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Drug development of autophagy-essential protease ATG4 for cancer therapy

Chih-Wen Shu
Kaohsiung Veterans General Hospital, Taiwan

Tumor cells require proficient autophagy for high metabolic demand, rapid proliferation and resistance to chemotherapy, suggesting reducing aberrant autophagic flux is an attractive route for cancer therapy. ATG4 is an essential protease required for autophagy and cell proliferation in tumor cells, which implies ATG4 is a potential therapeutic target for cancer therapy. Here, we report that a FDA-approved drug Tioconazole blocks active site of ATG4 to decrease ATG4 proteolytic activity and attenuate autophagic flux. The inhibition of the drug on ATG4 and autophagy causes tumor suppression and enhances chemotherapy efficacy. Besides, biological inhibitors against ATG4, including compound extracted from medical plant, rational designed peptide and antisense oligonucleotide, show selective inhibition on proteolytic activity of ATG4 and tumor cell suppression. Our results indicate that targeting ATG4 could be a promising treatment for cancer therapy.

cwshu@vghks.gov.tw
vcwshu@gmail.com