Tubule repair: with a little help from my “unexpected” friends

Tubule repair: with a little help from my "unexpected" friends

Letizia De Chiara[1,2] and Paola Romagnani[1,2,3]

Tubulointerstitial fibrosis is considered a hallmark of maladaptive repair processes after tubular injury leading to chronic kidney disease. Nakamura and colleagues show that, upon injury, myofibroblasts promote epithelial repair by producing retinoic acid in place of injured tubular cells. These results suggest that resident fibroblasts turning into myofibroblasts maintain a cross-talk that protects tubular epithelial cells from injury and can restore tissue integrity and functionality, challenging the concept that fibrosis is only detrimental in nature.

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see basic research on page 526

Tubulointerstitial fibrosis is a pathological process occurring after tubular injury that is characterized by an excessive accumulation of extracellular matrix and is associated with chronic kidney disease.[1] After tubular injury, extracellular matrix proteins, such as collagens, are mostly released from activated resident fibroblasts and pericytes, referred to as myofibroblasts, which are identified by the expression of alpha smooth muscle actin and platelet-derived growth factor receptor beta.[1] Thus far, fibrosis is generally considered a hallmark of poor renal outcome.[1] However, clinical trials using fibrosis antagonists have been mostly disappointing, suggesting the role of fibrosis in kidney repair may be complex and not univocal.[1] In support of this view, a study from Nakamura *et al.* (2019),[2] published in this issue of *Kidney International*, sheds new light on how the interplay between resident fibroblasts and injured tubules dictates the occurrence of fibrosis as well as the outcome of kidney injury. In this new study, taking advantage of a transgenic mouse model, Nakamura *et al.* show that, in the healthy mouse kidney, induced-fibroblast depletion upregulated the expression of neutrophil gelatinase–associated lipocalin, a marker of tubular injury (Figure 1). Next, they noticed that upon unilateral ureteral obstruction damage, the expression levels of tubular injury markers markedly increased upon targeting resident fibroblasts (Figure 1). More importantly, the authors identified a previously unknown mechanism through which activated fibroblasts help to preserve tubule integrity. They found that myofibroblasts stimulate regeneration of proximal tubular cells by acquiring retinoic acid (RA)–producing ability. Indeed, the switch from fibroblasts to myofibroblasts was associated with a strong expression of retinaldehyde dehydrogenase 2, a dehydrogenase converting retinal to RA (Figure 1). Instead, injured tubular cells lose retinaldehyde dehydrogenase 2 expression along with stimulated-by-retinoic-acid-6 expression, a receptor that uptakes dietary-derived retinol (Figure 1). This result would suggest that RA-producing myofibroblasts may be recruited by the injured tubules to maintain RA expression to support tubular integrity and repair. Indeed, Nakamura and colleagues provide evidence that a tight cross-talk between tubular epithelial cells and resident fibroblasts exists, thus suggesting that fibroblast differentiation into myofibroblasts can endorse tubule repair and hence have rather beneficial effects on renal outcome, at least in the early stage of tubular damage.[2] Previously, the same group had already established that fibrosis is secondary to tubular injury, showing that proximal tubular damage stimulates fibroblast-to-myofibroblast transition.[3] In this study, they add important clues on the mechanism mediating tubular repair and show that retinoids released by resident fibroblasts upon tubular damage represent the main driver of this process. Retinoids represent essential molecules during development and adult life. RA, the most important bioactive metabolite of vitamin A, induces a spectrum of pleiotropic effects by binding to the RA response elements and therefore altering transcription of different genes in a context-dependent and cell-dependent manner.[4] In particular, RA is considered a regeneration-inducing molecule in multiorgan systems, mostly thanks to its direct growth-promoting and/or differentiative effect on resident progenitor population.[4] In the kidney, RA was already shown to promote glomerular regeneration by stimulating differentiation of renal progenitors into podocytes after injury.[4] Likewise, Nakamura and colleagues suggest that RA signaling in tubular epithelium sustains regeneration by promoting proliferation. In fact, *in vitro* exposure to an inverse agonist of pan-retinoid acid receptors attenuates the expression of Ki67 and bromodeoxyuridine (a thymidine analog) incorporation in a tubular cell line.[2] Moreover, the authors reported a downregulation in Ki67-positive cells upon injury in mice where fibroblasts have been depleted, interpreted as a reduction in tubular proliferation and a decrease in tubular regeneration (Figure 1). However, caution should be applied to this conclusion, because cell cycle activation markers such as

