Megalin in acute kidney injury: foe and friend

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Megalin in acute kidney injury: foe and friend. Am J Physiol Renal Physiol 306: F147–F154, 2014. First published November 6, 2013; doi:10.1152/ajprenal.00378.2013.—The kidney proximal tubule is a key target in many forms of acute kidney injury (AKI). The multiligand receptor megalin is responsible for the normal proximal tubule uptake of filtered molecules, including nephrotoxins, cytokines, and markers of AKI. By mediating the uptake of nephrotoxins, megalin plays an essential role in the development of some types of AKI. However, megalin also mediates the tubular uptake of molecules implicated in the protection against AKI, and changes in megalin expression have been demonstrated in AKI in animal models. Thus, modulation of megalin expression in response to AKI may be an important part of the tubule cell adaption to cellular protection and regeneration and should be further investigated as a potential target of intervention. This review explores current evidence linking megalin expression and function to the development, diagnosis, and progression of AKI as well as renal protection against AKI.

ACUTE KIDNEY INJURY (AKI) is a serious complication to acute illness and/or medical intervention. Depending on the definition, it occurs in ~2% of all hospitalized patients and >40% of critically ill patients. It is associated with high mortality and the risk of chronic kidney disease (6). The pathophysiology of AKI is complex (31) and includes vasoconstriction, tubular obstruction, changes in cell structure and metabolism, and the activation of coagulation and inflammation (76, 77, 80). Proximal tubular endocytic uptake is an essential pathway for the renal accumulation of filtered, bioactive substances, and the proximal tubule is also the site of maximum accumulation of many drugs and toxins. Furthermore, proximal tubule epithelial cells (PTECs) are a major target in AKI and undergo a series of stress-induced events, such as loss of cell polarity, induction of cell death signals, and cell detachment, but also regeneration involving the differentiation and proliferation of neighboring, viable cells, which reestablishes the epithelial phenotype (3, 76, 77, 80). Disruption of the proximal tubule luminal membrane is a prominent feature of AKI (3), indicating interference with apical membrane function, such as endocytosis. Studies have shown that all three segments (S1, S2, and S3) of the proximal tubule are susceptible to ischemic and toxic injury (35). Cells of the S3 segment have been shown to differentiate and proliferate, thereby regenerating the proximal tubule structure (27). Proximal tubule phagocytosis has been implicated in protection against the progression of AKI (33), whereas tubular endocytic dysfunction results in increased excretion of biomarkers in AKI (89). Thus, numerous observations point to an important role of PTECs in AKI and suggest that endocytosis may play a role in the development and progression of AKI as well as protection against AKI. Megalin is a multiligand, endocytic receptor expressed in kidney proximal tubule luminal membranes and apical endocytic compartments. Absence of megalin leads to proximal tubule dysfunction with tubular proteinuria and a significant reduction in the apical, endocytic apparatus of PTECs (25, 47). This review will evaluate the potential role of megalin in AKI.

Megalin

Megaln is a 600-kDa single transmembrane receptor protein (Fig. 1). It belongs to the low-density lipoprotein receptor family. Megalin is responsible for the normal tubular reabsorption of virtually all filtered proteins, mediating the recovery of essential substances that otherwise would be lost in the urine (17). Megalin binds a very wide range of ligands, including carrier proteins, peptides, hormones, signaling molecules, enzymes, immune-related proteins, etc. The known ligands of megalin normally filtered in the glomeruli include retinol-binding protein, transcobalamin-B12, insulin, α1- and β2-microglobulin, EGF, albumin, lysozyme, cytochrome c, cystatin C, liver-type fatty acid-binding protein (L-FABP), α-amylase, and prolactin (for a review, see Ref. 17). Other ligands, which are normally only filtered in very limited amounts, are myoglobin, hemoglobin, and immunoglobulin light chains (17). Additionally, nonphysiological ligands are also filtered, including drugs and toxins such as gentamicin, polymyxin B, and aprotinin (17). Mutations in aprotinin decrease its affinity toward megalin, indicating that binding is charge dependent and favored by cationic sites on the ligands (55). However, many ligands of megalin are anionic proteins, suggesting that binding depends on the distribution of charge rather than the overall isolectric point (23).

