

## Loss of Bax-interacting factor-1 exacerbates Alzheimer's disease pathology

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Bax-interacting factor-1 (Bif-1) is a multifunctional protein involved in regulation of apoptosis, autophagy and mitochondrial function. We recently described neuron-specific alternatively spliced isoforms of Bif-1 that confer neuroprotection. To examine whether Bif-1 mediated neuroprotection could be a novel therapeutic target for Alzheimer's Disease (AD) we employed a double mutant amyloid precursor protein and presenilin 1 (APP<sup>swe</sup>/PS1<sup>dE9</sup>) mouse model of AD and observed that expression of neuron-specific Bif-1 isoforms is decreased with disease progression. To determine if reduced Bif-1 participates in AD pathogenesis, we crossed Bif-1 knockout mice (Bif-1 KO) with APP<sup>swe</sup>/PS1<sup>dE9</sup> mice. The absence of Bif-1 accelerated disease onset and progression in AD/Bif-1 KO mice, which showed more plaques, astrogliosis, synaptic degeneration, cognitive impairment and mortality than APP<sup>swe</sup>/PS1<sup>dE9</sup> mice. In mouse primary cortical neuron cultures, overexpression of neuron specific Bif-1 isoforms protected against beta-amyloid induced apoptosis and mitochondrial dysfunction. Protein and mRNA levels of neuron-specific Bif-1 isoforms were also selectively decreased in the cerebral cortex of patients with Alzheimer's disease, suggesting that loss of Bif-1 mediated neuroprotection may participate in AD pathogenesis and that restoration of Bif-1 function could be a novel therapeutic target for AD. We also observed that Bif-1KO mice develop synaptic degeneration and behavioral impairment by 12 months, underscoring the importance of Bif-1 in neuronal homeostasis. Since exposure to beta amyloid leads to reduced expression of Bif-1 and loss of Bif-1 leads to increased accumulation of beta amyloid in vivo, our findings suggest that Bif-1 is a key mediator of a feed forward mechanism of AD disease pathogenesis in which beta-amyloid deposition reduces neuron-specific Bif-1, which in turn enhances beta-amyloid accumulation and neuronal sensitivity to beta-amyloid toxicity.