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DECISIVE ROLE OF REELIN SIGNALING DURING EARLY STAGES OF ALZHEIMER'S DISEASE

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Abstract—Alzheimer's disease (AD) is one of the largest unmet medical concerns of our society. Around 25 million patients worldwide together with their families are still waiting for an effective treatment. We have recently initiated a re-evaluation of our knowledge of the molecular and cellular mechanisms underlying sporadic AD. Based on the existing literature, we have proposed a mechanistic explanation of how the late-onset form of the disease may evolve on the cellular level. Here, we expand this hypothesis by addressing the pathophysiological changes underlying the early and almost invariant appearance of the neurofibrillary tangles, the only reliable correlate of the cognitive status, in distinct brain areas and their consistent ''spread'' along interconnected neurons as the disease advances. In this review we present and discuss novel evidence that the extracellular signaling protein Reelin, expressed along the olfactory and limbic pathways in the adult brain, might hold a key to understand the earliest steps of the disease, highlighting the olfactory pathway as the brain's Achilles heel involved in the initiation of the pathophysiological characteristic of late-onset AD.

Key words: Reelin, aging, olfactory–limbic system, neuroinflammation, axonal degeneration, Alzheimer's disease.

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Abbreviations: Aβ, amyloid beta; AD, Alzheimer's disease; AON, anterior olfactory nucleus; ApoER2, apolipoprotein E receptor 2; APP, amyloid precursor protein; Dab-1, Disabled-1; GWA, genome-wide association; LTP, long term potentiation; MCI, mild cognitive impairment; NFTs, neurofibrillary tangles; NTs, neuropil threads; PI3K, phosphatidylinositol-3-kinase; PHFs, paired helical filaments; PS1, presenilin-1; SFKs, SRC family tyrosine kinases; SNPs, single-nucleotide polymorphisms; VLDLR, the very low density lipoprotein receptor.

INTRODUCTION

Alzheimer's disease (AD), a severe neurodegenerative condition with progressive cognitive decline, is characterized by the presence of two neuropathological hallmarks, neurofibrillary tangles (NFTs) and senile plaques (Castellani et al., 2010). The disease presents itself in two variants: (i) the familial form, accounting for a small percentage of all AD patients, that is induced by dominant mutations in the amyloid precursor protein (APP), presenilin-1 (PS1) or PS2 genes, and (ii) the aging-associated sporadic or late-onset form that is characterized by the early presence of inflammatory mediators both in plasma and in the brain (Holmes et al., 2009; Eikelenboom et al., 2011). Importantly, a major risk factor for both forms of the disease is the inheritance of the ApoE ε4 allele (Genin et al., 2011).

Despite the fact that AD imposes an enormous burden to the society and the health-care system, accounting for approximately 200 billion dollars of direct medical costs per year in the USA only (Association, 2012), a promising treatment is not yet at the horizon. We argued, recently, that a thorough re-examination of our knowledge of the pathophysiological characteristic of late-onset AD is a prerequisite for developing successful new therapies and presented evidence that sporadic AD develops as a consequence of chronic inflammatory conditions and associated cellular stress-induced axonopathy (Krstic and Knuesel, 2013). This model emphasizes that the amyloid-β plaques develop as a consequence of cytoskeletal impairments in the axons of the tangle-bearing neurons. However, in our model we have not addressed the striking observation that the formation of NFTs in AD brains appears to follow a very robust and consistent pattern along the olfactory and limbic pathways (Braak and Braak, 1991; Price and Morris, 1999).

To illuminate a molecular basis for this almost invariant NFT ''spread'' in AD, we first reviewed the existing data on neuropathological changes and the vulnerability of the olfactory–limbic system, including the peripheral olfactory epithelium, early in the course of

