uninjured contralateral kidney, cells were labeled solely by low-dose tamoxifen (left panel). In the IRI kidney, clone size of labeled cells expanded after repair (right panel). (**B**) Dilution analysis of SLC34a1$^{GCE/+}$, Rosa26$^{tomato/+}$ mice. These representative images indicate complete labeling of the proximal tubule in uninjured kidneys and remaining labeling (no dilution) after injury. Staining for BrdU (green) indicates the proliferating cells of the proximal tubule indeed came from the labeled (red) terminally differentiated tubular cells. (**C** and **D**) Immunostaining of dedifferentiation markers; vimentin and Pax2. In non-injured kidneys terminally differentiated labeled epithelial cells (red) did never stain for vimentin or Pax2. Whereas, following injury (IRI) these terminally differentiated cells became flattened and expressed both vimentin and Pax2, indicating dedifferentiation.

Kermann et al. NDT (2015) 30: 903–

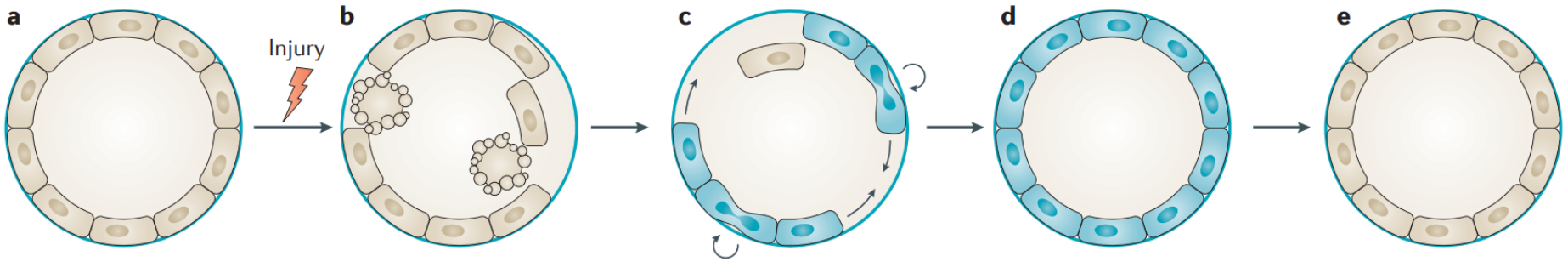

Figure 2 | **Tubular regeneration by dedifferentiation. a** | Healthy tubules consists of non-proliferative mature epithelial cells that express markers of differentiation. **b** | After injury, the epithelium is lost through apoptosis and necrosis. **c** | Surviving epithelial cells dedifferentiate, either in response to sublethal injury signals or owing to signals from other injured cells, and acquire a proliferative phenotype. **d** | The surviving dedifferentiated cells reconstitute the nephron epithelium. **e** | Ultimately, most dedifferentiated cells redifferentiate and downregulate the expression of dedifferentiation genes.

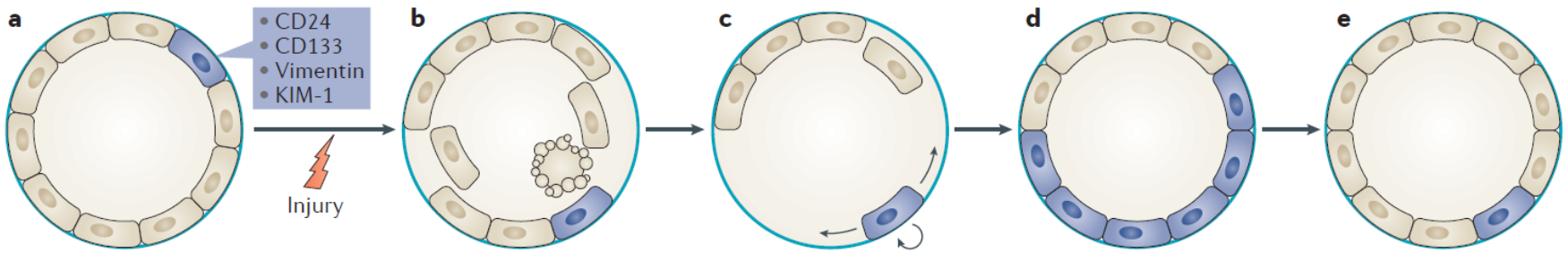

Figure 3 | **Tubular regeneration mediated by scattered progenitor epithelial cells. a** | Scattered tubular epithelial cells express signal transducer CD24, prominin-1 (CD133) and other genes that are characteristic of proximal tubule dedifferentiation, such as vimentin and KIM-1. **b** | After injury, mature tubular cells, but not scattered cells, undergo apoptosis. **c–d** | Scattered tubular cells expand in response to injury and their progeny reconstitutes the tubule. **e** | The small subpopulation of scattered tubule cells is preserved after regeneration.

