Adult Neurogenesis Is Altered by GABAergic Imbalance in Models of Alzheimer's Disease

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Early stages of Alzheimer's disease (AD) affect hippocampal function. In this issue of *Cell Stem Cell*, Li et al. (2009) and Sun et al. (2009) propose abnormal GABA signaling as a trigger for impaired network plasticity in the AD hippocampus.

The mammalian brain is one of the most complex structures in biology, and it possesses a remarkable capacity to adapt to a constantly changing environment and store a vast number of memories that can last a lifetime. Neuronal circuits are continuously modified by neuromodulators, activity-dependent modifications that strengthen or weaken synaptic transmission, and synapse formation and elimination. In addition, the entire brain contains neural stem cells with neurogenic potential, although only the hippocampus and olfactory bulb have demonstrated the potential to serve as niches that can support adult neurogenesis. Adult-born neurons develop for several weeks before integrating into the existing neural network, acquiring the capability to process information, and to play a critical role in hippocampal functions such as learning and memory (Zhao et al., 2008). GABAergic axons establish synaptic contacts onto newly formed neurons well before glutamatergic synapses form (Espósito et al., 2005). Early signaling by GABA plays a critical role in the proper development of adult-born neurons (Ge et al., 2006).

In the aging brain the capacity for synaptic modification and circuit remodeling decreases, neurogenesis is greatly reduced, and cognitive functions and memory decline (Burke and Barnes, 2006). These changes are associated with an increased risk of neurodegenerative disease: a person who lives more than 80 years has a very high probability of suffering Alzheimer's disease (AD), a high-incidence disorder characterized by cognitive impairment, memory loss, dementia, and death. During the late stages of the disorder, an AD brain displays amyloid plaques, a reduced number of synapses, neurofibrillary tangles formed by hyperphosphorylated tau, and massive neuronal death. The onset of AD pathology is most frequently observed in the hippocampus, yet the mechanisms underlying the early pathogenesis of the disease remain unclear. Conditions that alter adult hippocampal neurogenesis can also affect learning and memory performance. Therefore, impaired adult neurogenesis might contribute to the overall cognitive dysfunction observed in aging and diseased brains, particularly in AD. Genetic factors that contribute to AD have been investigated over the last several decades. Mutations in the gene encoding the amyloid precursor protein (APP) cause an increased production of the amyloid β peptide (Aβ). Aβ is the main component of amyloid plaques and may play a major role in an autosomal-dominant form of familial AD (FAD) (Laferla and Oddo, 2005). In addition, the apolipoprotein E4 (apoE4) haplotype has been identified as a genetic risk factor for a sporadic form of AD (Kim et al., 2009). The papers by Li et al. (2009) and Sun et al. (2009) published in this issue of *Cell Stem Cell* establish a link between AD and adult neurogenesis through a pathway that involves an imbalance in GABA, the major inhibitory neurotransmitter in the mammalian brain.

ApoE is an important player in lipid homeostasis, in that it serves as a ligand in receptor-mediated endocytosis of lipoprotein particles. It is present in several organs including the brain, where it is primarily expressed by glial cells. To investigate the connection between adult hippocampal neurogenesis and AD, Li et al. studied the differentiation and development of adult-born neurons in multiple mouse models of apoE dysfunction. ApoE was found to be expressed in adult neural progenitor cells. In the apoE knockout (KO) mouse, neurogenesis was reduced while the number of neural progenitor cells acquiring a glial fate was increased. ApoE KO mice are also known to exhibit cardiovascular and metabolic defects that might contribute to brain pathology (Wang, 2005). Approaches for conditional inactivation in the adult hippocampus or cell-specific replacement of apoE in neural progenitor cells would assist in revealing the mechanisms underlying these findings. To tackle this question, Li et al. cultured neural stem cells from apoE KO mice and found reduced levels of noggin that lead to increased gliogenesis, consistent with the in vivo results. This effect was reverted by exogenous recombinant noggin, highlighting a cell-autonomous pathway that links apoE with bone morphogenetic protein (BMP) in adult neurogenesis.

