Calcineurin-NFAT Complex: The Connection to Alzheimer’s Disease

Takeuchi K, Roehrl MH, Sun ZY, and Wagner G. (2007) “Structure of the calcineurin NFAT complex and its associated pathway - the normal activity of NFAT, the importance of calcium ion concentrations and the binding between calcineurin and NFAT- has become increasingly important.

Introduction

The Calcineurin-NFAT complex is one which has only recently appeared on the scene of modern scientific research, but holds great potential for impacting our understanding of genes controlling neuronal growth and connections. The potential benefits for people with Alzheimer’s disease who generally exhibit especially high NFAT-3 activity are particularly pertinent and intriguing. Consequently, study of the complex and its associated pathway - the normal activity of NFAT, the importance of calcium ion concentrations and the binding between calcineurin and NFAT- has become increasingly important.

Abstract: Patients with Alzheimer’s disease (AD), a progressive neurodegenerative disorder, exhibit neuronal degeneration. High levels of the protein calcineurin (Cn) have been found in regions of earliest pathology in AD. Elevated Cn signaling results in symptoms associated with AD. NFAT proteins are a family of transcription factors activated by calcineurin. Inappropriately active NFAT 3 is associated with intermediate to severe AD. One NFAT target gene is GAP 43 which is involved in axon growth and guidance. Transcription of this gene is negatively regulated by NFAT 3. Reduced GAP 43 expression has been found in post-mortem AD brains. NFAT molecules have a nuclear localization sequence (NLS) to which an importin protein attaches and then carries NFAT into the nucleus. In a resting cell the NLS is masked due to phosphorylation on serine residues. In a stimulated cell there is an increase in the intracellular calcium ion concentration. Calcium activates Cn, which then dephosphorylates the serine residues, exposing the NLS and allowing the nuclear transport of NFAT. In a region distinct from the phosphorylation sites of NFAT lies a conserved PxIxIT motif which acts as a calcineurin docking site. This model shows the complex between calcineurin and NFAT - the activation of the receptor triggers a signaling cascade that increases the calcium concentration in the cell.

Connection to Alzheimer’s Disease

Growth associated protein (GAP) 43 is encoded by the GAP 43 gene, which is expressed in high levels in neuron growth cones. Transcription of the GAP 43 gene regulates axon outgrowth in developing neurons and regenerating neurons. It may also have a role in the remodeling of synapses that occurs during learning and information storage. Axon outgrowth is the first step in the formation of neuronal connections. NFAT-3 represses transcription of GAP 43 at specific times, preventing inappropriate axon growth. Reduced GAP 43 expression has been found in post-mortem Alzheimer’s Disease (AD) brains.

Patients with Alzheimer’s Disease (AD), a progressive neurodegenerative disease, exhibit dementia, difficulty with problem solving and memory loss. The brains of these patients contain beta-amyloid plaques and areas of cell death. Inappropriate calcineurin (CN) signaling is linked to synaptic dysfunction and neuronal death in AD brains. NFAT signaling is selectively altered in AD and may play an important role in driving beta-amyloid mediated neurodegeneration. Changes in CN/NFAT-3 signaling are directly correlated to soluble beta-amyloid levels in the post-mortem brain.

The molecular story of the transcription factor, NFAT3

1. Extracellular Cue: a specific molecule binds to a receptor on the cell’s plasma membrane.
2. The activation of the receptor triggers a signaling cascade that increases the calcium concentration in the cell.
3. Calcium ions activate the protein phosphatase calcineurin.
4. Calcineurin binds to inactive NFAT3 and dephosphorylates it.
5. NFAT 3 can now enter the nuclear pores and bind to DNA.
6. Activated NFAT 3 now in the nucleus represses transcription of the GAP-43 gene.
7. Reduced GAP 43 expression has been found in post-mortem AD brains.

Increased proportion of nuclear NFAT3 in post-mortem AD brains

Summary

Inappropriately activated NFAT could lead to cognitive difficulties associated with Alzheimer’s disease. Discovering how to control NFAT could lead to a way to prevent symptoms of this disease.

Works Cited:
*Structural 5:567-597
*Neurosci: 29:12967-12969.