Revealing the role of c-Abl in Alzheimer's disease pathogenesis

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Bachelor Thesis – Biochemistry Degree
June 2014

INTRODUCTION

Alzheimer's disease (AD) is a neurodegenerative disorder characterized by the accumulation of amyloid-β (Aβ) peptides and phosphorylated tau in the brain. Often is accompanied by neuroinflamation, increase in reactive oxygen species and oxidative damage that results in neuronal loss, cognitive dysfunctions, loss of synapses as well as neurites dystrophy. All these features lead to memory loss and cognitive disorders that mainly will end in dementia.

Abelson non-receptor tyrosine kinase (c-Abl) is an important protein in the CNS that can acquire different cellular locations in response to different stimuli. This change in distribution leads to alternative roles; being some of them very important in the AD pathogenesis. For instance, activation of c-Abl contributes to aberrant cell cycle, apoptosis induction, tau phsophorylation and as a consequence, neuronal dysfunction [1].

For its vast implications and different activities in the nervous system, c-Abl has been enrolled in the neurodegenerative process of AD [1,2,3]. So, I hypothesize that the activity of c-Abl in the different cellular locations is required for the AD physiopathology in response to Aβ fibrils. I also assume this neurodegenerative phenotype could be largely modified by the alteration of normal redistribution of c-Abl.