Chang-Panesso, M., Nat.Rev.Neph,2016;13:39–46.

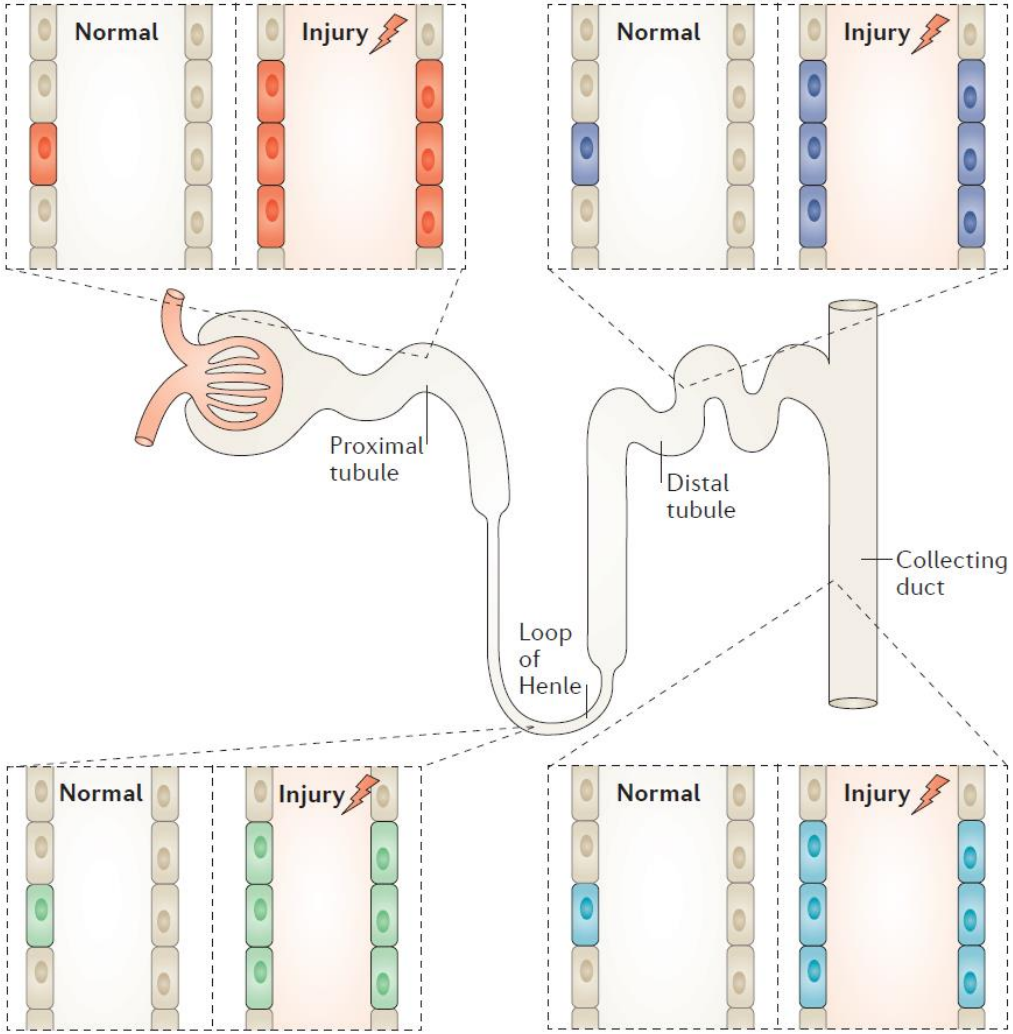

Figure 4 | **Nephron progenitors are unipotent and have segment-restricted progeny.** Although all nephron segments possess regenerative capacity after injury, the cellular potential of the progenitors is limited to their segment of origin. Whether a different injury stimulus might confer a higher degree of cell plasticity *in vivo* remains unknown.

Chang-Panesso, M., Nat.Rev.Neph,2016;13:39–46.

Benjamin Humphreys: “All injured PTECs have an equivalent capacity to repair, and argue against the existence of a fixed intratubular population of progenitor cells”

- Analysis of differential gene expression patterns showed changes in the levels of 1,457 genes between day 2 and 7 following IRI, which subsequently returned towards baseline levels by day 14.
- Gene ontology analysis showed upregulation of genes involved in the **cell cycle**, **DNA repair**, the **immune response** and **cilium assembly** at day 7 compared with day 2
- By contrast, genes that were upregulated by day 14 included those involved in **cell transport and metabolic processes**, indicating redifferentiation of these cells.
- The main involving gene/pathway: EGFR–FOXM1 signalling.

