Activation of p53 in Down Syndrome and in the Ts65Dn Mouse Brain is Associated with a Pro-Apoptotic Phenotype

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Down syndrome (DS) is the most common genetic cause of intellectual disability, resulting from trisomy of chromosome 21. The main feature of DS neuropathology includes early onset of Alzheimer's disease (AD), with deposition of senile plaques and tangles. We hypothesized that apoptosis may be activated in the presence of AD neuropathology in DS, thus we measured proteins associated with upstream and downstream pathways of p53 in the frontal cortex from DS cases with and without AD pathology and from Ts65Dn mice, at different ages. We observed increased acetylation and phosphorylation of p53, coupled to reduced MDM2/p53 complex level and lower levels of SIRT1. Activation of p53 was associated with a number of targets (BAX, PARP1, caspase-3, p21, heat shock proteins, and PGC1?) that were modulated in both DS and DS/AD compared with age-matched controls. In particular, the most relevant changes (increased p-p53 and acetyl-p53 and reduced formation of MDM2/p53 complex) were found to be modified only in the presence of AD pathology in DS. In addition, a similar pattern of alterations in the p53 pathway was found in Ts65Dn mice. These results suggest that p53 may integrate different signals, which can

result in a pro-apoptotic-phenotype contributing to AD neuropathology in people with DS.

Apoptosis

caspase

p53

sirtuins

trisomy 21

Ts65Dn mouse model

caspase 3

heat shock protein 27

heat shock protein 70

nicotinamide adenine dinucleotide adenosine diphosphate ribosyltransferase 1

peroxisome proliferator activated receptor gamma coactivator 1alpha

protein Bax

protein MDM2

protein p21

protein p53

sirtuin 1

sirtuin 2

protein p53

adult

Alzheimer disease

animal experiment

animal model

animal tissue

apoptosis

Article

controlled study

Down syndrome

female

frontal cortex

human

human tissue

male

mouse

neuropathology

nonhuman

oxidative stress

phenotype

priority journal

protein acetylation

protein phosphorylation

upregulation

acetylation

Alzheimer disease

animal

apoptosis

C3H mouse

C57BL mouse

disease model

Down syndrome

frontal lobe

immunoprecipitation

metabolism

middle aged

pathology

phenotype

phosphorylation

physiology

transgenic mouse

Western blotting

young adult

Acetylation

Alzheimer Disease

Animals

Apoptosis

Blotting, Western

Disease Models, Animal

Down Syndrome

Female

Frontal Lobe

Humans

Immunoprecipitation

Male

Mice, Inbred C3H

Mice, Inbred C57BL

Mice, Transgenic

Middle Aged

Phenotype

Phosphorylation

Tumor Suppressor Protein p53

Young Adult