In search of early events in the development of chronic kidney disease: the emerging role for lipocalin-2/NGAL *

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Summary of key findings

In the October 2010 issue of the Journal of Clinical Investigation, Viau et al. [1] provided primary evidence for lipocalin-2 ([Lcn2; also known as neutrophil gelatinase-associated lipocalin ([NGAL]), 24p3 protein, \(\alpha\rceil\rceil\)-microglobulin-related protein, or uterocalin]) as a central effector of progressive renal tissue damage upon acute kidney injury. Their studies are based on two experimental mouse strains which differed profoundly in their responses to 75% nephrectomy: whereas FVB/N mice develop severe renal lesions resembling features of human chronic kidney disease (CKD), B6D2F1 mice are protected from early deterioration and instead exhibit compensatory alterations only. Post-surgical microarray analyses of the remnant renal tissues unraveled Lcn2 as the most markedly up-regulated gene in the FVB/N mice when compared to the B6D2F1 strain. Moreover, renal expression levels and urinary excretion of Lcn2 highly reflected the degree of tubular damage in the FVB/N mice, quite similar to humans with various forms of chronic kidney disease (CKD). Introduction of a homozygous disruption of the Lcn2 gene (i) largely abolished tubular cell proliferation, (ii) prevented the development of chronic renal lesions and (iii) preserved kidney function in FVB/N mice, quite similar to humans with various forms of chronic kidney disease (CKD). Introduction of a homozygous disruption of the Lcn2 gene (i) largely abolished tubular cell proliferation, (ii) prevented the development of chronic renal lesions and (iii) preserved kidney function in FVB/N mice, quite similar to humans with various forms of chronic kidney disease (CKD). Introduction of a homozygous disruption of the Lcn2 gene (i) largely abolished tubular cell proliferation, (ii) prevented the development of chronic renal lesions and (iii) preserved kidney function in FVB/N mice, quite similar to humans with various forms of chronic kidney disease (CKD). Introduction of a homozygous disruption of the Lcn2 gene (i) largely abolished tubular cell proliferation, (ii) prevented the development of chronic renal lesions and (iii) preserved kidney function in FVB/N mice, quite similar to humans with various forms of chronic kidney disease (CKD). Introduction of a homozygous disruption of the Lcn2 gene (i) largely abolished tubular cell proliferation, (ii) prevented the development of chronic renal lesions and (iii) preserved kidney function in FVB/N mice, quite similar to humans with various forms of chronic kidney disease (CKD). Introduction of a homozygous disruption of the Lcn2 gene (i) largely abolished tubular cell proliferation, (ii) prevented the development of chronic renal lesions and (iii) preserved kidney function in FVB/N mice, quite similar to humans with various forms of chronic kidney disease (CKD). Introduction of a homozygous disruption of the Lcn2 gene (i) largely abolished tubular cell proliferation, (ii) prevented the development of chronic renal lesions and (iii) preserved kidney function in FVB/N mice, quite similar to humans with various forms of chronic kidney disease (CKD). Introduction of a homozygous disruption of the Lcn2 gene (i) largely abolished tubular cell proliferation, (ii) prevented the development of chronic renal lesions and (iii) preserved kidney function in FVB/N mice, quite similar to humans with various forms of chronic kidney disease (CKD). Introduction of a homozygous disruption of the Lcn2 gene (i) largely abolished tubular cell proliferation, (ii) prevented the development of chronic renal lesions and (iii) preserved kidney function in FVB/N mice, quite similar to humans with various forms of chronic kidney disease (CKD).

The study by Viau et al. confirms the significant up-regulation of Lcn2 after experimental nephron reduction...
There is extensive evidence that EGFR stimulation, e.g. via binding of EGF or other stress-induced ligands such as angiogenin II binding, promotes proliferation and apoptosis resistance in renal tubular cells [11, 12]. In vitro studies by Okada et al. [13] have shown that both transforming growth factor (TGF)-β1 and EGF synergistically drive EMT in cultured tubular cells. Transgenic mice with renal overexpression of a dominant-negative EGFR show reduced renal fibrosis upon 5/6 nephrectomy, suggesting that EGFR activation actively participates in the fibrotic process [14]. Accordingly, overexpression of a constitutively active form of EGFR results in excessive proliferation of tubular epithelial cells and contributes to an increased mortality of these mice [15].

HIF-1α is already known to play a central role in EMT development and renal fibrosis [16, 17]. The study by Viau et al. is the first to define HIF-1α as an intermediate between EGFR activation and Lcn2 up-regulation, however, future in-depth analyses will be necessary to unravel the molecular mechanisms in the EGFR:HIF-1α:Lcn2 framework.

Among the increasing number of “early indicators” of AKI that have been identified over the last decade, kidney injury molecule (KIM)-1 has undergone a comparable evolution from a mere biomarker to a key player in renal injury processes. The diagnostic and predictive potential of KIM-1 that emerged from various animal models of ischemic and drug-induced kidney injury has now been confirmed by studies in humans with AKI [18–20]. In contrast to the role of Lcn2 as a downstream mediator in profibrotic pathways, KIM-1 exerts protective effects in the functional recovery mechanisms following renal damage as it transforms epithelial cells to a phagocyte-like phenotype and thereby contributes to the clearance of apoptotic cells [21].

**Take-home-message**

The carrier protein Lcn2lipocalin-2 may not only serve as a promising biomarker for AKI, but it also mirrors proliferative changes in the kidneys and progression to CKD in mice and humans. Since it acts as a downstream signalling event upon EGF receptor activation, it may also bear the potential as a therapeutic target.

**Conflict of interest statement.** None declared.

11. Docherty NG, O’Sullivan OE, Healy DA et al. TGF-beta1-induced EMT can occur independently of its proapoptotic effects and is aided by EGF receptor activation. Am J Physiol Renal Physiol 2006; 290: F1202–F1212

**Fig. 1.** The EGFR:HIF-1α:Lcn2 network is a novel pathway involved in CKD progression. Activation of the epidermal growth factor receptor (EGFR) stimulates hypoxia-inducible factor (HIF-1α) and subsequent expression of Lcn2 resulting in increased cell proliferation, cytogensis, renal damage and CKD progression. The depicted structure of human Lcn2 demonstrating the typical 8-stranded antiparallel β barrel structure was generated with Ribbons XP version 3 using the coordinates that are deposited in the Brookhaven Protein Data Bank (acc. code 1NGL).


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