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"Astrocyte-neuron" Interaction Promoted by Moxibustion in Alzheimer's Disease: Evidence from Spatial Transcriptomics

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1. Abstract

Alzheimer's disease (AD), the most common type of dementia, is an irreversible neurodegenerative disease. Due to the increased incidence and the lack of specific therapeutics, it seems very important to understand it's pathology and find useful treatments. Fortunately, clinical and experimental studies have shown that moxibustion provided good therapeutic effects on AD. Here, we also discovered that "astrocyte-neuron" interaction played a vital role in central nervous system for moxibustion in AD.

Moxibustion, as an important Chinese traditional therapy, has the effects of anti-aging[1]. Previous studies have shown that moxibustion can improve the ability of learning and memory by regulating neurotransmitters in AD mice brain, enhancing the expression of neurotrophic factors and their receptors, such as BDNF/TrkB[2-4]. And it also can regulate the signal pathway, in which related to learning and memory, such as cAMP/PKA/CREB signaling pathway[5]. However, the exact mechanism of moxibustion in treating AD has not been fully illustrated.

"Astrocyte-neuron" interaction, based on the function between receptor and ligand, and the distance between cells, is a complex phenomenon that astrocytes can closely communicate with neurons through multiple pathways[6]. Astrocytes constitute the most abundant glial cell population in the mammalian brain which are considered to be crucial support members in neuronal function [7, 8]. The metabolic support has been recognized as the significant assisted program in the corsstalk. One of the main metabolic communications is the astrocyte-neuron lactate shuttle, wherein glial cells take up glucose from blood and provide lactate *via* glycolysis to neurons as an energy substrate, this lactate production is stimulated by neuronal activity[9]. In addition, Hayakawa et al.[10] reported a new energy shuttle that astrocytes released the functional mitochondrial which then was transferred into neurons to renew their mitochondrial. Thus, we envision whether moxibustion can alleviate the cognitive impairment of AD by promoting hippocampal "astrocyte-neuron" interaction and ultimately enhancing synaptic plasticity.

Previous studies assessed the strength of "astrocyte-neuron" interaction through counting the colocalization of GFAP and PSD95 *via* immunofluorescence and isotopically labeled lactate[11, 12]. Here, we firstly investigated by using Spatial transcriptomics (ST). ST uses spotted arrays with positional molecular barcodes that tag cDNA synthesized in intact tissue sections with a spatial location allowing gene expression to be mapped to a histological image[13], which can solve the problem of cell spatial heterogeneity that single-cell sequencing cannot achieve. ST allows the visualization and quantitative analysis of transcriptomics with spatial resolution in a single tissue section. It has the advantages of unbiased high-throughput gene expression, high spatial resolution, high detection efficiency (sensitivity) and a simple operation[14]. Here, we used ST to study the effect of moxibustion on the cellular interaction between astrocytes and neurons in hippocampus of APP/PS1 mice, and explore the related molecular mechanism[15].

Our study found that some decrease, including the number of ligand-receptor pairs, distance of cells and the number of astrocytes adjacent to neurons in APP/PS1 group. These results indicated that the communication between astrocytes and neurons reduced in neurodegeneration. Furthermore, we also found that not only the number and interaction strength score of ligand-receptor pairs but also spatial proximal and interaction state between astrocytes and neurons were enhanced by moxibustion in APP/PS1 mice. These results suggested that the improvement of communication relationship between astrocytes and glutamatergic neurons might be one of mechanisms under moxibustion intervention[15].

In a recent report, astrocytes could replenish the neuronal energy *via* CD38-cADPR-$Ca2^{+}$ signaling pathway[10]. Meanwhile, neuron glutamate was proved to up-regulate the expression of CD38 in astrocytes, causing a temporary increase of $Ca2^{+}$ and cADPR levels in astrocytes. The increase of Ca^{2+} signal in turn leaded to the glutamate release of astrocyte in the astrocyte-neuron coculture system[16]. CD38, also known as ADP ribosyl cyclase, is a type II transmembrane protein with both enzyme and receptor functions[17]. Here, significant differences of Pecam1_Cd38 ligand-receptor pair in cell-cell interaction were observed in the whole brain by ST. Our data also suggested that CD38-cADPR signal pathway might be one of the "astrocyte-neuron" interaction pathways, and moxibustion could affect this pathway and ultimately improve synaptic plasticity in APP/PS1 mice[15].

In conclusion, we provided new evidences that moxibustion could increase hippocampal "astrocyte-neuron" interaction thus to enhance synaptic plasticity of APP/PS1 mice *via* analyzing the ST data. And as a vital signaling molecule of "astrocyte-neuron" interaction, CD38 probably played an important role.

2. Author contribution

All authors have made intellectual contributions to the work.

3. Declaration of competing interest

The authors declare that they have no conflicts of interest.

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