MASTER'S THESIS

Fucoxanthin Exerts Its Anti-cancer Effects by Reducing c-Myc Expression and ATP Level

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ABSTRACT

Non-small cell lung cancer (NSCLC) and colorectal cancer (CRC) are two common cancers in the world. Although there are numerous first-line therapeutics that have been used for the treatments of NSCLC and CRC, the adverse effects and drug resistance remain the clinical challenges. Seeking new and effective natural therapeutic is needed.

Fucoxanthin (Fx) is a dietary carotenoid commonly found in seaweeds and diatoms which has multiple health benefits. It improves insulin resistance and has anti-obesity effect. Fx has been shown to affect cell metabolism. However, whether it affects the metabolism of the cancer such as NSCLC and CRC is less studied.

Cancers have reprogramed metabolism to meet the energy demand for growth. c-Myc is a master regulator of the cell metabolism, including glucose metabolism, glutamine metabolism and lipid metabolism. Targeting c-Myc in cancers is a feasible strategy to treat the cancers.

Here, we explored whether Fx affected the metabolism of NSCLC and CRC cells and whether c-Myc was involved.

In our study, we showed that Fx had cytotoxic and anti-proliferation effects in NSCLC and CRC cells, and significantly reduced the protein expressions of c-Myc. Overexpression of cMyc in the cancer cells reduced the cytotoxicity and reversed the anti-proliferative effects upon Fx challenges. Furthermore, Fx significantly reduced glucose transporter 1 (GLUT1) expressions in both NSCLC and CRC cells, suggesting its effect on glucose metabolism. However, Fx only reduced sterol regulatory element

binding proteins (SREBP1) expression in NSCLC cells but not in CRC cells, implying the effects of Fx on lipid metabolism in different cancers are different.

GLUT1 transports glucose into the cells. Since Fx reduced GLUT1 expressions, we next examined whether Fx affected the glucose metabolism in these cells. The Seahorse real-time cell metabolic analysis study showed that Fx reduced the glycolytic reserve in both NSCLC and CRC cells. The result implies that Fx may worsen the response of the cells to ATP demands. Moreover, our study also showed that Fx significantly lowered the ATP levels in both NSCLC and CRC cells. Nevertheless, overexpression of c-Myc failed to reverse the Fx-reduced ATP levels in these cancer cells, suggesting that Fx simultaneously modulates multiple metabolic pathways that leads to the reduction of ATP levels.

SREBP1 is a basic helix-loop-helix-leucine zipper (bHLH-Zip) transcription factor that plays a critical role in lipid metabolism. Our data showed that Fx reduced SREBP1 expression in NSCLC cells. Lipidomics results also showed that the fatty acid profiles of NSCLC cells were changed upon Fx challenge. However, Fx treatment did not significantly affect the total free fatty acid levels and C16:0-incorporated glycerol lipid levels in the cells. Interestingly, the treatment increased the C16:0-incorporated phospholipids levels, which deserves further investigation.

In summary, Fx has cytotoxic effects in NSCLC and CRC cells. The treatment significantly reduces the cancer proliferation and c-Myc expressions. The anti-cancer effect of Fx may be mediated by cMyc. The Fx treatment also reduces GLUT1 expressions, the glycolytic reserves, and ATP levels in these cancer cells. Although Fx reduces SREBP1 expressions in NSCLC cells, the consequential effect on lipid metabolism deserves further investigation.