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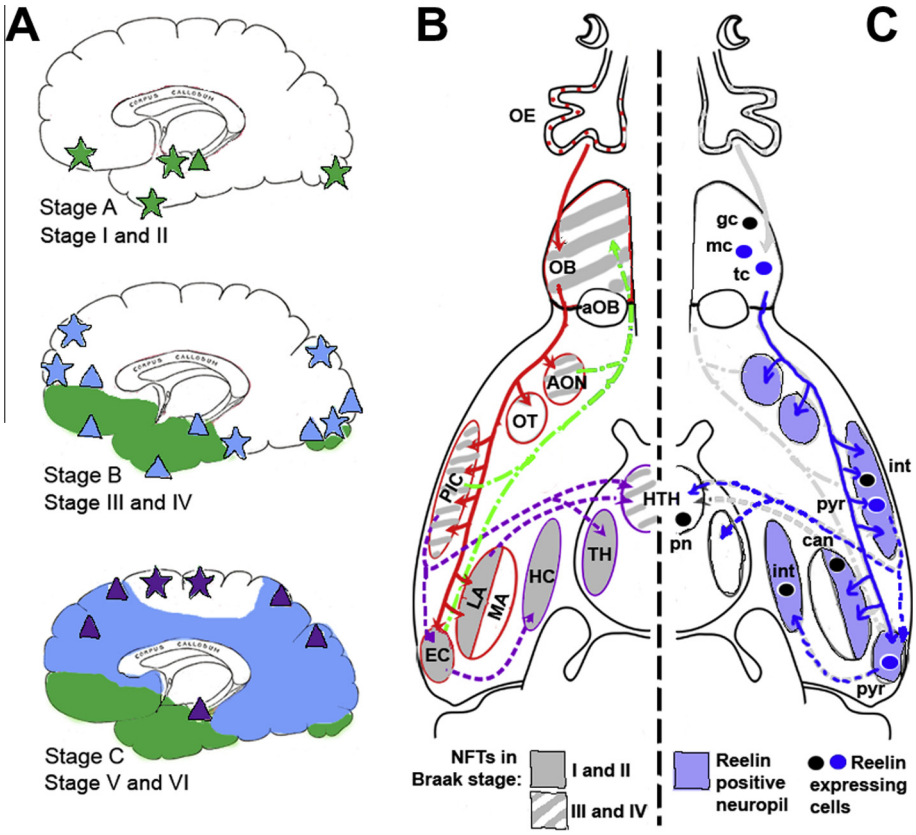

Fig. 1. Reelin is expressed along the pathways affected by NFTs in early AD. (A) Schematic drawing of a human brain showing the appearance of senile plaques (stars) and neurofibrillary tangles (NFT, triangles) in various stages of AD (Braak stages A–C/I–VI). Blue and green areas depict the areas affected by the pathology in the preceding stage (as indicated with the colored star and triangles). (B) Olfactory and limbic pathways are the first to be affected by the NFT pathology in AD. Schematic drawing of a rat brain showing olfactory/limbic connections is adapted from Canavan et al. (2011). *Abbreviations:* OE, olfactory epithelium; OB, olfactory bulb; aOB, accessory olfactory bulb; AON, anterior olfactory nucleus; OT, olfactory tubercle; PIC, piriform cortex; EC, entorhinal cortex; LA/MA, lateral/medial amygdala; HC, hippocampus; HTH, hypothalamus; TH, thalamus. Areas affected with NFT pathology in early Braak stages I and II (gray) and later Braak stages III and IV (striped). (C) Reelin expression along the olfactory and limbic pathways. *Abbreviations:* gc, granule cells; mc, mitral cells; tc, tufted cells; pyr, pyramidal neurons; int, GABAergic interneurons; can, corticomedial amygdaloid nuclei; pn, paraventricular nuclei. Reelin immunoreactivity in the neuropil (blue areas).

the disease. This is then followed by the integration of recent experimental findings addressing the role of the extracellular signaling protein Reelin that is selectively expressed along the affected circuits and is shown to be a potent suppressor of Tau phosphorylation (Herz and Chen, 2006; Knuesel, 2010). Moreover, the decline in Reelin expression is not only strongly affected by aging and chronic inflammatory conditions in animals (Knuesel et al., 2009), but also constitutes a very early phenomenon of AD pathophysiology in humans (Herring et al., 2012a). Based on the presented evidence we propose that reduction of Reelin-mediated signaling in the olfactory and limbic system accelerates and aggravates the age-associated hyperphosphorylation of Tau (Braak et al., 2011). This in turn is expected to profoundly impair cytoskeletal stability and axonal integrity and would facilitate the formation of NFTs and senile plaques in affected neurons, thereby tipping the balance from healthy to pathological aging and cognitive deterioration (Krstic and Knuesel, 2013). This view also strongly supports the hypothesis of a pivotal role of olfactory bulb-associated neuroinflammation (Calderon-Garciduenas et al., 2008; Majde, 2010) in the initiation of the late-onset AD.

OLFACTORY–LIMBIC PATHWAYS AND AD

In contrast to amyloid-β deposition that does not allow the formulation of a coherent distribution scheme (Braak and Braak, 1991) or a correlation to the cognitive state of the affected individuals (Bierer et al., 1995; Nelson et al., 2012), NFT formation shows a distinct propagation pattern with the disease progression (Braak and Braak, 1991; Price and Morris, 1999) and correlates well with the cognitive deterioration (Bierer et al., 1995; Nelson et al., 2012). As highlighted by Braak and Braak, the olfactory and limbic pathways of the allocortex are among the first affected brain areas in AD (Fig. 1A, B): Braak stage I is characterized by NFT formation in the transentorhinal cortex, in layer I of the entorhinal cortex, as well as in the antero-dorsal nucleus of the thalamus. Braak stage II includes the presence of NFTs in the deeper layer V of the entorhinal cortex, the CA1 of the hippocampus, and in the amygdala and its projection area – the basal magnocellular complex. Braak stages III–VI are characterized by the accumulation of NFTs in association areas of the isocortex and the aggravation of the pathology in all areas already affected.