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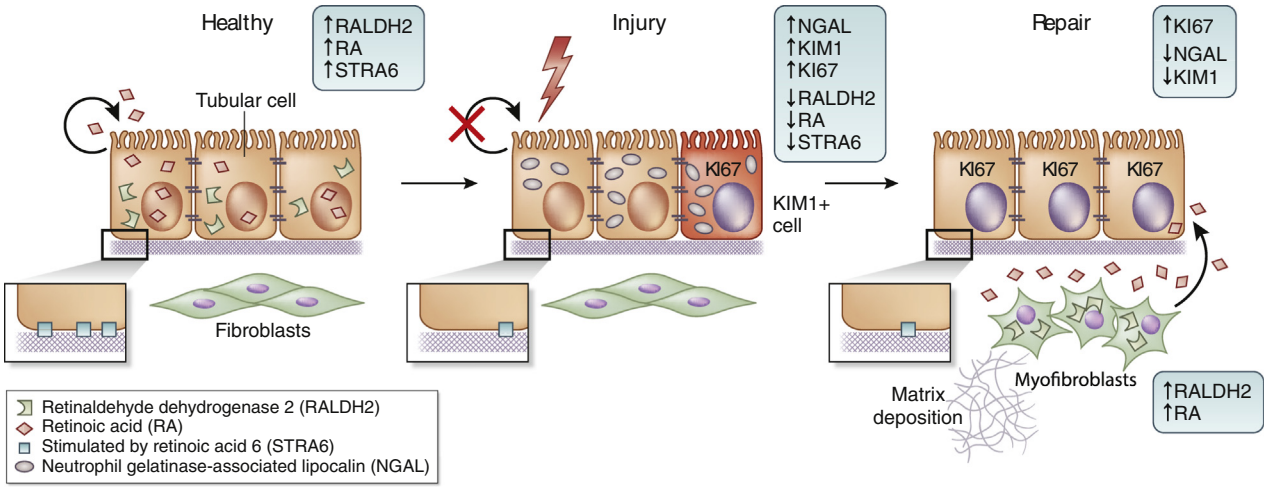

Figure 1 | Schematic representation of tubular epithelial cell cross-talk with resident fibroblasts. During steady-state condition (healthy kidney) tubular epithelial cells express retinaldehyde dehydrogenase 2 (RALDH2), stimulated by retinoic acid 6, and synthesize retinoic acid. Upon damage, proximal tubular cells start to express injury molecules (neutrophil gelatinase–associated lipocalin [NGAL] and kidney injury molecule 1 [KIM1]) and they lose RALDH2 and stimulated-by-retinoic-acid-6 expression. However, myofibroblasts acquire RALDH2 expression and start to produce retinoic acid in place of proximal tubular cells, restoring tissue integrity by downregulating injury markers and upregulating Ki67, indicating hypertrophy and/or proliferation.

bromodeoxyuridine or Ki67 may not always imply cell division (mitosis, i.e., proliferation). Indeed, upon kidney injury, bromodeoxyuridine/Ki67+ cell cycle activation may also indicate that the cell is undergoing endocycle-mediated hypertrophy, which also requires entering the S-phase, and nucleotide incorporation during DNA synthesis to enter polyploidization, as recently reported.[5] Nevertheless, these data suggest that activated fibroblasts are critical promoters of the repair process and in addition are essential to quickly recover kidney function, which is potentially lifesaving upon acute kidney injury. Collectively, these results point toward a protective effect of myofibroblasts on tubular injury and contribute to the ongoing revision of fibrosis role during kidney remodeling.

Previously, other authors noticed an association between myofibroblast distribution and nephron damage after injury.[6] Particularly, they reported that myofibroblasts emerge around injured tubules and subsequently disappear, thus suggesting that they may support the structural integrity and regeneration of damaged tubules.[6] Along this line, a recent paper from Buchtler *et al.*[7] showed that targeting fibrosis is not always beneficial, but it depends on the type of kidney injury. In fact, collagen I production by resident fibroblasts may even help to preserve renal function and survival, e.g., in mice upon ureteral obstruction.[7] Taken together, these new findings bring an important contribution to our knowledge of the kidney response to injury. First, they support the idea that in the early phase, fibrogenesis may rather help to maintain the integrity and repair of the surviving tubules. Second, they suggest that myofibroblasts may directly drive this process by a constant cross-talk with the damaged renal tubules involving RA, to stimulate cell hypertrophy and/or proliferation, which is pivotal for the kidney to survive the acute phase of damage. Indeed, supportive signals from other cells types are essential to initiate tubule repair, e.g., the secretion of interleukin 22 and other pro-regenerative signals from resident dendritic cells have been described, and in general the role of immune cells in wound healing is well established.[8] By contrast, production of pro-reparative factors by myofibroblasts during tubular damage comes somehow unexpected and revises the current concept of fibrosis being always detrimental. Importantly, mesenchymal-epithelial cross-talk is the central paradigm of kidney development, where reciprocal inductive signals between metanephric mesenchyme and ureteric bud cells induce tubule shaping and elongation.[9] It is intriguing to assume that a similar process takes place again during repair when reshaping of the tubule structure is needed.

