Beware the low HDAC11: males at risk for ischemic kidney injury

Michal Mrug and Paul W. Sanders

Division of Nephrology, Department of Medicine, Nephrology Research and Training Center, Center for Free Radical Biology, Center for Aging, and Department of Cell, Developmental and Integrative Biology, University of Alabama, Birmingham, Alabama and Department of Veterans Affairs Medical Center, Birmingham, Alabama

PLASMINOGEN ACTIVATOR INHIBITOR type 1 (PAI-1) is a member of the serine protease inhibitor (serpin) family. As such, it is well known as a physiological inhibitor of fibrinolysis, but PAI-1 also plays a key role in inflammation and production of extracellular matrix proteins (reviewed in Ref. 1). PAI-1 is implicated in the pathology of fibrosis in the heart, lung, kidney, liver, and skin. In pathologic states, excessive PAI-1 contributes to accumulation of collagen and other extracellular matrix proteins, while lack of PAI-1 protects from fibrosis in response to injury-related profibrotic signals. Involvement of PAI-1 has been implicated in disease states that include insulin resistance, diabetes, cardiovascular disease, kidney fibrosis in unilateral ureteral obstruction, and aldosterone-induced glomerular injury.

Regulation of PAI-1 levels is complicated and occurs through transcriptional, posttranscriptional, and posttranslational mechanisms (reviewed in Ref. 1). Multiple cytokines and growth factors, including transforming growth factor (TGF)-β, epidermal growth factor, and insulin, and endotoxin and oxidative stress impact local PAI-1 production through these mechanisms. Thus PAI-1 may have a role in outcomes in chronic kidney disease and especially acute kidney injury.

In an issue of the American Journal of Physiology-Renal Physiol, Kim et al. (4) examined the effect of both PAI-1 expression and gender in outcome of kidney ischemia/reperfusion (I/R)-induced injury in mice. Male gender and male hormone testosterone increase susceptibility to renal I/R injury (5); mechanisms that underlie these effects were elucidated by Kim et al. (4). They noticed an unimpressive increase in renal PAI-1-encoding gene (Serpine1) expression in females with or without ovariectomy 24 h after a 30-min I/R injury. In contrast, PAI-1-encoding gene expression in orchietomized males was also low, but administration of dihydrotestosterone (DHT) triggered an increase to levels comparable to those seen in males without orchietomy. Because I/R injury represents a well-established model of gender dimorphism in acute kidney injury (AKI) outcomes and since pharmacological PAI-1 inhibition attenuated adverse renal I/R effects, the authors then examined the gender-specific mechanisms regulating PAI-1 expression in this model. They observed that renal expression of several histone deacetylase (HDAC)-encoding genes (i.e., Hdac1, 5, 8, 9, and 11) decreased following 30 min of renal I/R injury. However, decreased expression of Hdac9 and Hdac11 did not occur in orchietomized males exposed to kidney I/R injury. In addition, among the five studied HDAC isotypes, only HDAC11 inhibited PAI-1 expression (using an activated monocyte/macrophage cell line and treatment with HDAC11 small interfering RNA). Based on chromatin immunoprecipitation assay, this inhibition was mediated by direct HDAC11 interaction with the PAI-1 gene (Serpine1) promoter. The I/R-induced release of HDAC11 from PAI-1 promoter then led to increased histone H3 acetylation. This effect was observed only in males without orchietomy but not in orchietomized males or intact or ovariectomized females. This observation, coupled with the fact that DHT reversed the effect of orchietomy on I/R-induced decreased HDAC11 expression, pointed to a testosterone-HDAC11-PAI-1 axis as a likely pathway regulating gender-induced differences in I/R-induced renal injury (Fig. 1).

Gender is an important regulator of susceptibility to AKI in a wide range of renal insults (reviewed in Ref. 3). These gender-induced differences have been attributed to biological effects of male and female sex hormones. While some of these differences may be explained by testosterone-enhanced susceptibility to endoplasmic reticulum stress (2), additional specific mechanisms underlying the sex hormone effects in AKI have remained elusive. The current study by Kim et al. (4) points to testosterone-induced HDAC11-regulated histone H3 acetylation as a key mechanism responsible for gender-related susceptibility to AKI.

This new concept offers a novel avenue for development of gender-based therapeutic strategies, an important component of emerging personalized medical care (7). While such strategies hold potential for reducing adverse outcomes in clinical care (e.g., in males with high risk of AKI), first it is necessary to confirm that the above concept is not murine specific but can

![Fig. 1. Schema of the effects of testosterone on plasminogen activator inhibitor type 1 (PAI-1)-enhanced renal injury. Testosterone increases severity of kidney ischemia/reperfusion (I/R)-induced renal injury in mice by inhibiting histone deacetylase 11 (HDAC11). Lack of HDAC11 activity in promoter region of PAI-1-encoding gene Serpine1 leads to increased H3 histone acetylation and expression of PAI-1. Increased PAI-1 enhances the I/R-induced renal injury.](http://www.ajprenal.org)
be also applied to humans and other mammals (e.g., unlike the outcome of the current study on mice, testosterone protected kidneys from I/R-induced AKI in rats; Ref. 6). In addition, the findings in the paper also raise questions of potentially unpredictable adverse effect of non-selective HDAC inhibitors in AKI. Unfortunately, specific HDAC11 activity-enhancing therapeutics have not been described; their development may hasten potential translation of this discovery to clinical care.

GRANTS

Supported was provided in part by the National Institutes of Health-funded University of Alabama at Birmingham (UAB) Hepato/Renal Fibrocystic Disease Core Center P30-DK-074038 and R01 DK097423 (to M. Mrug) and UAB-University of California San Diego O’Brien Center 1P30-DK-079337 (to M. Mrug and P. W. Sanders) and R01-DK-064199 (to P. W. Sanders) and 5-R01-BX001192 (to P. W. Sanders) and 1-IP1-BX001595 (to P. W. Sanders) from the Office of Research and Development, Medical Research Service, Department of Veterans Affairs.

AUTHOR CONTRIBUTIONS

Author contributions: M.M. prepared figure; M.M. drafted manuscript; M.M. and P.W.S. edited and revised manuscript; M.M. and P.W.S. approved final version of manuscript.

DISCLOSURES

M. Mrug is a consultant to Otsuka Corporation and Alexion Pharmaceuticals.

REFERENCES