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An ECSIT-Centric View of Alzheimer's Disease

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The accumulation of amyloid β-peptide (Aβ) may not be the earliest pivotal event in Alzheimer's disease (AD). Instead, processes that occur in the brain during normal aging can promote Aβ generation and self-aggregation including oxidative stress, cellular energy deficits and inflammation. In this issue of *Bioessays* Soler-Lopez et al. propose a role for a protein called ECSIT (evolutionarily conserved signaling intermediate in Toll pathways), believed to function in the integration of cellular stress responses, as a key node in the signaling networks gone awry in AD (1). Here I comment on this ECSIT-centered scheme, with emphasis on both its attractions and its immaturity.

Research on Alzheimer's disease (AD) has elucidated several genetic and environmental factors, and molecular and cellular mechanisms, that contribute to the dysfunction and degeneration of neurons. The β-amyloid precursor protein (APP) has been a major focus of investigation because: 1) neurotoxic self-aggregating forms of Aβ arise from APP; 2) mutations in APP or presenilin-1 (PS1; an enzyme that cleaves APP to generate Aβ) are sufficient to cause early-onset AD; 3) when in the process of aggregation, Aβ incites membrane-associated oxidative stress, inflammation and mitochondrial dysfunction, all of which occur in AD; 4) the function and plasticity of synapses is particularly sensitive to the noxious effects of Aβ; and 5) AD-related changes in APP processing may impair the normal functions of APP in synaptic plasticity (2, 3). On the other hand, even extensive accumulation of Aβ in the brain is not always associated with cognitive impairment (4), and agents that target APP processing or Aβ have thus far failed in AD clinical trials (5). Other therapeutic approaches should therefore be pursued.

The ECSIT gene is located within a region of chromosome 19 (p13.2) that is linked to AD risk; furthermore, bioinformatics analysis suggesting functional interactions between ECSIT and several pathways implicated in AD. Based on these observations, Soler-Lopez et al. (1) have developed a model for AD involving the protein ECSIT. ECSIT was first discovered as an adaptor protein involved in coupling toll-like receptors (TLR) and TRAF6 to MEKK-1 and NF-κB (6). Studies of ECSIT-deficient mice revealed a role for ECSIT in the bone morphogenic protein (BMP) and transforming growth factor β (TGFβ) signaling pathways (7). By considering the proteins that it does or may interact with, Soler-Lopez et al. elevate ECSIT to the status of "an integrating hub between oxidative stress, inflammation and mitochondrial dysfunction" that plays a critical role in the pathogenesis of AD (1). Their

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elaborate model, which is shown in Figure 2 of their article (1), has all roads leading to and from ECSIT. This scheme provides a framework for future studies to test the authors' hypothesis. The evidence is strongest that there are roles for ECSIT in modulating inflammatory signaling cascades and cellular responses to injury via TLR and NF-κB signaling, pathways implicated in AD pathogenesis (8, 9). The predictions that ECSIT may also influence mitochondrial welfare and oxidative stress responses remain to be tested. Moreover, the function(s) of ECSIT in neurons, glial cells and neural stem cells are completely unknown (Figure 1).

Outstanding questions include: Is ECSIT expressed in neurons and glia? Is the expression, post-translational modification, and/or functional status of ECSIT altered in brain cells in AD? Are such alterations in ECSIT associated with Aβ and/or tau pathologies and cognitive impairment? Will conditional deletion of ECSIT in neurons or glia accelerate the disease process and cognitive decline in mouse models of AD? Does ECSIT influence APP processing and Aβ accumulation? Do genetic defects that cause AD (APP and PS1 mutations) impinge upon ECSIT function? Even if ECSIT is found to play key modulatory roles in inflammation, oxidative stress and mitochondrial function in neurons and/or glial cells, establishing a role for ECSIT in AD pathogenesis will require considerable evidence from studies of AD patients and animal models.

Inflammation, oxidative stress and mitochondrial dysfunction are non-specific, age-related, alterations involved in most, if not all, neurodegenerative disorders. The authors propose that ECSIT may play a critical role in the maintenance of homeostasis to allay the latter three generic disease-related processes. If so, then the authors' hypothesis that ECSIT has a critical role early in the AD process may prove correct. Indeed, there is accumulating evidence that oxidative stress (10 – 12), inflammation (13) and mitochondrial perturbations (12, 14) can act upstream of Aβ accumulation by promoting amyloidogenic processing of APP (Figure 1). The latter pathological processes can be suppressed by diet (e.g., energy restriction) and lifestyle factors (e.g., exercise) that can reduce the risk of AD (15, 16). It will, therefore, be of interest to determine whether there is a role for ECSIT in the modulation of age- and AD-related cognitive impairment by such environmental factors.