The human apoE4 haplotype has been clearly linked to AD, whereas expression of apoE2 and apoE3 does not appear to correlate with disease. To investigate whether this difference in pathogenesis is relevant for adult neurogenesis, the authors compared apoE3 and apoE4 by using targeted replacement knockin (KI) mice. ApoE3 expression restored normal levels of neurogenesis and gliogenesis to apoE-deficient mice (Li et al., 2009). ApoE4 also restored wild-type levels of gliogenesis but, in contrast, it reduced neurogenesis. In addition, neurons developing in apoE4 KI mice displayed a mild delay in neuronal maturation, reflected by impairment in dendritic length and

complexity, increased membrane resistance, and diminished GABAergic connectivity. ApoE4 mice also exhibited a global reduction in the number of GABAergic interneurons and GABAergic synapses, while ApoE KO and apoE3 KI were both normal. Interestingly, increasing GABA neurotransmission with pentobarbital, a $GABA_A$ receptor potentiator, restored neuronal maturation. Additional in vitro experiments showed that apoE4 can increase phosphorylation of the microtubule-associated protein tau, leading to GABAergic interneuron death; hyperphosphorylated tau forms neurofibrillary tangles in brains from AD patients. Therefore, impairment of adult neurogenesis is specific for the apoE4 haplotype and it is mediated by an imbalance in the network of GABAergic interneurons, rather than a cell-autonomous effect. Whether abnormal neurogenesis has an impact in cognitive performance in this AD model would require further investigation.

In their independent analysis, Sun and colleagues investigate how newborn granule cells develop in the hippocampus of J20 transgenic mice, which express a variant of the human APP that harbors mutations associated with FAD, and produce higher levels of Aβ because of enhanced cleavage of APP by the beta and gamma secretases. The J20 mouse displays a significant degree of hyperexcitability (nonconvulsive seizures) and a compensatory enhanced synaptic inhibition (Palop et al., 2007) that makes it a suitable model to investigate the role of neural activity on adult hippocampal neurogenesis. Newly generated granule cells in the J20 mouse were distinctly affected depending on their developmental stage. Young neurons (18–21 days) displayed accelerated differentiation characterized by altered GABA signaling, longer dendrites, higher spine density, and stronger synaptic inputs when compared to age-matched controls. In contrast, older neurons (>28 days) exhibited an age-dependent dystrophic phenotype characterized by a sharp decrease in anatomical and functional complexity. The aberrant morphology was less pronounced when developing neurons were exposed to a $GABA_A$ receptor antagonist. These observations are in agreement with previous findings that neuronal development in the adult hippocampus is highly sensitive to the activity of surrounding networks and, in particular, to GABA signaling (Ge et al., 2006; Overstreet-Wadiche et al., 2006). The contribution of Aβ production to aberrant neuronal development might be complemented in a mouse model where aberrant network activity is minimal or absent.

Although both new manuscripts are focused on GABA, transgenic mice used in these studies display a range of global alterations that might also contribute to the impaired neurogenesis phenotypes, such as an altered neurogenic niche. In fact, proliferation, differentiation, and maturation of adult neural stem cells are very sensitive to homeostatic imbalance. In general, transgenic mice display several limitations for modeling human disease and therefore findings would require validation with alternative models of AD as well as other neurodegenerative disorders. Yet, it is remarkable that the new studies both converge in the identification of GABA imbalance as an early abnormality affecting adult-born neurons, despite having utilized distinct mouse models. If GABA was indeed implicated in early neurodegeneration, simple pharmacological manipulations might be utilized to delay cognitive decline. In fact, very potent and specific drugs targeting GABA receptors are already available for clinical use.

The role of neural stem cells and adult neurogenesis in the healthy and diseased brain are currently the subjects of intensive experimentation and debate. Altered adult neurogenesis might contribute to brain dysfunction by causing a decline in circuit plasticity over time. It is very well established in animal models that adult neurogenesis decreases sharply with age. Is this finding representative of what occurs in the human brain? Addressing this question with thorough studies combining animal models and clinical research will be crucial to determine the precise role of adult neurogenesis in AD and other neurodegenerative diseases. Loss of neurogenesis may contribute to the dysfunction observed in the diseased aging brain, but probably only if significant levels of neurogenesis are present in healthy aging brains—which has yet to be clearly determined. However, endogenous or artificially induced differentiation of neural stem cells could mitigate ongoing degeneration by contributing new functional neurons under situations of stress or injury. Understanding the behavior and potential of neural stem cells under physiological and pathological conditions will be demanded for understanding neurodegeneration and for future repair therapies, which require that differentiation and integration of endogenous or grafted neuronal progenitors occurs in a manner that is both safe and functionally relevant.

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