The Proximal Tubule in Cystinosis: Fight or Flight?

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Although rare, nephropathic cystinosis is a devastating mono-
genic disorder leading to renal failure in the second decade of
life. Fanconi syndrome, the initial renal manifestation of
cystinosis in the young child, established the proximal tubule
as a primary target of injury now recognized as the result of
mutations in cystinosin (CTNS), the lysosomal cystine-proton
cotransporter. A major challenge in understanding the path-
ophysiology of cystinosis remains: what is the link between
lysosomal cystine accumulation and proximal tubular dysfunc-
tion? Most of the data generated to date are based on in vitro
studies of proximal tubular cells incubated with cystine di-
methyl ester or of cells from cystinotic patients. These have
resulted in the formulation of three major hypotheses regard-
ing cystine-induced injury of proximal tubular cells: altered
ATP metabolism, altered glutathione metabolism, and apopto-
tic cell death. Mitochondria in cystinotic proximal tubules are
abnormal, and cells contain decreased ATP and glutathione
and undergo increased apoptosis. The interpretation of ATP
metabolism in cell culture studies is hampered by the stimu-
lation of glycolytic activity in vitro, whereas ATP is derived
from mitochondrial oxidative phosphorylation in vivo.

Progress has been accelerated by the recent availability of an
animal model with a renal phenotype similar to human nep-
thropathic cystinosis. The C56BL/6 Ctns−/− mouse exhibits most
of the features of the human disease, including the formation of
the “swan-neck deformity,” a marked progressive narrowing of
the proximal tubule beginning at the glomerulotubular junction. Two
papers in this issue of JASN have elucidated cellular mech-
анизms underlying the proximal tubular injury in the Ctns−/−
mouse. Using a combination of techniques, including light,
multiphoton, and electron microscopy, as well as functional
docytosis assays, Chevonnay et al. demonstrate the evolu-
tion of lysosomal inclusions in proximal tubular cells leading to
apical dedifferentiation, characterized by the loss in the S1
segment of expression of megalin, cubulin, and other trans-
porters. This is accompanied by cellular adaptation, including
expulsion of cystine crystals and tubular remodeling by down-
stream proximal tubular segments.

Using in vitro studies of human peripheral blood mononu-
clear cells exposed to cystine crystals, as well as in vivo studies of
the Ctns−/− mouse model, Prencipe et al. conclude that cy-
tine crystals activate inflammasomes, most likely in proximal
tubular cells, resulting in the release of IL-1β and IL-18. This,
in turn, may contribute to the interstitial inflammation and
fibrosis present in terminal phases of the human and murine
Ctns mutants. The relative contribution of crystal-induced
inflammasomes to cystinotic tubular injury remains to be
determined, however. It is estimated that only 1% of intra-
cellular cystine crystals are retained, due to lysosomal dis-
charge of the crystals linked to endocytic recycling.

The swan neck, a morphologic hallmark of cystinosis, can
be viewed as a degenerative process that leaves a nonfunc-
tional proximal tubular “atrophic” segment. However, the
development of extremely thin cells lining thickened tubular
basement membrane may instead represent an adaptation to
mitochondrial injury resulting from defective intracellular
cystine processing. The proximal tubules comprise the bulk of
renal mass and consume the majority of energy in reabsorption
of glomerular filtrate. This tubular segment is particularly sus-
ceptible to oxidative injury resulting from a variety of stimuli,
ranging from metabolic toxins (cystine accumulation) to ische-
ic or obstructive processes. Such oxidative injury is compoun-
ded by the generation of reactive oxidant species by damaged
mitochondria. Compared with the distal nephron, which has
robust endogenous antioxidant defenses, the proximal tubule is
more vulnerable to oxidative injury. Thus, thinning of proximal
tubular cells and thickening of tubular basement membrane
can be viewed as an adaptive response: the machinery
for cystine uptake has been eliminated by the tubular segment
first exposed to cystine-rich glomerular filtrate. In this regard,
megalin activity has been shown to contribute to early injury
of proximal tubular cells in a model of nonselective proteinuria:
loss of megalin is protective. Moreover, by markedly decreasing
mitochondrial content, formation of the swan neck in Ctns−/−
mice reduces energy consumption and provides a structurally
sound conduit to transport filtrate to functioning tubular cells
downstream. This is, of course, only a temporizing measure—
the transfer of function by the S1 segment of the proximal
tubule to the S3 segment demonstrated by Chevonnay et al.3
eventually fails to maintain nephron function, and proximal
tubular cell death ensues, with the eventual formation of
atubular glomeruli. What begins as an effective short-term
adaptation ultimately becomes maladaptive.

A useful paradigm to explain adaptations to injurious
stimuli was drafted by Goligorsky, who applied Cannon’s
“fight or flight” response to tissues and individual cells.9 The fate of a cell therefore depends on a balance between survival and death signals and is dictated by evolutionarily conserved pathways, with multiple regulatory checkpoints (fail-safes) to protect against inappropriate responses. This is illustrated by the demonstration that cystine crystal–induced IL-1β secretion requires a combination of caspase-1 activation, actin polymerization, lysosomal protease activity, potassium efflux, and the generation of reactive oxygen species.4

The remarkable plasticity of the proximal tubule manifested in cystinosis, with dramatic phenotypic and functional changes depending on nephron segment, is also demonstrated in AKI. In an ingenious experiment, Grgic et al. selectively induced acute diphtheria toxin–induced epithelial injury to the S1 and S2 tubular segments of noncystinotic mice.10 This acute toxic injury results in successful repair and remodeling of the proximal tubule. However, repeated injury leads to maladaptive repair with interstitial fibrosis and glomerulosclerosis.10 Because tubular basement membrane is preserved along the swan-neck segment, flattened epithelial cells may respond to therapies by remodeling and re-establishment of a functional S1 segment in the cystinotic nephron. The most commonly used animal model of CKD, unilateral ureteral obstruction, leads to massive proximal tubular cell death and the ultimate formation of atubular glomeruli.11,12 Reduction of proximal tubular mass reduces energy consumption, while remodeling of the Bowman capsule by sealing the urinary pole allows ongoing renin production by the juxtaglomerular apparatus.11 These responses may also be viewed in the context of the fight-or-flight paradigm.13 Release of obstruction can arrest the process, but this does not reverse established damage and nephron loss, possibly because of disrupted tubular basement membrane.14

Although a rare disorder, nephropathic cystinosis may provide unique opportunities to understand the mechanisms of response to metabolic tubular injury. The development of an animal model of cystinosis that parallels many of the characteristics of human disease has opened new avenues of investigation. In particular, this model affords an opportunity to study the evolution of the disease from birth to senescence. Progression of the tubular lesions in the Ctns−/− mouse is characterized by marked internephron heterogeneity in the rate of extension of the swan-neck lesion.3 Great variability in the progression of nephron injury is reported for many types of renal disease, including polycystic kidney disease and obstructive nephropathy.13 It is notable that these disorders (as well as many vascular, glomerular, and tubulointerstitial diseases) ultimately result in the formation of atubular glomeruli.15 Rather than representing a mechanism of progressive renal disease, however, the formation of atubular glomeruli probably reflects decreasing proximal tubular mass, the hallmark of renal contraction in CKD. As in cystinosis, the development of significant interstitial fibrosis is also a late event in most renal disorders. In considering new therapies to preserve functional renal mass, it may be time to shift our attention from the glomerulus and the interstitium to the proximal tubule.

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DISCLOSURES

None.

REFERENCES
