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Corylifol A ameliorates muscle atrophy by inhibiting TAOK1/p38-MAPK/FoxO3 pathway in cancer cachexia

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Abstract

Background Corylifol A (CYA) is one of the main active components of *Psoralea corylifolia* L. CYA had been reported to have ameliorating effects on dexamethasone-induced atrophy of C2C12 mouse skeletal myotubes, but its effects on cancer cachexia were unclear. Here, we checked the influence of CYA on muscle atrophy in cancer cachexia mice and tried to clarify its mechanisms.

Methods C26 tumour-bearing mice were applied as the animal model to examine the effects of CYA in attenuating cachexia symptoms. The in vitro cell models of TNF-α-induced C2C12 myotubes or ad-mRFP-GFP-LC3B-transfected C2C12 myotubes were used to check the influence of CYA on myotube atrophy based on both ubiquitin proteasome system (UPS) and autophagy-lysosome system. The possible direct targets of CYA were searched using the biotin-streptavidin pull-down assay and then confirmed using the Microscale thermophoresis binding assay. The levels of related signal proteins in both in vitro and in vivo experiments were examined using western blotting and immunocytochemical assay.

Results The administration of CYA prevented body weight loss and muscle wasting in C26 tumour-bearing mice without affecting tumour growth. At the end of the experiment, the body weight of mice treated with 30 mg/kg of CYA (23.59 ± 0.94 g) was significantly higher than that of the C26 model group (21.66 ± 0.56 g) with $P < 0.05$. The values of gastrocnemius muscle weight/body weight of mice treated with 15 or 30 mg/kg CYA (0.53 ± 0.02% and 0.54 ± 0.01%, respectively) were both significantly higher than that of the C26 model group (0.45 ± 0.01%) with $P < 0.01$. CYA decreased both UPS-mediated protein degradation and autophagy in muscle tissues of C26 tumour-bearing mice as well as in C2C12 myotubes treated with TNF-α. The thousand-and-one amino acid kinase 1 (TAOK1) was found to be the direct binding target of CYA. CYA inhibited the activation of TAOK1 and its downstream p38-MAPK pathway thus decreased the level and nuclear location of FoxO3. siRNA knockdown of TAOK1 or regulation of the p38-MAPK pathway using activator or inhibitor could affect the ameliorating effects of CYA on myotube atrophy.

Conclusions CYA ameliorates cancer cachexia muscle atrophy by decreasing both UPS degradation and autophagy. The ameliorating effects of CYA on muscle atrophy might be based on its binding with TAOK1 and inhibiting the TAOK1/p38-MAPK/FoxO3 pathway.

Keywords Autophagy; Cancer cachexia; Corylifol A; Muscle atrophy; Proteasome

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