Transgenic Mouse Model Expressing C217G Uromodulin

Transgenic mouse model expressing a human uromodulin mutant mimicking hereditary human mutant uromodulin caused kidney diseases for testing diagnostics and therapy.

Background

Of all the proteins present in the healthy human urine, Tamm-Horsfall protein (THP), also known as uromodulin, is by far the most abundant, with a daily urinary excretion rate of up to 100 milligrams. The highly restricted expression of THP in the thick ascending limb (TAL) of the loop of Henle and the tendency of THP to self-aggregate and form a gel prompted earlier investigators to hypothesize that the protein contributes to the water impermeability of TAL. Among other proposed functions for THP are modulation of urinary mineral crystallization, defense against bacterial infection, immune suppression, promotion of renal cast formation and stimulation of interstitial inflammation. However, few of these proposed functions or disease roles were proven experimentally or clinically until relatively recently.

It has now been fairly well established that THP/uromodulin-associated diseases (UAKD) belong to endoplasmic reticulum (ER)-storage diseases. Like other proteins in this family, mutations of THP cause the protein to mis-fold and aggregate precociously, reducing its ability to exit the ER and translocate to the cell surface. The mutated THP can also exert cytotoxic effects on the TAL cells and adversely affect the biosynthesis and functions of the host cell proteins. Preliminary evidence, based on clinical observations and expression of THP mutants in various cultured cells, suggests that the deleterious effects of THP mutations could be site-dependent, i.e., some mutations might cause more severe phenotypic alterations than others. Of particular interest are the mutations within the so-called “domain of 8 cysteines” (D8C). D8C contains a stretch of 130 amino acid residues in THP and is highly homologous to the same domain present in liver-specific zona pellucida protein (LZP), pancreas-specific glycoprotein 2 (GP-2) and several uncharacterized proteins. The 8 highly conserved cysteines are predicted to form 4 pairs of disulfide bridges that are believed to be crucial for maintaining the correct conformational structures of the proteins. Experimental verification to this prediction remains scare.

When we previously compared a cysteine-altering mutation outside D8C (C126R) of THP with another inside it (C217G) in MDCK cells, we observed significantly greater deleterious effects of the latter in terms of ER-retention, reduced apical surface translocation, reduced release into culture media, apoptosis induction and entrapment of co-expressed wild-type THP. Nonetheless, one could still argue that the phenotype could vary in intact animals as compared to cell-culture systems. While two THP-mutant-expressing transgenic mouse models have already been developed, both involved mutations outside the D8C. Additionally, analyses of the existing models have primarily focused on relatively young animals (up to 24 weeks or 6 months of age) and, as a result, the progressive nature, one of the hallmarks of UAKD, has not been adequately recapitulated in mice. Finally, whether and precisely how THP mutations lead to hyperuricemia in transgenic models have not been assessed, probably due to the assumption

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Authors

Xue-Ru Wu, MD

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that mice naturally make uricase, a uric acid degrading enzyme, and therefore that it would not be meaningful to measure uric acid in rodents. The present study was therefore carried out to address some of these major issues and to gain a deeper understanding of the pathophysiology underlying UAKD. Additionally, human-relevant uromodulin mutant mouse models should be instrumental in evaluating novel diagnostic and therapeutic strategies.

References

1. Ma L, Liu Y, Landry NK, El-Achkar TM, Lieske JC, Wu XR.(2017 Nov 16) , https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0186769, PLoS One, 12(11)