DAF-16

DAF-16 is a transcription factor that plays a crucial role in the regulation of lifespan and stress response in the model organism Caenorhabditis elegans. DAF-16 is a member of the FOXO family of transcription factors and is regulated by the insulin/IGF-1 signaling (IIS) pathway.

In C. elegans, reduced signaling through the IIS pathway leads to the translocation of DAF-16 from the cytoplasm to the nucleus, where it binds to target genes involved in stress resistance, metabolism, and lifespan regulation. DAF-16 is essential for the extension of lifespan in response to reduced IIS pathway activity and is also involved in other physiological processes such as dauer formation and fat metabolism.

The discovery of DAF-16 has helped to shed light on the molecular mechanisms underlying the aging process and has led to the identification of potential targets for interventions that could extend healthy lifespan in humans.

Ninety C57BL/6 mice were randomized into sham-operated group, middle cerebral artery occlusion (MCAO) model group, and low-, medium and highdose (10, 20, and 40 mg/kg, respectively) FB groups. The expression levels of MDA, ROS, PCO, 8-OHdG, SOD, GSTα4, CAT and GPx in thebrain tissue of the mice were detected using commercial kits, and those of AMPK, P-AMPK,DAF-16, FOXO3 and P-FOXO3 were detected with Western blotting. Compound C (CC), an AMPK inhibitor, was used to verify the role of the AMPK pathway in mediating the therapeutic effect of FB. In another 36 C57BL/6 mice randomized into 4 sham-operated group, MCAO model group, FB (40 mg/kg) treatment group, FB+CC (10 mg/kg) treatment group, TTC staining was used to examine the volume of cerebral infarcts, and the levels of ROS and SOD in the brain were detected; the changes in the protein expressions of AMPK, P-AMPK, DAF-16, FOXO3 and P-FOXO3 in the brain tissue were detected using Western blotting.

In mice with cerebral IR injury, treatment with FB significantly reduced the levels of ROS, MDA, PCO and 8-OHdG, increased the activities of antioxidant enzymes SOD, GSTα4, CAT and GPx, and enhanced phosphorylation of AMPK and FOXO3 and DAF-16 protein expression in the brain tissue ($P < 0.01$). Compared with FB treatment alone, the combined treatment with FB and CC significantly reduced phosphorylation of AMPK and FOXO3, lowered expression of DAF-16 and SOD activity, and increased cerebral infarction volume and ROS level in the brain tissue of the mice ($P < 0.01$).

FB inhibits oxidative stress injury caused by cerebral I/R in mice possibly by enhancing AMPK phosphorylation, promoting the downstream DAF-16 protein expression and FOXO3 phosphorylation, increasing the expression of antioxidant enzymes, and reducing ROS level in the brain tissue [1].

1)
Chen X, Wang K, Chu D, Zhu Y, Zhang W, Cao H, Xie W, Lu C, Li X. [Forsythiaside B inhibits cerebral ischemia/reperfusion-induced oxidative stress injury in mice via the AMPK/DAF-16/FOXO3 pathway]. Nan Fang Yi Ke Da Xue Xue Bao. 2023 Feb 20;43(2):199-205. Chinese. doi: 10.12122/j.issn.1673-4254.2023.02.06. PMID: 36946038.

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