

# No ECSIT-stential evidence for a link with Alzheimer's disease yet

(retrospective on DOI 10.1002/bies.201100193)

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Early-onset familial Alzheimer's disease (AD), which affects ~5% of AD patients, is characterized by aggregation of Amyloid- $\beta$  (A $\beta$ ) in the form of neurotoxic extracellular protein oligomers and plaques and hyperphosphorylated tau protein like intracellular neuritic tangles. This mechanism, however, may not explain the more common sporadic AD, which affects ~95% of all AD patients, in which elevated levels of A $\beta$  are not always associated with cognitive impairment [1]. Familial AD is associated with mutations in A $\beta$  precursor protein (APP) expression and processing, resulting in elevated levels of A $\beta$  oligomers and plaques [2]. Aging-related abnormal oxidative stress, inflammation, and cellular energy deficit can all promote A $\beta$  generation and self-aggregation [1, 2]. A $\beta$  plaques are associated with active gliosis, which can increase reactive oxygen species (ROS) production [2], further exacerbating oxidative stress, inflammation, and mitochondrial dysfunction, promoting AD progression [1].

Evolutionarily conserved signaling intermediate in toll pathway (ECSIT), located on chromosome 19 (p13.2), is associated with AD risk [2]. ECSIT seems to exert pleiotropic roles: (i) mediating inflammation-related gene transcription following TLR activation [2], (ii) increas-

ing mitochondrial biogenesis and cellular ROS generation following TLR activation [3], and (iii) assembling mitochondrial oxidative phosphorylation complex I [4]. The translocation of ECSIT to the mitochondria is probably an attempt to optimize available cellular energy. Inadvertently, this also causes mitochondrial ROS levels to increase, which may lead to disintegration of the respiratory complex and induction of glycolysis and a vicious cycle of ROS generation.

Due to its extensive interactions with mitochondrial proteins, inflammation and cellular response to oxidative stress, Soler-López et al. had hypothesized that ECSIT is a central hub in the AD-protein interaction network [2]. According to this network, ECSIT is thought to associate with apolipoprotein E [2, 5] (which binds to A $\beta$ ) and to interact with presenilin 1 and 2 (which directly influence A $\beta$  production) [2, 5], suggesting that ECSIT is involved in A $\beta$  production and clearance.

Unfortunately, since the inception of this hypothesis, no further evidence on this possible link was provided, limiting our ability to speculate on the plausibility of this hypothesis. Thus, as properly put by [1], while ECSIT undeniably has important roles in modulating inflammatory signaling cascades and cellular responses to injury via TLR, TGF, and BMP signaling pathways, the predictions that ECSIT may also influence mitochondrial function and oxidative stress responses remain to be tested. The possible expression and functions of ECSIT in neurons, glial cells, and neural stem cells are yet unknown, as is the

expression, post-translational modification, and/or functional status of ECSIT in brain cells of AD patients. Since it is not known whether ECSIT activity is altered in AD patients, it is also not known whether ECSIT is associated with A $\beta$  and/or tau pathologies and cognitive impairment. A straightforward way to test this would be a conditional deletion of ECSIT in neurons or glia in a mouse model of AD, and assessment of whether this accelerates the disease process and/or cognitive decline. It is also important to assess whether ECSIT influences APP processing and accumulation, and whether genetic defects involved in AD affect ECSIT function. If ECSIT is involved in mitochondrial function as Soler-López suggests, it will be of interest to determine whether there is a role for ECSIT in the modulation of age- and AD-related cognitive function.

## References

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DOI 10.1002/bies.201400179

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