Knockout of the megalin gene in mice causes abnormalities in epithelial tissues such as the lung and kidney (47). Abnormal
brain development has been described in megalin-deficient mice (47), and increased excretion of megalin ligands has also been observed in these mice (47). In humans, megalin deficiency is associated with Donnai Barrow/facio-ocular-acustico-renal syndrome (37). The Donnai Barrow/facio-ocular-acustico-renal syndrome is an extremely rare condition associated with characteristic facial features, hearing loss, and low-molecular-weight proteinuria (79).

Expression. In the kidney, megalin is expressed in the proximal tubule and at a much lower level in glomerular podocytes (Fig. 2A) (67). In addition, megalin is expressed in many extra renal epithelial tissues, including the choroid plexus, ependymal cells, the epididymis, type II pneumocytes, parathyroid hormone-secreting cells of the parathyroid gland, the endometrium, the oviduct, the ciliary epithelium, the strial marginal cells and epithelial cells of Reissner’s membrane in the inner ear, and the thyroid (16). In the proximal tubule, megalin is localized to the brush border, coated pits, endocytic vesicles (1, 4, 13), and the membrane recycling compartment, dense apical tubules (7, 18, 19, 22) (Fig. 2B). Megalin is essential for maintaining a structurally normal endocytic apparatus in PTECs (47). The expression of megalin in the proximal tubule varies between different segments (22). In early segment S1 of rats, brush border labeling for megalin is present only at the base of microvilli, whereas extensive microvillar labeling is present in later segments 1 and 2 (22). In segment 3, a patchy megalin brush border labeling has been identified (22). Also, greater expression of megalin is found in apical pits, apical vacuoles, lysosomes, and dense apical tubules of segments 1 and 2 compared with segment 3 (22). The higher expression of megalin in segments 1 and 2 may reflect a higher rate of protein reabsorption by endocytosis (22). Proteins that escape reabsorption in the initial segments, however, may be taken up in segment 3. Normal expression of megalin is dependent on 40-kDa receptor-associated protein (RAP) (10). Newly synthesized megalin binds with high affinity to RAP within the endoplasmic reticulum (ER), which protects megalin from premature binding of endogenously expressed ligands (10). RAP acts as chaperone, ensuring proper folding of megalin (11) and normal expression and subcellular distribution of megalin in PTECs (9). RAP is able to block the binding of almost all other ligands, which has made it an important tool for the study of megalin function.

Signaling in the kidney. Like other membrane-associated proteins, megalin has been suggested to undergo ectodomain shedding by regulated intramembrane proteolysis (49, 97). Along with solubilization of the extracellular domain, subsequent γ-secretase-mediated cleavage of the megalin COOH-terminal domain leads to the formation of a soluble megalin.

Fig. 1. Structural representation of megalin. The cDNA sequence of megalin has been identified in many species, including humans (41). The receptor has a large NH2-terminal extracellular domain, a single transmembrane domain, and a short COOH-terminal cytoplasmic tail. The extracellular domain contains four clusters of cysteine-rich complement-type/low-density lipoprotein receptor class A repeats, which constitute ligand-binding regions. These clusters are separated by 17 EGF-like repeats and 8 cysteine-poor spacer regions, which contain YWTD motifs. YWTD motifs are responsible for the pH-dependent release of ligands in the endosomal compartments. The cytoplasmic tail contains two NPXY motifs and a similar VENQNY motif. The NPXY motifs are known to bind adaptor proteins like disabled homolog 2, autosomal recessive hypercholesterolemia protein, and adaptor protein-2, which is involved in the formation of coated pits during endocytosis. In addition, the cytoplasmic tail also contains potential signaling motifs, although such signaling pathways have not yet been fully established in the kidney. [Modified from Ref. 24.]
intracellular domain (MICD) (49, 97). MICD is predicted to interact with the nucleus and regulate gene expression. Overexpression of MICD in cultured cells in vitro has been shown to downregulate megalin and Na\(^{+}/H^{+}\) exchanger 3 transcripts (49, 97); however, overexpression of MICD in vivo in the mouse had no apparent effect on renal proximal tubule function (15). So far, no physiologically important direct signaling effects of megalin have been demonstrated in the kidney in vivo.

