Journal Club

Editor's Note: These short, critical reviews of recent papers in the Journal, written exclusively by graduate students or postdoctoral fellows, are intended to summarize the important findings of the paper and provide additional insight and commentary. For more information on the format and purpose of the Journal Club, please see http://www.jneurosci.org/misc/ifa_features.shtml.

Alzheimer's Disease Affects Progenitor Cells through Aberrant β-Catenin Signaling

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Review of He and Shen

In the adult mammalian brain, neural stem cells in the subventricular zone (SVZ) of the lateral ventricle and the subgranular zone (SGZ) of the hippocampal dentate gyrus generate new functional neurons throughout adulthood. These new neurons contribute to network plasticity and may replace degenerating neurons in the circuit (Zhao et al., 2008). Interestingly, neural progenitor cells have also been isolated from a variety of adult brain regions such as the cortex, the substantia nigra, and the striatum (Lie et al., 2004). Given the potential of these progenitor cells to generate new neurons *in vitro*, many investigators have begun to explore the potential use of these progenitor cells for the repair of circuits damaged by traumatic injury or neurodegenerative disease, such as stroke, Parkinson's disease, and Alzheimer's disease (AD) (Lie et al., 2004).

AD, the most common cause of dementia in elderly people, is a progressive and irreversible neurodegenerative disorder characterized by neuronal loss in the hippocampus, in the entorhinal cortex, and in the association neocortex which underlies severe learning and memory deficit (Schaeffer et al., 2009). Characteristic of AD are abnormal intracellular protein aggregates called intraneuronal neurofibrillary tangles, which are composed of hyperphosphorylated forms of the microtubule-associated protein tau, and extracellular protein deposits of initially soluble 40-42-aa amyloid-β (Aβ) peptides derived from amyloid precursor protein (APP) (Geschwind, 2003). Production of $A\beta_{42}$, which is more subject to aggregation, is considered the "event" in AD pathology (Hardy and Selkoe, 2002).

In the May 20, 2009 issue of *The Journal of Neuroscience*, He and Shen (2009) compared the neurogenic potential of $NG2^+$ glial progenitor cells (GPCs) isolated from the cortex of AD patients with that of cells from healthy controls. They observed that GPCs from AD patients and their progeny produced and released more $A\beta_{40}$ and $A\beta_{42}$. Moreover, AD GPCs generated drastically fewer new neurons. Also, the expression of proneural basic helix-loop-helix (bHLH) transcription factors neurogenin 2 (Ngn2), mammalian achaete scute homolog 1 (Mash1), and neurogenic differentiation factor 1 (Neuro D1) was significantly decreased. In contrast, increased differentiation into astrocytes was observed, suggesting that GPCs from AD brains are more likely to differentiate into astrocytes than into neurons.

Transplantation as well as coculture experiments has provided strong evidence that the fate choice of neural progenitor cells (NPCs) in the adult brain is controlled by interaction of NPCs with the environment. In the dentate gyrus, astrocyte-induced Wnt/β-catenin signaling promotes the generation of new neurons through induction of neuronal fate commitment and proliferation of neuroblasts (Lie et al., 2005). The rate-limiting step in canonical Wnt signaling is the stabilization of β-catenin. In the absence of Wnt, β-catenin is phosphorylated by glycogen synthase kinase (GSK)-3β and is targeted for degradation by ubiquitination-dependent proteolysis (Logan and Nusse, 2004). Wnt signaling inhibits GSK-3β activity and so increases the amount of β-catenin, which enters the nucleus and associates with T-cell factor/lymphoid enhancer binding factor (TCF/LEF) transcription factors, leading to the transcription of Wnt target genes (Logan and Nusse, 2004).

He and Shen (2009) did not observe a significant difference in the expression levels of Wnt3 or frizzled (a Wnt receptor) between AD and control GPCs. However, they found a decrease in nonphosphorylated β-catenin, whereas phosphorylated β-catenin and GSK-3β were increased. Importantly, retroviral overexpression of β-catenin was sufficient to rescue the defect in neuronal differentiation of GPCs from AD brains, suggesting the presence of a factor that

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disrupts proper β-catenin function in these cells.

How Aβ inhibits Wnt/β-catenin signaling and proneural transcription factor expression was not explored in this study. But previous studies have shown that Aβ can bind to several members of the frizzled receptor family, acting as an antagonist of Wnts (Magdesian et al., 2008), and that Aβ can lead to upregulation of the Wnt/β-catenin signaling inhibitor Dickkopf1 (Krupnik et al., 1999). Such interference at the level of the frizzled receptor and the subsequent reduction of the downstream effector β-catenin could lead to downregulation of proneural bHLH factors, which are direct targets of Wnt/β-catenin signaling during cortical development (Hirabayashi et al., 2004).

