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Research Highlight

The Achilles heel of γ-secretase: can we contain Alzheimer's disease by reducing synthesis of β-amyloid?

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Alzheimer's disease is the ultimate scourge of mankind that haunts the ageing population and increasingly becomes the major health and social problem faced by our society. Alzheimer's disease (AD), described by Alois Alzheimer[1] as *dementia praecox* (and named Alzheimer's disease by Emil Kraepelin several years later[2]), is a severe neurodegenerative pathology associated with specific histopathological markers represented by focal extracellular deposits of fibrillar β-amyloid (also called neuritic or senile plaques) in the parenchyma of the brain and in the walls of blood vessels, and intraneuronal accumulation of neurofibrillary tangles that are composed of abnormal hyperphosphorylated tau filaments[3].

Abnormal formation and accumulation of β-amyloid is generally considered as a key pathological event in the progression of AD[4]. The β-amyloid is a small (~4 KD) poorly soluble protein that forms the fibrillar component of senile plaques. Synthesis of β-amyloid protein is catalysed by an ubiquitous multi-subunit protease γ-secretase, which has many substrates including amyloid precursor protein (APP). In a recent issue of *Nature* Paul Greengard's group[5] reported the discovery of a protein that regulates the activity of γ-secretase. This protein, named γ-secretase activating protein (GSAP) acts as a specific and potent activator of γ-secretase. Inhibition of GSAP synthesis (with siRNA) in the cell line overexpressing APP695 decreased production of all β-amyloid variants by ~50%. Conversely, addition of recombinant GSAP to membranes isolated from HEK293 cells overexpressing γ-secreatse increases synthesis of β-amyloid. Even more striking, the paper in *Nature* has demonstrated that conditional knockout of GSAP in a transgenic mouse model of AD (double transgenic mice that express APP_{swe} and PS1ΔE9 mutations) reduced β-amyloid production and plaque load by ~40% when compared to the controls.

GSAP is the very first natural regulator of γ-secretase detected in living tissues; it can be considered therefore as an ideal therapeutic target. Incidentally, the pharmacological agent that inhibits GSAP has already been synthesized; this agent is the anti-cancer drug imatinib (also known as STI571 or Gleevec), which has been previously shown (by the same group[6]) to inhibit γ-secretase activity. The biotinylated derivative of imatinib was used to isolate GSAP. This drug unfortunately cannot penetrate the brain-blood barrier, and therefore cannot be used in AD treatment; nonetheless specific search for a GSAP inhibitor that can reach the brain parenchyma could produce a successful drug that reduces β-amyloid load in the diseased brain.

Can such a drug (or any other agent preventing synthesis and accumulation of β-amyloid) cure or prevent the Alzheimer's disease? The fundamental question of whether β-amyloid represents the cause of AD or whether it accumulates as a result of the disease remains open. Indeed the cognitive deficits precede the histopathology by at least a decade, and numerous investigations have failed to detect a direct correlation between β-amyloid load or plaque density and cognitive deficit[4]. Furthermore, the initial stages of AD are primarily driven by synaptic failure, synaptic loss and imbalance of neurotransmitters, rather than by neuronal cell death[7–9]. The mechanism of synaptic failure in neurodegeneration remains virtually unknown and may include multiple pathways. In particular, synaptic strength and synaptic maintenance can be influenced by the neuroglia that structure the brain parenchyma, form the neuronal-vascular unit and provide a physical and functional cover for the majority of synapses in the CNS. Experiments on a triple-transgenic model of AD (mice expressing APP_{swe}, PS1M146V and tauP301L; and thus developing both senile plaques and intraneuronal tangles[10, 11]) identified early astroglial atrophy[12, 13]. This atrophy of astrocytes can cause reduced synaptic cover-

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age, which, in turn, may result in both impaired synaptic transmission and loss of synapses. In addition, the neurodegenerative process is associated with mobilization and partial activation of microglia, which can further contribute to synaptic removal and hence affect synaptic transmission[14, 15].

The fundamental problem of understanding the etiology and pathogenesis of Alzheimer's disease is still open. Similarly open is the choice of the best therapeutic strategy. These two problems are in fact inseparable because identifying the molecular markers that are associated with early pathological changes allows diagnosis at the pre-symptomatic stage and thus the employment of various agents (hopefully including GSAP inhibitors) to keep the disease at bay.

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