Megalin in AKI

Megalin-mediated uptake of nephrotoxins. Many polybasic drugs, such as aminoglycosides, aprotinin, chemotherapeutic agents, and toxins, are known to be nephrotoxic, and the study of these in animal models has provided insights into the mechanisms of nephrotoxicity. Megalin has been shown to bind such drugs and mediate uptake in PTECs (Table 1). Gentamicin uptake studies in rats have shown more accumulation of gentamicin in segments 1 and 2 of the proximal tubule (91), which was later demonstrated to be megalin dependent (55). The molecular dynamics of gentamicin binding involves an initial weak binding to acidic phospholipids on the brush border membrane in the proximal tubule (71) followed by delivery to megalin for uptake (55). It has been suggested that gentamicin accumulates in the lysosomes and may be transported to the Golgi network and ER (70). When the concentration of gentamicin inside the lysosomes, Golgi network, and ER exceeds a threshold, it destabilizes the organelle membrane and is released into the cytoplasm, where it induces oxidative stress and apoptosis (for a review, see Ref. 68). This mechanism of toxicity may also be true for other less-studied aminoglycosides, such as tobramycin, streptomycin, neomycin, netilmicin, and kanamycin, which have also been shown to bind to megalin (83). In both megalin- and RAP-deficient mice, the proximal tubule accumulation of gentamicin is reduced (73), and reduced megalin expression may prevent aminoglycoside-induced nephrotoxicity (55).

Nephrotoxins in plant extracts, such as aristolochic acid and trichosanthin, have also been shown to bind to megalin, which mediates their uptake (12, 45). Both aristocholic acid- and trichosanthin-induced AKI are associated with low-molecular-weight proteinuria, indicating proximal tubule endocytic dysfunction.

Megalin binds and mediates the uptake of heme complexes such as myoglobin and hemoglobin (28, 29). Increased filtration of myoglobin and hemoglobin causes AKI by inducing tubular necrosis (95). Studies on hemoglobin-induced nephrotoxicity in rats have shown an increase in lipid peroxidation, which results in free radical production and apoptosis (65). Iron is also known to reduce ATP, ADP, and AMP inside the cell and induces ischemic shock (94). Furthermore, megalin is a receptor for the PTEC uptake of heavy metal complexes by the binding of the heavy metal carrier protein metallothionein (MT) and plays a major role cadmium-MT- and zinc-MT-induced nephrotoxicity (40). Cadmium-MT-induced nephrotoxicity can be ameliorated by inhibition of megalin function (61). Megalin has also been shown to bind and mediate light chain uptake in the proximal tubule, inducing myeloma kidney disease (5, 8, 75).

Table 1. Nephrotoxins that bind to megalin

<table>
<thead>
<tr>
<th>Nephrotoxins</th>
<th>References</th>
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<tbody>
<tr>
<td>Gentamicin</td>
<td>Moestrup et al. (55), Nagai et al (58), Schmitz et al. (73)</td>
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<tr>
<td>Aprotinin</td>
<td>Moestrup et al. (55), Nagai et al (58), Schmitz et al. (73)</td>
</tr>
<tr>
<td>Polymyxin B</td>
<td>Moestrup et al. (55), Nagai et al (58), Schmitz et al. (73)</td>
</tr>
<tr>
<td>Tobramycin</td>
<td>Tauris et al. (83)</td>
</tr>
<tr>
<td>Streptomycin</td>
<td>Tauris et al. (83)</td>
</tr>
<tr>
<td>Neomycin</td>
<td>Tauris et al. (83)</td>
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<tr>
<td>Netilmicin</td>
<td>Tauris et al. (83)</td>
</tr>
<tr>
<td>Kanamycin</td>
<td>Tauris et al. (83)</td>
</tr>
<tr>
<td>Aristocholic acid</td>
<td>Lebeau et al. (45)</td>
</tr>
<tr>
<td>Trichosanthin</td>
<td>Chan et al. (12)</td>
</tr>
<tr>
<td>Myoglobin</td>
<td>Gburek et al. (28)</td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>Gburek et al. (29)</td>
</tr>
<tr>
<td>Cadmium-metallothionein</td>
<td>Onodera et al. (61)</td>
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phism occurs in higher frequency in patients with cisplatin-induced ototoxicity (69). Although the authors suggested that megalin may be linked to the transport of cisplatin or cisplatin adducts, no direct binding of cisplatin to megalin has been demonstrated, and other mechanisms for cellular cisplatin uptake have been identified (69).

