Molecular mechanism of Maf1 on regulating dendrite growth and injury repair in neurons

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Abstract

Background:

Maf1, as a negative transcriptional regulator, has been shown to play an important role in cancer, lipid metabolism, reproductive fertility and other aspects, but other functions are not yet known. Maf1 is highly expressed in the central nervous system, especially in the hippocampus and cortex, but no study has been done on the function of Maf1 in neurons. In this study, we explored the function and molecular mechanism of Maf1 in dendritic growth and provide new ideas for dendritic growth-related diseases.

OBJECTIVE: Exploring the molecular mechanism of Maf1 affecting dendritic growth and repair of neurons

Methods:

1. Detection of Maf1 expression distribution and specificity by immunofluorescence and Western blotting.

2. Maf1 function: The effect of Maf1 on the dendritic growth of hippocampal neurons cultured in vitro and its molecular mechanism were

detected by knockdown of shRNA or overexpression.

3. Maf1 regulates neuronal dendritic growth in PI3K/AKT/mTOR signaling pathways: combined with mTOR inhibitor rapamycin and shRNA knockdown PTEN to assay Maf1 effects on PI3K/AKT/mTOR signaling pathways and the effect of neuron dendritic growth.

4. Overexpression and shRNA knockdown assays were used to examine the effect of Maf1 on neuron dendritic spines, synapses and learning and memory in mice.

5. Role of Maf1 in Traumatic Brain Injury: The expression of Maf1 after TBI was detected by immunofluorescence and Western blotting, and the expression of Maf1 was intervened by shRNA knockdown to detect its role on neuron dendritic spines, synapses, learning and memory after following TBI.

Results:

1. Maf1 was highly expressed in mouse brain tissue by immunoblotting and immunofluorescence, especially in the cortex and hippocampus. Maf1 is highly expressed in axons and dendrites in subcellular localization in hippocampal neurons.

2. In vitro knockdown of endogenous Maf1 in hippocampal neurons can increase the dendrite branching complexity of neurons, increase the length of projections, increase the number of dendritic branches, and increase the density of dendritic spines, among which mushroom-like dendritic spines

increase Mainly; Overexpression of Maf1 in vitro can reduce the dendrite branching complexity of neurons, reduce the length of projections, reduce the number of dendritic branches, and reduce the density of dendritic spines, in which mushroom-type dendritic spines reduce mainly. Overexpression of rat Maf1 reversed the morphological effects of Maf1 knockdown in mouse hippocampal neurons.

3. Maf1 negatively regulates PI3K/AKT/mTOR signaling pathway during neuronal dendritic growth. Knockdown of Maf1 in hippocampal neurons significantly increased the expression of p-AKT, p-mTOR, p-P70S6K, and p-S6 in the PI3K/AKT/mTOR signaling pathway and significantly reduced PTEN expression. Overexpression of Maf1 significantly decreased the expression of p-AKT, p-mTOR, p-P70S6K and p-S6 in the PI3K/AKT/mTOR signaling pathway, and significantly increased the expression of PTEN. The use of the mTOR inhibitor rapamycin rescues the phenotype of Mafl in knockdown neurons, whereas knockdown of PTEN can partially rescue the effect of overexpression of Mafl negatively regulated cell growth.

4. Knockdown of endogenous Maf1 in hippocampal neurons in vivo can increase the dendritic spine density of neurons, promote the maturation of dendritic spines of neurons, increase the synaptic density and enhance the ability of learning and memory in mice; overexpression of exogenous Maf1 can reduce the dendritic spine density of neurons, inhibit the maturation of

dendritic spines of neurons, reduce the synaptic density, limited ability of learning and memory in mice.

5. Maf1 was highly expressed in the injured area 3 days and 7 days after TBI, and the closer to the damaged area, the higher the expression of Maf1.

6. Knockdown of Maf1 by shRNA can increase dendritic spine density of neurons, increase synaptic density and enhance learning and memory in mice following TBI.

Conclusions:

1. Maf1 is highly expressed in mouse brain and negatively regulates the growth of dendrites and dendritic spines.

2. Knockdown of Maf1 promotes the growth of dendritic spines in mice following TBI and promotes recovery of learning and memory in mice.

Keywords: Maf1, dendritic growth, dendritic spine growth, PI3K/AKT/mTOR pathway, traumatic brain injury