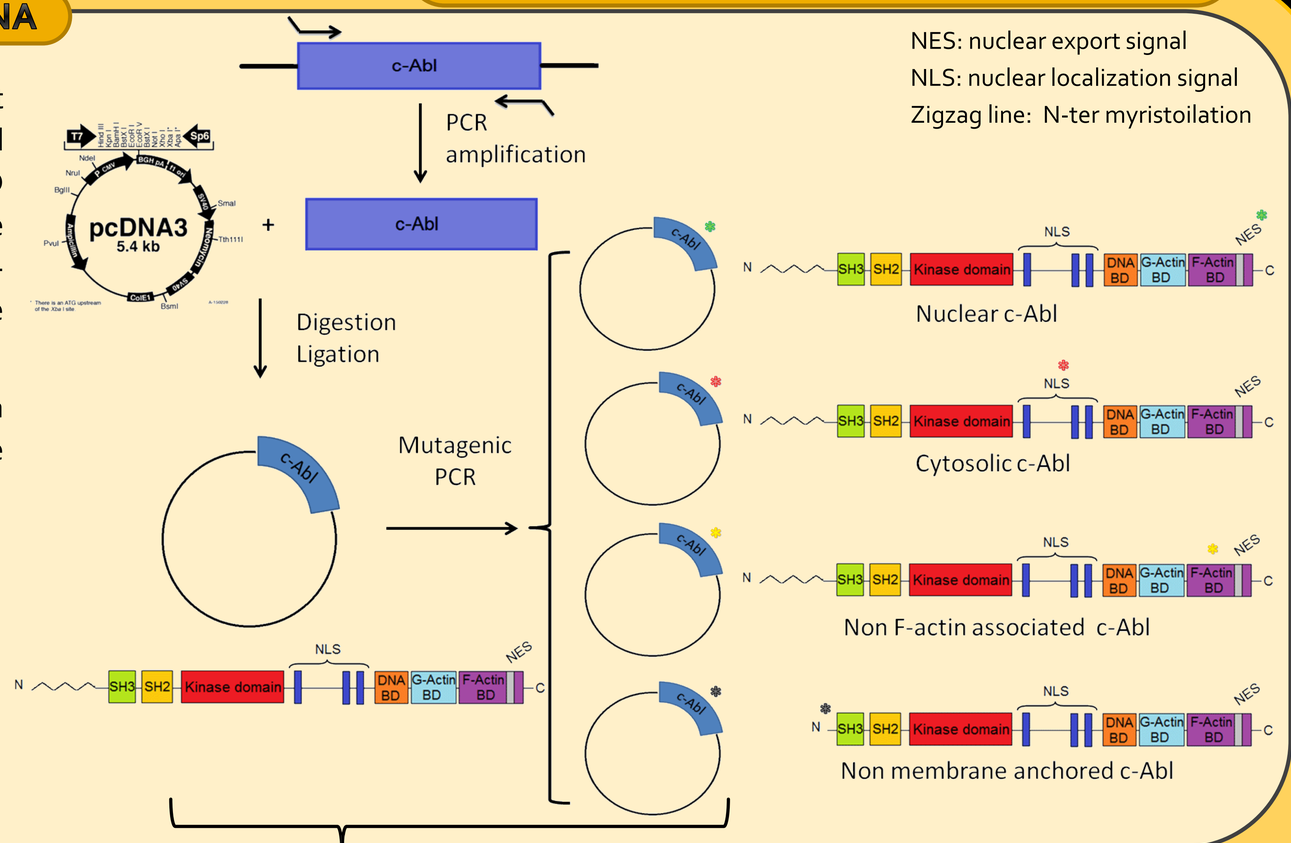
EXPERIMENTAL PROCEDURE

Recombinant DNA

To study the different implications of c-Abl localization in AD pathogenesis, the generation of different c-Abl mutants will be required.

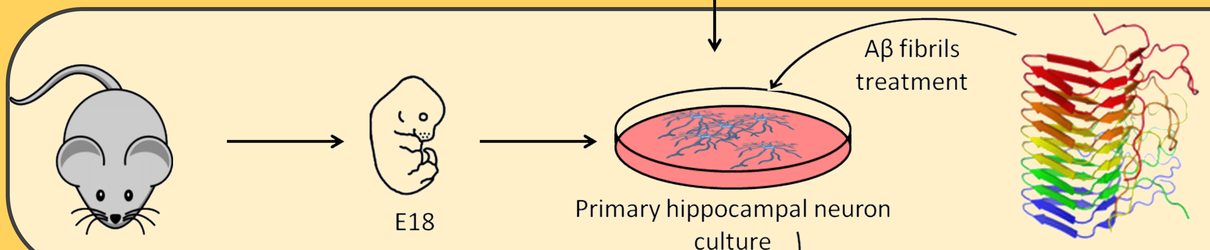
Each mutant will have a preferable location in the cell:

