Topiroxostat improved the apoptosis of cells expressing Uromodulin Mutation C112Y Causing Familial Juvenile Hyperuricemic Nephropathy (FJHN)


Familial juvenile hyperuricemic nephropathy (FJHN) is an autosomal dominant disorder caused by mutations in UMOD characterized by hyperuricemia and renal failure. UMOD encodes uromodulin, which is expressed on tubular epithelial cells in the loop of Henle and is excreted in urine. Although uric acid lowering agents control their serum uric acid level, they could not impair their renal function. We previously reported a patient who carried a novel UMOD mutation G335A (C112Y) in cases of FJHN and found that cellular apoptosis was prominent in HEK293 cells expressing C112Y. In the present report, we studied the effects of a new xanthine oxidase inhibitor, topiroxostat, on the cellular apoptosis in cells expressing C112Y. We expressed the mutant uromodulin in HEK293 and MDCK cells. The levels of both cytosolic and secreted C112Y protein were significantly decreased compared with the WT, whereas the level of ubiquitination was higher in C112Y than that in the WT. The expression of C112Y induced cellular apoptosis as examined by annexin V staining and flow cytometry. Pro-apoptotic proteins such as p53, Bax and cytochrome c were significantly increased while the anti-apoptotic proteins were significantly decreased in HEK293 cells expressing C112Y. Topiroxostat at 30 μM normalized pro- and anti-apoptotic proteins and significantly decreased their cellular apoptosis. These findings indicated that instability of C112Y leads to cellular apoptosis and that xanthine oxidase inhibitor might be of a therapeutic value for treatment of FJHN.

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