A Novel Uromodulin Mutation C112Y Causing Familial Juvenile Hyperuricemic Nephropathy (FJHN) : Hsp70 Rescued the Cellular Apoptosis due to Its Protein Instability

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Familial juvenile hyperuricemic nephropathy (FJHN) is autosomal dominant disorder caused by uromodulin mutation. Uromodulin is expressed on kidney tubular epithelial cell and is abundant in urine, but its role is unclear. We reported a patient with a novel UMOD mutation C112Y, with a family history of gout and renal failure. To study effects of the mutation on the protein stability and cellular apoptosis, and effects of Hsp70 overexpression and Hsp70 inducer (GGA), we expressed WT and C112Y in HEK293 cells. The levels of cytosolic and secreted C112Y were lower than WT. The level of ubiquitination was higher in C112Y than in

the WT. The C112Y half-life was shortened and was restored by proteasome inhibitor MG132. The C112Y induced cellular apoptosis as examined by annexin V staining and flow cytometry. C112Y co-immunoprecipitated with Hsp70. Hsp70 overexpression or GGA treatment stabilized the mutant protein, normalized the levels of apoptotic proteins and suppressed apoptosis. Hsp70 and GGA also stabilized the secretion-incompetent mutant (C217G). These findings showed that C112Y instability caused cellular apoptosis and that Hsp70 induction might be a therapeutic value for FJHN.

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