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The yin and yang of autophagy in acute kidney injury

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ABSTRACT

Antagonizing the strongly activated pathway of autophagy in renal ischemic injury has been associated with poor outcome. In our recent study we used mice with a selective deletion of *Atg5* in the S3 proximal tubule segment, which is most susceptible to ischemic damage. In line with the notion that autophagy is a prosurvival mechanism our studies revealed an early accelerated cell death of heavily damaged tubular cells in the S3 segment of these mice. Interestingly, this expedited loss of cells was associated with better long-term outcome as reflected by less inflammation, improved tubular repair, and function and reduced accumulation of senescent cells. While these data confirm the role of tubular autophagy as a prosurvival mechanism in ischemic kidney injury, they also show that autophagy may enable severely damaged cells to persist and exert deleterious effects. Such ambivalent effects might be of relevance if modulating autophagy is considered as a therapeutic option.

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Acute kidney injury (AKI), which is defined as a rapid decline in renal function, is a common problem in hospitalized patients. Apart from its important association with in-hospital mortality, AKI carries a significant risk of transitioning into chronic kidney disease. Therapeutic options for treating AKI or targeting its transition to chronic kidney disease are not available yet. One of the increasingly recognized targets for potential therapies might be cellular senescence. Cellular senescence is a state in which the cells enter an irreversible cell cycle arrest while remaining viable with a high metabolic activity. As senescent cells cannot divide they are unable to contribute to reparative cell replacement. Moreover, they secrete factors that promote inflammation, further hampering the normal repair process. In the aging kidney senescent cells accumulate mainly in the tubular compartment. While the age-associated accumulation is a slow process, tubular cell senescence also develops in an accelerated fashion during times of acute stress. A potent inducer of accelerated renal senescence is ischemic AKI and it has been shown in mice that antagonizing pro-senescent pathways after ischemia/reperfusion (I/R) improves structural and functional outcome.

Among the many additional pathways that are also activated as part of the renal stress response during I/R, autophagy has attracted a lot of interest in recent years. I/R is a strong trigger for autophagy in renal tubular cells and experimental data suggest that the upregulation of autophagic activity serves a protective role. In our recent study we were interested in defining the potential interdependence of autophagy and cellular senescence in the context of renal I/R. Whereas a decline in basal autophagy has generally been suggested as a contributor to aging, activation of autophagy may facilitate the accelerated occurrence of senescence under various circumstances and in various cell types. To study this link in the kidney, we used the Cre/lox system for conditional ablation of *Atg5* in the outer medullary part of the renal proximal tubule. This tubular segment (S3 segment) suffers the most extensive damage after I/R due to its high metabolic activity in a low-oxygen environment (Fig. 1). Other groups had previously shown that disrupting autophagy in larger tubular segments (e.g., the proximal tubule or the entire tubule) by conditional ablation of *Atg5* or *Atg7* results in increased injury and worsened renal function after I/R. While the previous studies had focused on the first post-ischemic wk, we chose a longer followup (30 d) to allow for the establishment of potential differences in post-ischemic cellular senescence.

Thirty d after I/R, we observed significantly fewer phenotypically senescent cells and a reduced expression of senescence markers in $atg5^{\Delta flox/\Delta flox}$ kidneys. This is paralleled by a reduced tubular injury pattern, significantly fewer peritubular leukocytes, less tubular atrophy and markedly decreased fibrotic matrix expansion. Concomitantly, renal function as measured by glomerular filtration rate is significantly better in $atg5^{\Delta flox/\Delta flox}$ kidneys. Compared to the previous reports demonstrating a detrimental effect of autophagy deletion from the tubular system our data thus indicated a clear benefit of ablating autophagy when only the S3 segment was targeted. We next investigated earlier time points after I/R. In line with the results after 30 days we found that already 3 d after I/R $atg5^{\Delta flox/\Delta flox}$ kidneys display less tubular damage and a strong trend for fewer infiltrating leukocytes. Surprisingly, an opposite pattern is seen in kidneys analyzed as early as 2 h after reperfusion