Inhibition of megalin may provide protection against drug-induced nephrotoxicity and AKI (73). Competitive inhibitors of binding, such as RAP, low-molecular-weight proteins, and peptide fragments of cytochrome c, can effectively reduce the uptake of nephrotoxic drugs by occupying megalin-binding sites (57). These proteins can be administered separately or in combination with the drug. Microinfusion of RAP along with gentamicin into rat proximal tubules blocked gentamicin uptake significantly and increased urinary excretion of gentamicin (55). In a cadmium-MT-induced AKI animal model, pre-injection of soluble RAP decreased the accumulation of cadmium-MT and reduced kidney damage (61). Similarly, a decrease in the renal accumulation of gentamicin was observed in rats treated with gentamicin along with cytochrome c (90). In recent studies using target-specific short interfering RNAs against megalin and cubilin mRNA, light chain endocytosis was blocked, ameliorating the nephrotoxic effects in human PTEC cultures (5, 48, 75).

**Megalin-mediated uptake of renoprotective proteins during AKI.** The iron-carrying protein neutrophil gelatinase-associated lipocalin (NGAL) is an established urinary and plasma marker of AKI. NGAL has been suggested to have additional renoprotective effects in AKI. In a mouse model of ischemia-reperfusion (I/R) injury, intravenously injected recombinant NGAL was rapidly taken up by PTECs, which was associated with reduced histopathological damage compared with mice injected with saline (54, 56). The amount of tubular damage was dependent on the timing of NGAL injections, i.e., before, during, or after ischemia (54). Exogenous administration of NGAL also enhances tubular cell proliferation (54, 85). This proliferative effect was most prominent in mice that underwent 30 min of ischemia and 96 h of reperfusion (85). NGAL has been shown to bind megalin (32), and the localization of filtered NGAL in late endosomes and lysosomes during I/R in mice suggests that megalin mediates uptake into PTECs (53, 56) and thus is important for the observed renoprotective effect. Other proteins that have been shown to bind to megalin, such as L-FABP, clusterin, and survivin (34, 42, 63), may also have renoprotective effects in AKI. This has been demonstrated in L-FABP-overexpressing mice exposed to ischemia, cisplatin, or aristolochic acid (51, 59, 92). In an in vitro model of AKI, clusterin was shown to be protective against gentamicin-mediated cytotoxic injury, although by an apparent megalin-independent mechanism (30). Survivin is expressed in the heart, brain, liver, lung, and kidney, where it regulates cell division and survival (2). Filtered survivin binds to megalin, mediating proximal tubule uptake (34), and is also known to be expressed in PTECs under normal physiological conditions (46). Studies using kidney-specific survivin deletion have shown that survivin increases the functional and structural recovery of PTECs after I/R injury in mice (14) and reduces tubular injury (39) in cisplatin-induced AKI. Since L-FABP and survivin are also expressed in PTECs, megalin may mediate the uptake of both filtered and locally secreted protein. So far, it is not known to what extent megalin-mediated uptake of these is important for renal protection and recovery in AKI. Furthermore, the subsequent intracellular mechanism involved in protection varies between these proteins. NGAL, an iron-transporting protein, is suggested to mediate protection either by transporting iron into viable cells after injury or by removing iron from the site of injury (72, 78). L-FABP has antioxidative properties (87) and acts as a carrier of free fatty acids. During acute ischemic injury, L-FABP directs unsaturated fatty acids, a source of peroxiradicals produced as a result of ischemia, to peroxisomes and mitochondria for lipid peroxidation or to the luminal membrane for excretion in the urine (92). Clusterin is important for cell survival, and knockdown of clusterin enhances the sensitivity of cells to apoptotic injury (96). Absence of clusterin expression is associated with increased tubular necrosis, intratubular cast formation, and reduced survival after I/R injury in mice (96).

