HHS Public Access

Author manuscript

Kidney Int. Author manuscript; available in PMC 2015 November 01.

Published in final edited form as:

Kidney Int. 2015 May ; 87(5): 873–875. doi:10.1038/ki.2015.14.

NODding off AKI with Progranulin?

Raghu K. Tadagavadi and **W. Brian Reeves**

Division of Nephrology, Department of Medicine, Penn State Hershey Medical Center and College of Medicine, Hershey, PA 17033

Abstract

Inflammation is a common feature of murine models of AKI. The endogenous mechanisms which serve to limit inflammation and reduce the severity of AKI are poorly understood. Zhou et al identify progranulin as one such protective mediator. Deficiency of progranulin was associated with increased inflammation and increased injury in both ischemic and nephrotoxic models of AKI. Moreover, administration of exogenous progranulin reduced AKI even when delivered after AKI was established. Interference in NOD2 pathways is suggested as a possible mechanism for protection. PRGN-based therapeutics are under development and might have application in the treatment or prevention of AKI.

Keywords

acute kidney injury; ischemia reperfusion; nephrotoxicity; inflammation

Acute kidney injury (AKI) is a common and serious condition often initiated by ischemia and/or nephrotoxins. In addition to increasing short-term morbidity and mortality, AKI can also result in long-term complications, including chronic kidney disease and end-stage renal disease. Although diverse mechanisms have been implicated in the pathogenesis of AKI, activation of inflammatory processes is a common observation in most AKI models. Indeed, the literature is replete with reports of the beneficial effects of anti-inflammatory interventions alleviating renal dysfunction in various animal models of AKI. However, despite our growing knowledge of the role of inflammation, and potential strategies to reduce inflammation, clinicians still have few therapeutic and/or preventive options for patients with AKI. In this issue of *Kidney International*, Zhou et. al. identify a glycoprotein, progranulin (PGRN), that is expressed in the kidney and exerts protective functions in ischemic and nephrotoxic AKI (1). Furthermore, the authors provide data supporting the therapeutic potential of progranulin in mitigating renal dysfunction and tubular injury associated with AKI.

Corresponding author: W. Brian Reeves, Division of Nephrology, Room C5830, Penn State College of Medicine, 500 University Drive, Hershey, PA 17033, Tel: 717-531-8156, FAX: 717-531-6776, wreeves@psu.edu.

Disclosure:
RKT and WBR report no conflict of interest.

PGRN, also known as acrogranin, proepithelin or GP88/PC cell-derived growth factor, is a secreted glycoprotein, that can be converted by proteases to granulin (GRN) (2). PGRN and GRN can bind to a variety of intracellular and extracellular proteins, including metalloproteinases, TNF receptors, TLR9 and ER chaperones. The ability of PRGN to bind diverse proteins likely accounts for its observed role in multiple physiologic functions underlying the maintenance and regulation of normal tissue homeostasis, including regulation of inflammation, wound healing and host defense (2). PGRN was originally identified as a growth factor for cancer cells and was shown to mediate tumorigenesis in many forms of cancers. PGRN also functions as neurotropic factor, and mutations in the human gene encoding PGRN are associated with frontotemporal dementia (3). Recent work has discovered that PGRN has potent anti-inflammatory properties and ameliorates certain inflammatory disorders, such as rheumatoid arthritis.

PGRN is expressed in epithelial cells, neurons, immune cells and chondrocytes (2). Considering the abundance of PGRN in epithelial cells of other tissues, Zhou et al. examined PGRN expression in the kidney (1). High levels of PGRN transcript and protein were found in kidney, with expression largely observed within tubular epithelial cells. Since renal ischemia and nephrotoxins affect the tubular epithelium, the authors examined the pattern of PGRN expression after an ischemic insult. In response to ischemia, the expression of PGRN in the kidney decreased rapidly followed by a gradual increase several days later. Likewise, proximal tubular epithelial cells subjected to in vitro hypoxia showed a decrease in PGRN expression. Paradoxically, plasma PGRN levels increased after a renal ischemia. Although the mechanisms behind the contrasting PGRN kinetics in plasma and kidney are not known, it is possible that PGRN within epithelial cells is released into the circulation subsequent to ischemic injury. Measurements of PRGN in the supernatant of tubular epithelial cells and urine and venous effluent of ischemic kidneys might provide more insight into its fate after ischemia.