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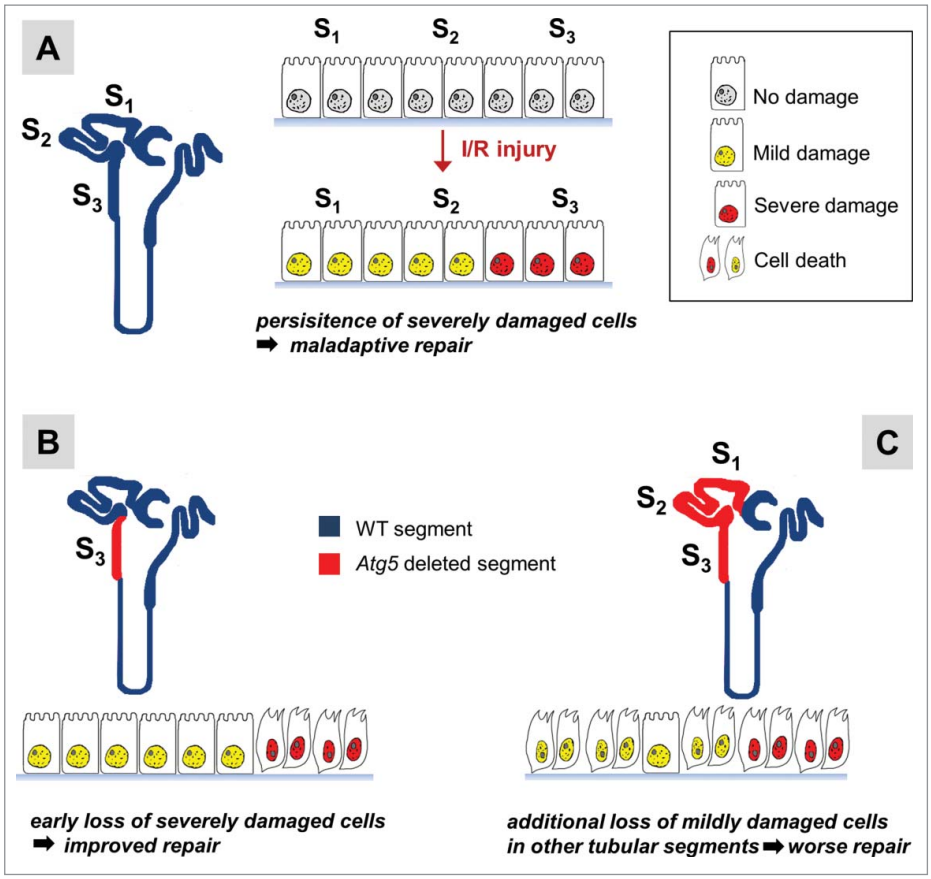

Figure 1. Schematic illustration of targeted deletion of *Atg5* in the 3 segments of the proximal tubule (S1-S3) and its effect on the course of ischemic kidney injury. Renal ischemia/reperfusion (I/R) results in tubular epithelial cell injury where the S3 segment of the proximal tubule is most susceptible to damage. (A) Epithelial cell injury in autophagy-enabled wild-type tubular segments results in survival and persistence of severely damaged cells leading to aberrant renal repair. (B) The targeted deletion of *Atg5* in S3 tubular segment results in rapid and selective loss of severely damaged autophagy-suppressed epithelial cells. This improves the regenerative milieu leading to improved renal repair. (C) The extended deletion of *Atg5* in S1-S2-S3 segments or the entire tubule results in a worse outcome as less damaged epithelial cells are lost that would normally contribute to tubular repair.

(a time point generally not analyzed in renal I/R studies). At this early time point $atg5^{\Delta flox/\Delta flox}$ kidneys show significantly greater structural damage with abundant necrosis of tubular cells in the S3 segment. Consistent with the data from the abovementioned previous reports the 2 h findings thus indicate that *Atg5* deletion leads to aggravated cell injury and increased cell death in the I/R model.

However, if $atg5^{\Delta flox/\Delta flox}$ kidneys show significantly more damage at 2 h after I/R, how can the superior outcome 3 and 30 d after I/R be explained? We conclude that this discrepancy at first sight can be explained by an expedited loss of severely injured cells from tubules not protected by autophagy. By targeting the S3 segment in our model, ablation of autophagy selectively affects only the segment harboring the strongest cell damage. Compromised cells within this S3 segment are driven into an accelerated cell death due to their lack of a regular autophagic response. Persistence of these heavily compromised tubular cells on the other hand, as observed in wild-type kidneys, would have driven maladaptive changes of the local microenvironment including increased inflammation and disrupted tubular repair. It is conceivable that targeting larger portions of the tubular system might compromise an adequate stress-response in less heavily injured cells, in which autophagy is needed for successful survival and for pro-regenerative functions (Fig. 1). This notion would be consistent with the previous data showing detrimental effects of tubular autophagy deletion.

In summary, our data confirm that the upregulation of autophagy is a prosurvival mechanism in acute tubular cell injury in the context of ischemic AKI. However, in the particular case of very severe cell damage, e.g., in cells of the highly ischemia-susceptible S3 segment, this prosurvival mechanism seems to have deleterious secondary effects by allowing the survival of damage-promoting compromised cells. In our model the early clearance of autophagy-deficient cells prevents detrimental long-term consequences including increased cellular senescence, tubular atrophy, interstitial fibrosis and loss of renal function.

Disclosure of potential conflicts of interest

No potential conflicts of interest were disclosed.

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