**Megalin expression in AKI.** Changes in megalin mRNA expression have been demonstrated in different models of AKI. In LPS-induced acute endotoxemia and AKI, a decrease in renal megalin mRNA expression was observed (74). This decrease was associated with increased urinary albumin excretion. The results were confirmed in an ex vivo experiment using rat kidney slices showing decreased megalin mRNA expression after 6 h of incubation with LPS (74). In aristolochic acid nephropathy, megalin mRNA expression decreased on day 2 after aristolochic acid injection in rats (45). A similar decrease in megalin mRNA expression was observed in cultured opossum kidney cells 24 h after incubation with aristolochic acid (44). I/R-induced AKI in mice was associated with a differential response in megalin mRNA levels compared with sham-operated control mice, showing a decrease when kidneys were subjected to 30 min of ischemia and 24 h of reperfusion; however, after 96 h of reperfusion, the amount of megalin mRNA was increased compared with control mice (85).

The cellular pathways responsible for changes in megalin mRNA expression in AKI have not been clarified; however, studies have provided some insights. A decrease in megalin mRNA expression has been observed in vitro in rat PTEC cultures in the presence of TNF-α (36). Incubation of rat PTECs with TNF-α reduced megalin mRNA expression along with reduced RAP mRNA levels. RAP is required for the normal intracellular processing of megalin. Similar results were observed in an I/R model of AKI in mice in which treatment with a cytokine cocktail containing IL-1β, TNF-α, and interferon-γ after ischemia reduced megalin mRNA expression compared with both untreated I/R mice and sham-operated control mice (85). Furthermore, human plasma from burn patients with AKI reduced the expression of megalin in immortalized tubular cells in vitro compared with cells exposed to plasma from burn patients without AKI (50). Examination of the plasma from burn patients with AKI revealed a high concentration of TNF-α.

Another in vitro study using immortalized rat PTECs treated with LPS suggested that the decrease in megalin mRNA expression is mediated via the TNF-α-ERK1/2 signaling pathway (82). Treatment of rat PTEC cultures with LPS increased TNF-α and ERK1/2 expression and decreased megalin mRNA levels. The decrease in megalin was prevented by the addition of an ERK1/2 signaling blocker after LPS treatment. Based on these studies, the authors concluded that megalin is downregulated by the LPS-TNF-α-ERK1/2 signaling pathway (82).
mechanistic details and functional implications of possible TNF-α-mediated regulation of megalin expression need further investigation.

In addition to a decrease in expression, megalin protein levels may also be reduced due to shedding of megalin or loss of total apical membranes. The megalin extracellular domain has been claimed to be cleaved by intramembrane proteolysis (49), and megalin has been identified in urinary exosomes (66). The latter is believed to contain apical membrane proteins undergoing endocytosis followed by exocytosis through multivesicular bodies (84). While the role of megalin shedding by these mechanisms has not been specifically studied in AKI, observations in patients with diabetes suggest disease-dependent differences in the urinary excretion of intact and ectodomain fragments of megalin (60). Finally, megalin trafficking may be affected in AKI. Glycogen synthase kinase (GSK)-3-dependent phosphorylation of the cytoplasmic tail of megalin has been shown to negatively regulate receptor recycling to the apical membrane (93). GSK-3 is activated by cell injury and has been implicated in the cellular response to AKI (88). Thus, it is possible that increased phosphorylation of megalin may lead to decreased apical expression due to impaired recycling of megalin. In contrast to the above observations, an increase in rat cortical megalin content has also been observed on days

### Table 2. Common urinary biomarkers of acute kidney injury bound to and recovered from the ultrafiltrate by megalin

<table>
<thead>
<tr>
<th>Biomarkers</th>
<th>Molecular Weight, kDa</th>
<th>Urinary Excretion</th>
<th>Binding by Megalin in PTECs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutrophil gelatinase-associated lipocalin</td>
<td>25</td>
<td>Filtered and secreted in distal tubule</td>
<td>Hvidberg et al. (32)</td>
</tr>
<tr>
<td>Clusterin</td>
<td>70</td>
<td>Secreted by PTECs</td>
<td>Kounnas et al. (42)</td>
</tr>
<tr>
<td>α-Microglobulin</td>
<td>27–33</td>
<td>Filtered</td>
<td>Leheste et al. (47)</td>
</tr>
<tr>
<td>β2-Microglobulin</td>
<td>11.8</td>
<td>Filtered</td>
<td>Orlando et al. (62)</td>
</tr>
<tr>
<td>Cystatin C</td>
<td>13</td>
<td>Filtered</td>
<td>Kaseda et al. (38)</td>
</tr>
<tr>
<td>Liver-type fatty acid-binding protein</td>
<td>15</td>
<td>Filtered in mouse models and secreted in PTECs in humans</td>
<td>Oyama et al. (63)</td>
</tr>
<tr>
<td>Retinol-binding protein</td>
<td>21</td>
<td>Filtered</td>
<td>Christensen et al. (20)</td>
</tr>
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PTECs, proximal tubule epithelial cells.

