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Urolithin A targets the AKT/WNK1 axis to induce autophagy and exert anti-tumor effects in cholangiocarcinoma

Abstract:

Urolithin A (UA; 3,8-dihydroxybenzo[c]chromen-6-one) is gut microbiota-derived metabolites of the natural polyphenol ellagic acid. Since UA is known to undergo enterohepatic recirculation, we hypothesized that UA might have significant antitumor effects in Cholangiocarcinoma (CCA) which grows in a special environment constantly exposed to both blood and bile. Here, we investigated the therapeutic potential of UA in CCA and aimed to elucidate its mechanisms, including autophagy. UA treatment inhibited cell proliferation and induced G2/M phase cell cycle arrest in CCA cells. UA also suppressed cell migration and invasion, but did not cause apoptosis. Furthermore, Western blotting and immunocytochemistry demonstrated increased LC3-II accumulation, suggesting that UA upregulated autophagy in CCA cells. In xenograft mice treated with UA, tumor growth was inhibited with increased LC3-II levels. On the other hand, phospho-kinase array demonstrated downregulation of the AKT/WNK1 pathway. LC3-II expression was elevated in WNK1 knocked down cells, indicating that WNK1 is the key signal for regulating autophagy. In conclusion, UA, a natural, well-tolerated compound, may be a promising therapeutic candidate for advanced CCA.