DOCTORAL THESIS

Fucoxanthin as a Neuroprotective Agent in Cell Cultures, 3D Biological Printed Brain Organoids and Animal Models of Neurodegenerative Diseases

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ABSTRACT

Neurodegenerative disease has become a major health challenge for the global elderly population. Seaweed extracts have been extensively studied and have attracted attention for their potential neuroprotective effects. At the same time, 3D bioprinting technology provides new tools for biomedical research, can better simulate the complex structure and function of human organs, and provides a new way for drug screening and treatment research. Our research is dedicated to exploring co-culture cell models in 3D bio-printed organoids to compare with traditional 2D cell culture models to evaluate the effectiveness of fucoxanthin as a seaweed extract in the treatment of neurodegenerative diseases. We constructed 3D brain organoid models that simulated the neural tissue environment and co-cultured different types of cells, including neurons and glial cells, in them. We evaluated the therapeutic effects of fucoxanthin through a series of biochemical and molecular biology experiments, as well as behavioral tests.

Firstly, we utilized the traditional 2D monoculture method to assess the effects of fucoxanthin on hippocampal neurons. The results indicated that fucoxanthin could increase the cell survival rate of hippocampal neurons in the presence of neurotoxins. Additionally, fucoxanthin was able to reduce the levels of reactive oxygen species in hippocampal neurons affected by neurotoxins, decrease the level of cell apoptosis, and enhance the cells' antioxidant capacity.

Next, we utilized 3D biological printing technique to create a brain organoid composed of three types of cells. This model includes microglia, astrocytes, and hippocampal neurons. In addition, we developed a biocompatible hydrogel suitable for printing all

types of brain organoids, which is composed of sodium alginate, gelatin, and collagen. Experimental results show that this bio-scaffold can maintain its structure without collapsing for over 20 days in vitro, and the cell viability within this scaffold exceeds 99%. To demonstrate that activated microglia and astrocytes release proinflammatory factors that can lead to the death of normal hippocampal neurons, we co-printed activated microglia, astrocytes, and normal hippocampal neurons. The results show that this model can simulate the hippocampal degeneration process caused by brain inflammation due to neurodegenerative diseases. Following our construction of the brain inflammation model, we examined the effects of fucoxanthin on this it. The results indicated that fucoxanthin could alleviate brain inflammation by reducing the release of proinflammatory factors from microglia and astrocytes. Additionally, fucoxanthin was also capable of decreasing oxidative damage to cells by lowering levels of reactive oxygen species within the cells, thereby reversing cell death.

In conclusion, in our study, we utilized 3D bioprinting technology to construct a multi-layered brain-like tissue composed of three cell types (microglia, hippocampal neurons, and astrocytes) to simulate the exacerbation of neurodegenerative diseases. We detected the systemic therapeutic mechanism of fucoxanthin against neurodegenerative diseases and, by comparing the results with animal experiments, we demonstrated the feasibility and authenticity of using 3D bio-printed brain organoid for drug testing.

Key words: 3D biological printing, Fucoxanthin, hippocampus neurons, microglia and astrocyte, Neurodegenerative diseases, animal model