Fig. 3. Potential roles of megalin in acute kidney injury (AKI). A: AKI caused by ischemia or toxins, which may involve megalin-mediated uptake, induces stress within the cell. B: decrease in megalin expression during the early course of AKI and/or possible loss of megalin through cleavage or shedding at the apical membrane activated by yet-unknown cellular mechanisms (?). C: subsequent or alternative megalin upregulation and uptake of cytoprotectants. D: we hypothesize that both events may have beneficial effects during the course of AKI by balancing damaging and protective cellular effects. The initial decrease in megalin expression (B) could ameliorate cell injury by reducing the uptake of nephrotoxins, cytokines, chemokines, and proapoptotic molecules. In contrast, the later increase in megalin expression (C) could promote cellular recovery and repair by increasing the cellular uptake of potential cytoprotective molecules, such as antioxidants, vitamins, and cell differentiation markers that include neutrophil gelatinase-associated lipocalin (NGAL), liver-type fatty acid-binding protein (L-FABP), and clusterin.
3 and 7 after low-dose treatment with cisplatin (5 mg/kg), which was seen to normalize on day 14 (81).

These experiments may indicate differential membrane expression of megalin during AKI (Fig. 3). Downregulation of megalin during the early course of AKI may protect PTECs by reducing the uptake of nephrotoxins (61, 95) as well as filtered or secreted cytokines, chemokines, proinflammatory mediators, and other stress proteins released during AKI (Fig. 3). Downregulation of megalin expression may also switch the usage of ATP from megalin-mediated endocytosis to the expression of housekeeping proteins and proteins important for the proliferation of PTECs and the subsequent renal recovery (78). In this context, an increase in megalin expression observed in the later phases of AKI may promote renal recovery by increasing the uptake of proteins stimulating the scavenging of oxidative radicals (85), antiapoptosis, and proliferative pathways (14, 85), thereby stimulating the regeneration of PTECs.

Megalin and markers of AKI. Several urinary proteins have been identified as early markers of AKI (26, 64). Many of these are low-molecular-weight proteins that may be filtered and/or secreted by renal tubules and excreted in urine, and several are ligands to megalin (Table 2). Thus, in the normal kidney, any such filtered biomarker would normally be reabsorbed by megalin-mediated endocytosis and catabolized by PTECs, reducing the urinary excretion to trace amounts. In AKI, some biomarkers, such as L-FABP and NGAL, are secreted by tubular cells into the urine; however, these are also present in increased amounts in the plasma during AKI (52) and thus may also be filtered. During AKI, increased urinary excretion of biomarkers may be the result of both tubular secretion and defective proximal tubule reabsorption due to megalin dysfunction (43, 86).

Conclusions

Megalin-mediated endocytosis plays an important role in the development of drug- and nephrotoxin-induced AKI. Well-established biomarkers of AKI are known ligands for megalin, and megalin function is a key regulator of the urinary excretion of these. The early increase in biomarker excretion suggests that megalin dysfunction may be an early manifestation of AKI. Differential expression of megalin during the course of AKI has been identified. Downregulation of megalin during the early course of AKI may reduce the uptake of nephrotoxins, and cytokines, thus protecting viable cells during the initial phase. In later phases of AKI, megalin expressed in viable proximal tubule cells may facilitate the uptake of filtered and/or secreted NGAL, L-FABP, clusterin, and other molecules, providing protection against continued cell damage. The importance of this functional and temporal relationship is yet to be established in vivo using experimental models of AKI; however, it suggests that modulation of megalin function should be evaluated as a new approach for the treatment of AKI.

AUTHOR CONTRIBUTIONS

Author contributions: R.M. and R.N. prepared figures; R.M. drafted manuscript; R.M., R.N., E.I.C., and H.B. edited and revised manuscript; R.M., R.N., E.I.C., and H.B. approved final version of manuscript.

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