Having found high expression of PGRN in kidney, the authors examined its role in ischemic AKI. Mice deficient of PGRN showed more renal dysfunction, tubular injury and cell death compared to ischemic wild type mice. In addition, mice lacking PGRN showed extensive infiltration of neutrophils and macrophages and enhanced production of pro-inflammatory chemokines and cytokines suggesting a protective role for endogenous PGRN in ischemic AKI. Apart from ischemia, nephrotoxins are a common cause of AKI. Cisplatin is a widely used and highly effective anti-cancer drug with a major adverse effect of nephrotoxicity. Similar to their observation in ischemic AKI, mice deficient in PGRN also showed more renal dysfunction and tubular injury in response to cisplatin. These studies provide strong evidence that endogenous PGRN is protective against AKI. Further work will be required to establish the source of PRGN which exerts this effect.

A crucial part of the study examined the therapeutic potential of PGRN in AKI. First, the authors found that recombinant PGRN reduced apoptosis and cytokine production in tubular epithelial cells subjected to hypoxia in vitro. The authors next examined the preventive and therapeutic potential of PGRN in ischemic AKI. Both wild type and PGRN deficient mice were treated with PGRN and subjected to renal ischemia. Pretreatment of mice with PGRN resulted in a dramatic reduction in renal dysfunction, tubular injury, infiltration of

neutrophils and macrophages, and production of proinflammatory cytokines and chemokines. Of even more translational interest, the authors also demonstrated that administration of PRGN as long as 12 hours after ischemia still produced significant reductions in renal dysfunction and tubular injury. A comparison of kidney injury in PGRN deficient mice and in PGRN treated mice indicates that recombinant PGRN had a greater protective effect than endogenous PGRN.

Damage-associated molecular pattern (DAMP) recognition receptors, such as NOD-like receptors and Toll-like receptors, are important mediators of tissue injury in sterile inflammation of various organs, including kidneys. Recently, NOD2 was shown to mediate ischemic AKI (4). While examining the mechanism behind PGRN protection in kidney injury, Zhou et al noted an increase in NOD2 expression after ischemia and a negative correlation between PGRN and NOD2 expression, i.e. kidneys from mice deficient in PGRN had higher expression of NOD2 than wild-type mice. In renal epithelial cells, hypoxia increased NOD2 expression and this was prevented by recombinant PGRN. In addition, PGRN treatment diminished activation of NF-kB, a major mediator of proinflammatory cytokine and chemokine production and also a regulator of NOD2 expression (5). These results are consistent with negative regulation of NOD2 by PGRN and provide a possible mechanism by which PGRN attenuates kidney injury (Figure 1). To explore this pathway further, the authors assessed the effects of PGRN in NOD2 deficient mice. As shown by others (4), NOD2 deficient mice had attenuated ischemic renal dysfunction and kidney injury. PGRN administration to mice lacking NOD2 did not impact renal dysfunction and tubular injury as compared to vehicle treated NOD2 deficient mice, suggesting that PGRN mitigates ischemic kidney injury through NOD2. Studies in mice lacking both NOD2 and PGRN would provide more definitive information about the relation between these two mediators.

These observations of Zhou et al. are or particular interest in light of recent findings regarding the inhibitory actions of PGRN and Atsttrin (a synthetic fragment of PGRN) in TNF signaling (6). TNF is one of the major drivers of inflammatory diseases, including ischemic and nephrotoxic AKI. TNF acts through two receptors, TNFR1 and TNFR2. While screening for PGRN binding partners, Tang et al. found that PGRN binds to TNF receptors with high affinity and blocks TNF-TNFR interactions. Treatment of mice with PGRN or Atsttrin prevents inflammation and TNF-mediated intracellular signaling in a mouse model of arthritis (6). The possible importance of PGRN blockade of TNF signaling to the inhibition of NOD2 expression and attenuation of ischemic AKI was not addressed by Zhou et al. (1) and deserves further investigation. Studies in a variety of forms of kidney injury point to a causal relation between TNF and tissue injury. TNF is an inducer of NOD2 in epithelial cells. Therefore, it is possible that PGRN binding to TNF receptors and attenuating TNF signaling leads to a reduction in NOD2 expression and ischemic kidney injury (Figure 1). PGRN has also been shown to promote the expansion of regulatory T cells (7). Since regulatory T cells reduce both ischemic and cisplatin AKI (8), this constitutes another plausible mechanism of action for PGRN. Additional studies in mouse models deficient in PGRN, TNF, TNF receptors and/or T regulatory cells would provide more insight into the mechanism behind PGRN protection from inflammation and AKI. Nonetheless, with the development of a PGRN-derived protein, Atsttrin, which binds TNF receptors and exhibits

potent anti-inflammatory activity with less adverse effects and far greater half-life than PGRN, the findings of Zhou et al. in AKI are very significant and perhaps can be exploited for therapeutic intervention against AKI.