-Nuclear
-Cytosolic
-Non F-actin associated
-Non-membrane anchored



Transfection

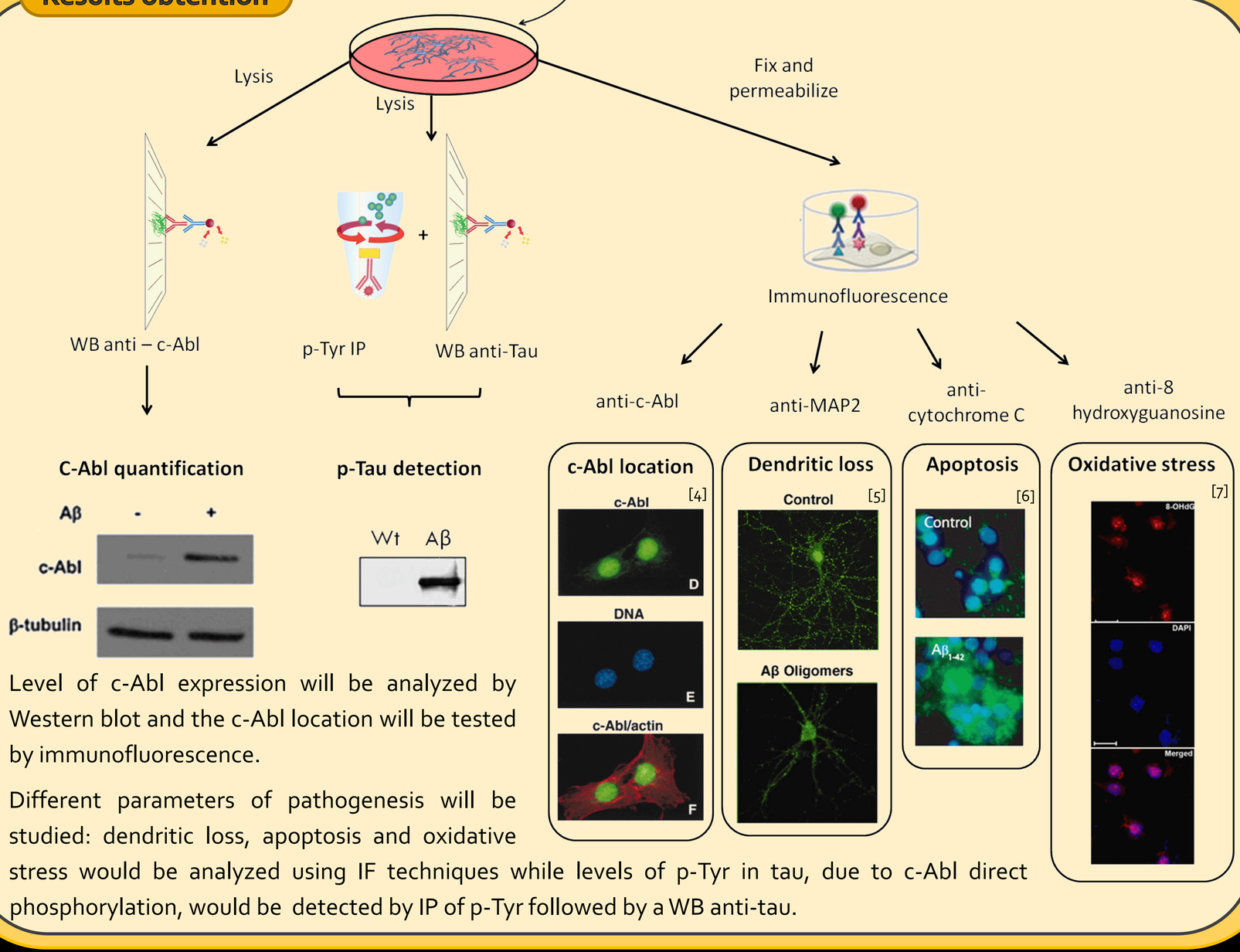
Neuronal culture



The plasmids generated will be transfected in different primary hippocampal neuron cultures. The Aβ induction will be performed after 48 h.

Results obtention

1, 6, 24 and 48 h



Level of c-Abl expression will be analyzed by Western blot and the c-Abl location will be tested by immunofluorescence.

Different parameters of pathogenesis will be studied: dendritic loss, apoptosis and oxidative stress would be analyzed using IF techniques while levels of p-Tyr in tau, due to c-Abl direct phosphorylation, would be detected by IP of p-Tyr followed by a WB anti-tau.

OBJECTIVES

The aims of this study are:

1. Analyze the wt c-Abl distribution in the neuron acquired due to the Aβ induction.
2. Study in depth the role of the different localizations of c-Abl in the context of AD pathogenesis.
3. Analyze whether the subcellular alteration of the protein induced by Aβ fibrils is essential for the AD development.

EXPECTED RESULTS

1. In response to Aβ fibrils, wt c-Abl changes it's location in the neuron showing important evidences of neuronal pathology.
2. Each c-Abl mutant shows potentiated one or few characteristic features of AD pathogenesis.
3. These results would reveal the importance of the induced distribution in the AD physiopathology.

SOCIAL IMPACT

This study could help to improve the understanding, still insufficient, about AD and the pathogenesis generated by Aβ fibrils focusing on the role of c-Abl implicated in this process.

New approaches and strategies could be introduced against not only AD, but also other neurodegenerative diseases.

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