The concept that myofibroblasts may not only have a pathological role but also directly protect injured tubular epithelium and promote kidney repair changes our view of these cell types as the "bad guys" of kidney fibrosis. Nevertheless, to address the functional relevance of fibrosis development in the kidney and the role of myofibroblasts, further analyses are mandatory, especially to analyze the long-term effects of their depletion.

In summary, the study of Nakamura and colleagues suggests that also targeting fibrosis may not always represent an effective strategy to promote renal regeneration and to preserve kidney function. Repair-promoting approaches may rather be explored, for example, administering RA, as suggested by their and other studies.[4] Unfortunately, RA administration is associated with life-threatening side effects.[4] However, conceptually, identification of new compounds with repair-promoting activity may be an appealing strategy to treat chronic kidney disease. Learning from the study of Nakamura *et al.* we

may conclude that such molecules may sometimes even be produced from unexpected players.

DISCLOSURE

All the authors declared no competing interests.

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DAMPening sterile inflammation of the kidney

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Renal ischemia reperfusion injury (IRI) is a serious cause of acute kidney injury (AKI). Danger-associated–molecular pattern molecules (DAMPs) are thought to promote IRI by initiating immune cell infiltration and driving disease progression, but the underlying pathophysiological mechanisms are mainly unclear. Poluzzi *et al.* demonstrate that soluble biglycan is a bimodal DAMP that both recruits proinflammatory macrophages and initiates resolution of inflammation and tissue remodeling in IRI, identifying a potential therapeutic target.

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see basic research on page 540

Renal ischemia reperfusion injury (IRI) is the main cause of acute kidney injury (AKI) in humans. It is caused by a temporary impairment of the renal blood flow, for example, after organ transplantation, infarction, trauma, or sepsis. Subsequent restoration of perfusion followed by reoxygenation of the organ provokes the production of reactive oxygen species leading to a profound inflammatory response. This inflammatory response is characterized by a variety of pathophysiological processes including cell death, infiltration of immune cells, and acute kidney failure.[1]

In the early stage of IRI, not only resident renal cells such as tubular epithelial cells and endothelial cells are activated, but also innate immune cells such as neutrophils and macrophages that start infiltrating the kidney as early as 30 minutes after IRI induction. Both renal cells and immune cells release proinflammatory mediators such as cytokines and chemokines that lead to apoptosis and progress necrosis in the tubular system followed by a rapid loss of renal function. In later stages of IRI, a dynamic interplay between pro- and anti-inflammatory signals released from kidney-resident and recruited immune cells mediates disease progression, and later either resolution of inflammation and healing of the injured tissue or progression to chronic kidney disease.[1]

Because the underlying pathophysiological mechanisms of IRI-induced AKI are poorly understood, therapeutic approaches regarding this complex human condition are still limited. As a consequence, IRI remains an important risk factor for developing chronic kidney disease and disease progression is still associated with high mortality rates and long-lasting hospitalization, representing a growing burden for the health care system. Therefore, a better understanding of the cellular mechanisms underlying kidney injury is required to design therapies to prevent and treat IRI-induced AKI.

During the last years, several studies showed that kidney-infiltrating innate immune cells not only contribute to inflammation in IRI, but also play an important protective role in the healing and regeneration process. Thus, targeting the innate immune system might be a potential entry point for developing novel therapies for IRI-induced AKI. But how is the innate immune system activated in the pathogenesis of sterile inflammation as it occurs in IRI? In the context of sterile inflammation, innate immune cells do not respond to foreign pathogen-associated molecular pattern molecules, but rather to so-called danger-associated pattern molecules (DAMPs). DAMPs are a diverse group

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