The Cell Source for Regeneration

- **Surviving renal epithelium cells** now prevail as the most relevant source for the regenerating tissue
- The renal ECs seem to possess poor regenerative capacity: Angiogenesis ?
- ~~Bone marrow derived cells~~
- ~~Scattered tubular cells with stem cell properties~~

Coelho S. Nephrology 23 (2018) 805

Can We Target Inflammation in AKI?

Table 1 – Targeting regulated cell death in experimental AKI.

Preclinical model	Pathway targeted	Tool to target pathway	Effect	Reference
Renal IRI	Apoptosis	zVAD	↑ renal function ↓ inflammation	51
		zVAD Caspase-8-KO mice	No protection	29
		Bax and Bak KO mice	↑ renal function ↓ apoptotic cells Not change tubular necrosis	50
	Necroptosis	Nec-1 RIPK3 KO mice	↑↑ renal function ↓↓ renal damage score	29
	MPT-RN	CypD-KO mice SfA	↑ renal function ↓ renal damage score	29
	Ferroptosis	Fer-1 16–86	↑ renal function ↓ tubular injury	35
	Necroptosis+ MPT-RN+ Ferroptosis	CypD-RIPK3-dKO Nec-1 + Sfa + Fer-1	↑↑↑ renal function ↓↓↓ tubular injury	29,35
Cisplatin	Apoptosis	Not tested alone in vivo		
	Necroptosis	Nec-1 RIPK3-KO MLKL-KO	↑↑ renal function ↓ tubular injury ↓ inflammation ↑ survival	29,58
	MPT-RN	CypD-KO	↑↑ survival	29
	Necroptosis+ Apoptosis	RIPK3-KO + zVAD RIPK3-caspase-8-dKO	↑↑ survival	29
Folic acid overdose	Apoptosis	zVAD	No protection	36
	Necroptosis	Nec-1 MLKL-KO	No protection	36
		RIPK3-KO	No protection ↓ inflammation	36
	Apoptosis+ Necroptosis	zVAD + Nec-1 RIPK3-KO + zVAD	No protection	36
	Ferroptosis	Fer-1	↑↑ renal function ↓↓ tubular injury ↓↓ cell death ↓ inflammation	36
CaOx crystals	Apoptosis	zVAD	No protection	32
	Necroptosis	RIPK3-KO MLKL-KO Nec-1	↑ renal function ↓↓ tubular injury ↓↓ cell death ↓ inflammation	32
	Ferroptosis	Fer-1	↑ renal function ↓↓ tubular damage ↓ inflammation	35
Rhabdomyolysis	Apoptosis	Not tested		
	Necroptosis	Nec-1	↑ renal function ↓↓ tubular injury	33

CaOx: calcium oxalate. IRI: ischemia-reperfusion injury. Fer-1: ferrostatin-1; MPT-RN: mitochondria permeability transition-regulated necrosis; Nec-1: necrostatin-1; SfA: sanglifehrin A; zVAD: pan-caspase inhibitor z-VAD-fmk.

Can We Target Repair in AKI?

- Hepatocyte growth factor (HGF) gene therapy: increased the number of bone marrow-derived M2 macrophages and induced kidney repair in diabetic kidneys.
- Cell therapy with M2 macrophages that had been stabilized with Lcn-2 effectively reduced kidney fibrosis in murine kidney disease, probably by the modulation of the renal inflammatory milieu.
- Senescent Cell Clearance (Senotherapies): Removal of senescent cells with senolytics, SASP suppression with senostatics, or boosting blockers of cellular senescence triggers:
  - Flavonoids have been explored to deplete senescent cells in kidney injury.
  - The combination of Dasatinib, a tyrosine kinase inhibitor which promotes apoptosis, and the pro-apoptotic natural flavonoid Quercetin has been tested in vitro and in vivo

Conclusions

- AKI can lead to CKD/ESKD in a substantial percentage of patients depending on the inciting factor and baseline patient characteristics.
- The tubules have a high regenerative potential mainly based on surviving tubular cells, which achieve progenitor characteristics.
- Necroinflammation /Apopotisis are important determinants of the outcome of renal repair.
- Innate immunity may lead to progression to fibrosis or regenerative profile.
- Cell senescence phenotype is another important determinant of the kidney regenerative pathway.
- Future therapies will target these pathways, alongside timely action for prevention.


Nadia Trip