The Benefits of Tubular Proteinuria: An Evolutionary Perspective

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Constituting more than one half of renal mass, the proximal tubule is the main reabsorptive segment of the nephron. Proximal tubular cells (PTCs) take up almost all macromolecules filtered by the neighboring glomerulus, making use of a dense brush border and a dedicated endocytic apparatus. The energy to achieve this tremendous task is provided by a high number of mitochondria that mainly use fatty acids as metabolic fuels. The high energy demand makes PTCs very vulnerable to ischemia, metabolic dysfunction, or external toxins, such as drugs. In nephrotic syndrome or diabetic nephropathy, glomerular proteinuria imposes a large burden on the PTC (Figure 1), with the result that PTC damage becomes a main driver of disease progression. In addition to the protein overload, PTCs are also damaged by the molecules brought inside by the proteins, such as fatty acids or advanced glycation end products.

As early as in 1982, Moorhead et al. proposed the hypothesis that lipid abnormalities contribute to the progression of kidney injury. Summarized under the term “lipotoxicity,” fatty acids, particularly those with saturated acyl chains, were since then repeatedly reported to damage the PTCs and their organelles. The most efficient carrier of fatty acids is albumin, which possesses about seven binding sites for fatty acids. The study of rare genetic diseases and animal models have suggested that albumin not only is best answered from the human genetic perspective. LRP2, CUBN, and AMN are all genes with mutations that cause low molecular weight proteinuria and albuminuria in humans. LRP2 mutations lead to Donnai–Barrow syndrome (Online Mendelian Inheritance in Man: 222448), a multisystem developmental disorder causing facial dysmorphism, vision, and hearing problems among other symptoms. CUBN and AMN, however, are both causative genes for Iverslund–Gräsbeck syndrome (IGS; Online Mendelian Inheritance in Man: 261100). This disease is a rare autosomal recessive disorder initially described in Scandinavia that is characterized by a selective vitamin B(12) malabsorption, resulting in megaloblastic anemia, which is responsive to parenteral vitamin B(12) therapy (additional reading is in refs. 3 and 4). The phenotypic differences between Donnai–Barrow syndrome and IGS are explained by the fact that megalin can act independently of the other two proteins and has a broader tissue expression pattern. By contrast, cubilin and amnionless need each other for surface transport and function, and they are mainly expressed in the kidney and the small intestine.

Genome-wide association studies have linked a variant in the CUBN gene with an increased risk for albuminuria. Moreover, Ovunc et al. identified two siblings in a consanguineous family with isolated proteinuria caused by a homozygous deletion of one base pair in exon 53 of the CUBN gene. The amount of proteinuria in these
patients was variable, ranging from complete absence to 2 g/24 h. Similar patients with CUBN mutations have also been identified in our molecular diagnostic unit (C. Antignac, personal communication). What is important to point out is that neither the patients with IGS nor the patients with isolated proteinuria seem to show signs of renal failure, let alone to progress to ESRD. Although more patient follow-ups are needed, this would suggest that human kidneys continue to function, despite significant urinary protein loss.

With the advent of large reference genome databases (ExAC and gnomAD), it has been possible not only to improve the interpretations of specific candidate variants but also, determine allele frequencies in the normal population over the entire coding region of a gene of interest. Here, the following rule of thumb can be applied: the more essential that a gene is for survival, the fewer damaging variants (frameshift, stop gain, or essential splicing) can be found for this gene, even in the heterozygous state. Intolerance to functional variation can be quantified with the probability of being loss-of-function intolerant (pLI) metric. Low pLI scores are typically seen for redundant genes, genes that are not required for survival or reproduction, or genes with variants that may confer some selective advantage. Despite being disease genes, CUBN and AMN (but not LRP2) have very low pLI scores, suggesting that damaging variants are tolerated in these two genes in humans.

The mutation c.208–2A>G in intron 3 of AMN deserves particular attention. This mutation accounts for over 50% of the patients with IGS outside Scandinavia. It is found among diverse ethnicities and cultures, even Muslim and Jewish families. Studying the flanking sequences, it was possible to backdate the founder event to around 11,600 BC in the northern Mesopotamia region. There is only one human mutation that is thought to be older, and this is the Delta F508 CFTR mutation. This mutation is the most common cause of cystic fibrosis, and it is primarily found in European and European-derived populations.

With mutations as old as the pre-Neolithic era, one is, of course, invited to ponder over any selective advantages for the heterozygous carriers. Applying Darwinian logic to the origin of a human genetic disease that persists, we have to consider both genetic adaptations to an ancient environment and the more recent benefits of these disease alleles, despite their negative effects. The high frequency of the Delta F508 CFTR mutation has been hypothesized to arise from selective pressures generated by cholera outbreaks or the transmission of diarrhea-causing agents from domesticated animals, such as bovine, to humans. Also, the lactase polymorphism arose >5000 years ago as a consequence of domestication and spread rapidly due to strong positive selection. Although the CFTR mutation may limit fluid

Figure 1. The role of proximal tubular reabsorption in normal and proteinuric conditions. On the left, normal filtration and reabsorption of proteins, protein-bound lipids and toxins (such as drugs) is depicted. Protein and lipid catabolism in lysosomes and mitochondria is important to meet energy demands of PTC. In glomerular diseases, such as nephrotic syndrome or diabetic nephropathy (DN), PTC are exposed to protein, lipid and toxin overload (middle). Particularly, saturated fatty acids bound to albumin are known to cause cell damage through endoplasmic reticulum stress. Damage may be prevented by reducing PTC uptake, e.g. in patients with CUBN/AMN mutations (right).
secretion in diarrhea, the lactase polymorphism is suggested to allow for lifelong lactose digestion.

What might be the selective advantage of the AMN founder mutation? Recently, the suppression of PTC uptake by targeting LRP2 has been shown to be protective against kidney damage caused by nephrotoxic therapeutics, hemo- and myoglobin, and high-fat diet. Interestingly, in most mouse models, LRP2 inactivation was either incomplete or mosaic, implying that, also for humans, the renoprotective effect may be achieved by the loss of only one allele. Moreover, the CUBN gene has been shown to be expressed in a monoallelic fashion in the mouse kidney, which could be another evolutionary trick to maximize the effect in CUBN heterozygotes.

Proving this hypothesis will not only require more vigorous phenotyping in animal models with CUBN or AMN deficiency but also, thinking about nephrotoxic agents present in prehistoric times. One thing, however, is possibly already safe to conclude from these evolutionary lessons: identifying drugs that downregulate PTC receptor complex activity might be a good strategy for renal diseases with PTC damage.

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DISCLOSURES

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REFERENCES