Another potential mechanism, whose contribution to suppression of neurogenesis was not explored in the study, is the activation of gliogenic pathways such as Notch and JAK/STAT signaling (Sugaya, 2008). It was previously shown that human NPCs exposed to high concentrations of secreted APP differentiated into astrocytes rather than into neurons. *In vivo*, human NPCs transplanted into the brain of APP transgenic mice preferentially differentiated into glia (Kwak et al., 2006), indicating that under physiological conditions APP plays a role in neural stem biology, probably by inducing STAT3 phosphorylation and JAK1 gene expression (Sugaya, 2008). APP was also shown to increase generation of Notch intracellular domain and expression of Hes1, a mechanism which may work in concert with the JAK/STAT pathway to push differentiation of human NPCs toward glia (Sugaya, 2008).

One striking observation by He and Shen (2009) that needs further investigation is that 2 d of treatment of GPCs with $A\beta_{1\text{-}42}$ led to reduced expression of proneural transcription factors and to increased expression of GSK-3β and in the amounts of phosphorylated β-catenin even 14 d after Aβ treatment. Because several studies indicate that the intracellular domain of APP can act as a transcriptional regulator interacting with the histone acetyltransferase Tip60 (Cao and Südhof, 2004), one interesting hypothesis is that Aβ mediates changes in gene transcription through long-lasting histone modifications in GPCs.

A general concern with the study by He and Shen (2009) is the focus on the $NG2^+$ population. Buffo and colleagues have described that the neurosphere-forming capability and the neurogenic potential following cortical injury are largely confined to the glial fibrillary acidic protein-positive ($GFAP^+$) astrocyte population and does not extend to the $NG2^+$ population (Buffo et al., 2008). It will be important to examine whether the Aβ-induced inhibition of Wnt signaling and neurogenesis also holds true for the $GFAP^+$ cells, especially given the evidence that $GFAP^+$ astrocytes constitute the neural stem cell population in the SVZ and the SGZ (Zhu and Dahlström, 2007) and the observation that $GFAP^+$ astrocytes have the potential to generate functional neurons upon expression of proneural transcription factors (Berninger et al. 2007).

The clinical relevance of the findings from He and Shen (2009) for understanding AD pathology remains to be determined. Indeed, the generation of new neurons in regions of the adult mammalian brain other than the DG and the SVZ/olfactory bulb system remains a matter of debate. Gould and colleagues described that in primates new neurons are added to the prefrontal, inferior temporal, and posterior parietal cortex (Gould et al., 1999); in contrast, Kornack and Rakic found evidence for cell proliferation but not for neurogenesis in the primate cortex (Kornack and Rakic, 2001). Even though $NG2^+$ GPCs, i.e., the cells studied by He and Shen (2009), self-renew and differentiate into neurons after exposure to stress conditions (Arsenijevic et al., 2001), retrospective birth-dating of cells in the human brain has not revealed any evidence for the production of new neurons in the cortex during adulthood (Spalding et al., 2005; Bhardwaj et al., 2006) arguing strongly against the possibility that inhibition of constitutive neurogenesis from precursor cells in the human cortex contributes to AD pathology. Moreover, the failure of endogenous NPCs to generate significant numbers of functional neurons in response to different lesion paradigms (Magavi et al., 2000; Arvidsson et al., 2002; Buffo et al. 2005, 2008; Winner et al., 2008) indicates that extrinsic signals and progenitor cell-intrinsic mechanisms which are not specific to AD prevent neuronal cell replacement in disease conditions.

Despite these caveats, the study by He and Shen (2009) provides a glimpse at the possible impact of AD on stem cells in the human brain and may have further implications related to the impact of AD on adult hippocampal neurogenesis and neurogenesis-dependent learning and memory formation. What if Aβ affects Wnt/β-catenin signaling in stem cells of the dentate gyrus in a manner similar to the progenitor cells in the cortex? Will such impairment lead to decreased neurogenesis and consequently affect hippocampal function? Indeed, the triple transgenic (APP, presenillin-1, and tau) mouse showed a marked reduction in the number of newborn neurons in the DG, suggesting degenerative effects of the mutated proteins on neural precursor cells. The reduction in hippocampal neurogenesis in this mouse is directly associated with the increasing number of Aβ-containing neurons in the hippocampus (Rodríguez et al., 2008). A seemingly puzzling finding is the increase in the number of doublecortin (DCX)-positive immature neurons in the dentate gyrus of AD patients (Jin et al. 2004), which has been interpreted as a compensatory increase in neurogenesis in response to AD-induced neuronal cell loss. However, an alternative explanation for the increased DCX population is that new neurons in the DG are stalled in an immature state and do not mature into functional neurons. Intriguingly, loss of β-catenin impairs dendritic development of newborn neurons in the adult hippocampus, indicating that β-catenin fulfills an important function in neuronal maturation during adult neurogenesis and suggesting that decreased levels of β-catenin in AD may affect hippocampal neurogenesis through impairment of neuronal maturation (He and Shen, 2009). The present study should therefore be extended to the stem cell population in the adult hippocampus to gain further insight into the impact of AD on Wnt/β-catenin signaling in the human hippocampal stem cell niche, neurogenesis, and neurogenesis-dependent hippocampal function.

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