Acknowledgments

RKT and WBR are supported by NIH DK081876

References

1. Zhou et al reference_KI this issue
2. Jian J, Konopka J, Liu C. Insights into the role of progranulin in immunity, infection, and inflammation. J Leukocyte Biol. 2013; 93:199–208. [PubMed: 23089745]
3. Baker M, Mackenzie IR, Pickering-Brown SM, et al. Mutations in progranulin cause tau-negative frontotemporal dementia linked to chromosome 17. Nature. 2006; 442:916–9. [PubMed: 16862116]
4. Shigeoka AA, Kambo A, Mathison JC, et al. Nod1 and nod2 are expressed in human and murine renal tubular epithelial cells and participate in renal ischemia reperfusion injury. J Immunol. 2010; 184:2297–304. [PubMed: 20124104]
5. Gutierrez O, Pipaon C, Inohara N, et al. Induction of Nod2 in myelomonocytic and intestinal epithelial cells via nuclear factor-kappa B activation. J Biol Chem. 2002; 277:41701–5. [PubMed: 12194982]
6. Tang W, Lu Y, Tian QY, et al. The growth factor progranulin binds to TNF receptors and is therapeutic against inflammatory arthritis in mice. Science. 2011; 332:478–84. [PubMed: 21393509]
7. Hu Y, Xiao H, Shi T, et al. Progranulin promotes tumour necrosis factor-induced proliferation of suppressive mouse CD4+ Foxp3+ regulatory T cells. Immunology. 2014; 142:193–201. [PubMed: 24383743]
8. Jang HR, Rabb H. Immune cells in experimental acute kidney injury. Nature Reviews Nephrology. 201410.1038/nrneph.2014.180

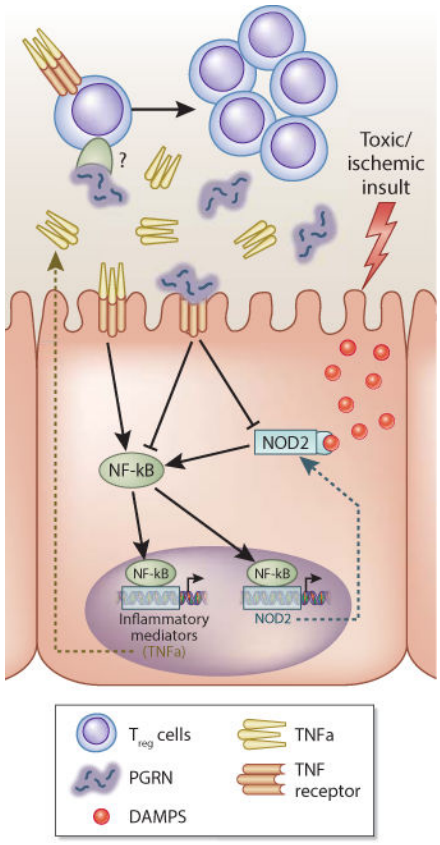

Figure 1.

A hypothetical schema of PGRN function in AKI. Toxic or ischemic insults stimulate renal epithelial cells to produce proinflammatory mediators of tissue injury including DAMPS and cytokines. The cytokines secreted by epithelial cells and infiltrated immune cells activate NF-kB signaling and incite a cascade of inflammation characterized by the production of further cytokines and chemokines and upregulation of NOD2, a DAMP recognition receptor. TNF produced during kidney injury binds to TNF receptors and activates NF-kB signaling. PGRN can bind to TNF receptor and inhibit TNF signaling. PGRN is constitutively expressed by renal epithelial cells and also found abundantly in serum. In AKI, PGRN protects kidneys from renal tubular injury and attenuates production of inflammatory cytokines and chemokines and infiltration of leukocytes, possibly by inhibiting TNF receptor-mediated NF-kB activation and NOD2 induction. In addition, PGRN may cause activation and proliferation of T regulatory cells with subsequent protection from AKI.