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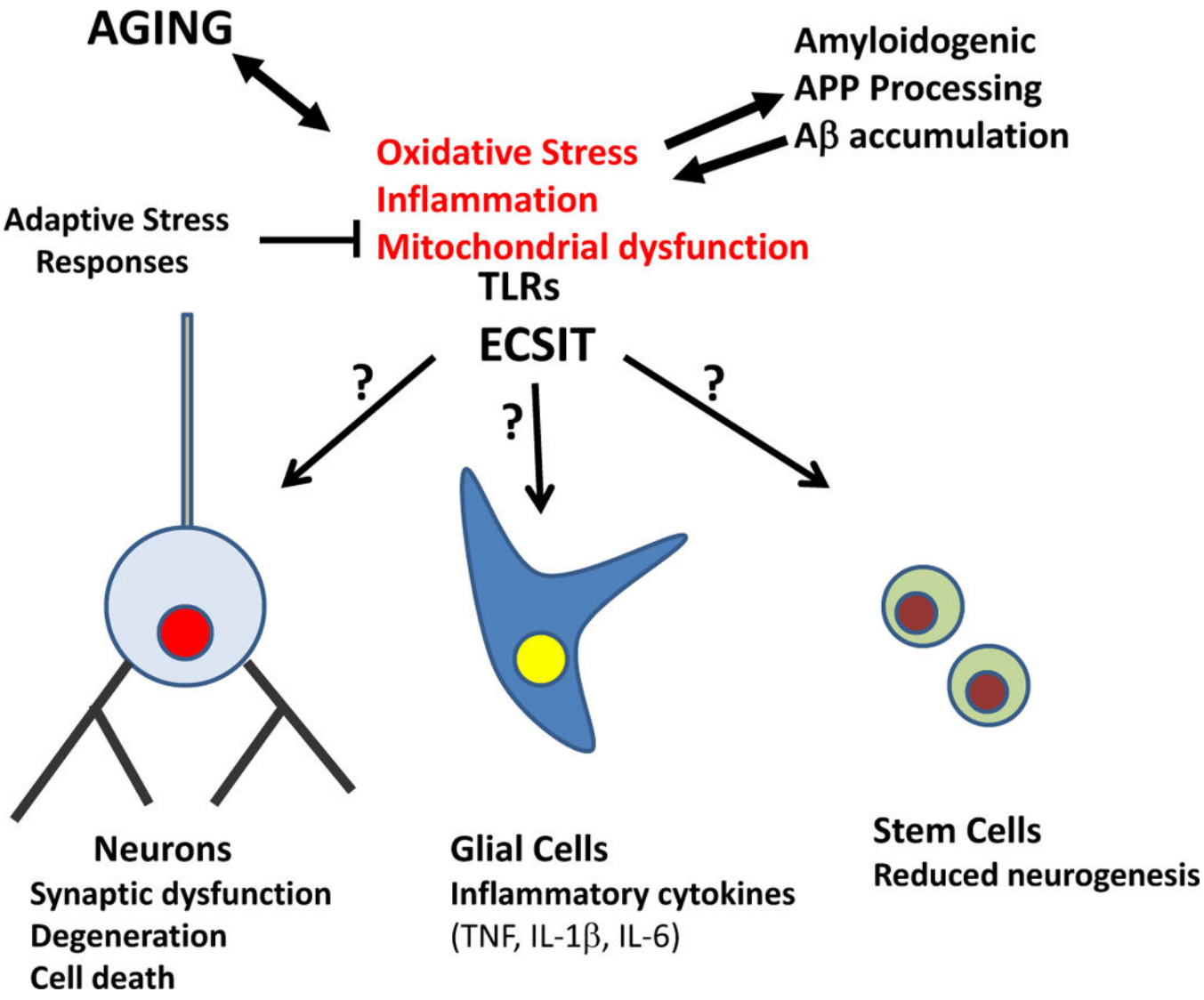

Figure 1.

Model of the influences of aging and Aβ generation on brain cells; oxidative stress, inflammation and impaired energy metabolism are fundamental and modifiable disease processes. Aging, the major risk factor for AD, promotes the accumulation of oxidatively modified molecules resulting in altered (amyloidogenic) APP processing, Aβ aggregation and associated cytotoxicity. Aging and oxidative stress also activate local inflammatory processes involving toll-like receptor (TLR) signaling, NF-κB activation and the production of pro-inflammatory cytokines such as tumor necrosis factor, interleukin-1β and interleukin-6. The resulting oxidative, metabolic and inflammatory stress likely contributes to synaptic dysfunction and impaired neurogenesis (the production of new neurons from neural stem cells) early in the disease process. As the disease progresses neurons degenerate and die and activation of inflammatory pathways in glial cells escalates. ECSIT (evolutionarily conserved signaling intermediate in Toll pathways) may play roles in modifying (amplifying or suppressing) the oxidative, inflammatory and metabolic alterations believed to be intimately involved in the demise of neurons in AD. The functions

and potential pathogenic roles of ECSIT in neurons, glia (microglia and astrocytes) and neural stem cells remain to be determined.