We read with interest the article by Jeong et al. (1) showing how ascofuranone induces G1 arrest through a p53-independent activation of p21WAF1/CIP1 due to the disruption of c-Myc in human cancer cell lines. Interestingly, defects in cell cycle arrest occur in autosomal dominant polycystic kidney disease (ADPKD) and are correlated with polycystin-1 (PC-1) malfunctioning and with secondary failure to upregulate p21 in renal and biliary epithelial cells (2), in addition to increased expression of c-Myc. Renal and liver cysts are key features of ADPKD, in which they develop through a cellular recessive mechanism involving loss-of-heterozygosity and somatic mutations (3), as in the case of onco-suppressor gene–related cancers. Recently, it has been shown how p21 is decreased in cysts of ADPKD patients, in which p21 levels are inversely correlated with renal tubular epithelial cell proliferation (4). A high PKD1 mutation rate has been considered to explain the number of cysts observed in ADPKD. Furthermore, lowering the PKD1 expression is sufficient to cause polycystic disease, leading to the hypothesis that, in patients heterozygous for PKD1 (ADPKD patients), reduction of the normal allele products below a critical level, due to genetic, environmental, and stochastic factors, can determine the formation of cysts and other ADPKD manifestations (5). As PC-1 upregulates p21 levels, the latter can vary following the genetic and/or acquired PC-1 modifications. The p21 impairment observed in ADPKD can be considered even pivotal in determining the loss of heterozygosity, as the premature transition from G1 phase to S phase and the increased proliferation of the epithelial cells could enhance the probability of second mutations. A cyclin-dependent kinase inhibitor, roscovitine, has been already shown to arrest progression in a murine model of ADPKD, to increase p21 levels, and to decrease renal tubular epithelial cell proliferation, with no effect on apoptosis (4). Therapies acting on pivotal molecules of the early phase of ADPKD pathogenesis could not only slow the growth of the formed cysts but also prevent the development of new cysts, reducing the probability of somatic mutations acting on cell cycle and proliferation, as conceived for the cyclin-dependent kinase inhibitor roscovitine (4) or the mTOR inhibitor rapamycin. Another therapeutic with these features is ascofuranone; recent discovery shows that it induces G1 arrest through p21WAF1/CIP1 activation and c-Myc disruption (1). The recent findings by Jeong et al. lead us to consider the possibility to evaluate ascofuranone as a therapeutic tool for ADPKD.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

References

4. Park JY, Schulzer WE, Lindsay JN, et al. p21 is decreased in polycystic kidney disease and leads to increased epithelial cell cycle progression: roscovitine augments p21 levels. BMC Nephrol 2007;8:12.
Ascofuranone: A Possible Therapeutic Tool for Autosomal Dominant Polycystic Kidney Disease? – Letter

Vincenzo Cardinale and Domenico Alvaro

Mol Cancer Ther  Published OnlineFirst October 26, 2010.