Letters to the Editor

Therapeutic Possibility of Ascofuranone for Autosomal Dominant Polycystic Kidney Disease – Response

Ji-Hak Jeong, Junji Magae, and Young-Chae Chang

ADPKD1 is mainly associated with mutations in the PKD1 gene encoding PC-1. PKD1 overexpression leads to increased expression of c-Myc and failed upregulation of p21WAF1/CIP1, resulting in abnormal increase of RTE proliferation. c-Myc is reported as a major downstream effector of PKD1 signaling pathways and as a transcriptional repressor of p21WAF1/CIP1. Because there is no effective treatment available for PKD, it is reasonable that downstream target genes of PKD, including c-Myc and p21WAF1/CIP1, are considered as therapeutic targets for autosomal dominant polycystic kidney disease (ADPKD). In this regard, roscovintine is a salutary agent that has antiproliferative effects by increasing p21WAF1/CIP1 in RTE. Rapamycin, a mTOR inhibitor, prevents cyst formation, and thus is also considered an effective agent against ADPKD.

In our experience and that of our collaborative groups, ascofuranone has antitumor activities and various physiologic effects without inducing DNA damage in vivo and in vitro, similar with roscovintine, and it is a more safe and useful agent than other prenyl-phenol compounds, such as aschocrin and derivatives, in animal studies. Ascofuranone activates p53 through phosphorylation of serine 392, involved in mitochondrial respiration, and ascofuranone activates p53 through phosphorylation such as ascochlorin and derivatives, in animal studies.

Ascofuranone is associated with the p53-independent and downstream kinase pathways, such as the Ras/Raf/ERK pathway. On the basis of our results, ascofuranone has appropriate properties that could be developed as a therapeutic tool for ADPKD as follows. First, ascofuranone induces cytostatic G1 arrest without DNA damage. Second, ascofuranone not only upregulates p21WAF1/CIP1 but also suppresses c-Myc, both proteins being therapeutic targets for ADPKD. Finally, ascofuranone inhibits the phosphorylation of ADPKD-related kinases including EGFR and ERK. Further study on the pharmacologic action of ascofuranone might provide a new therapeutic tool for ADPKD.

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