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Adult neurogenesis as a cellular model to study schizophrenia

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Psychiatric diseases with complex traits, such as schizophrenia, pose a unique challenge to the identification of etiological factors and critical loci for clinical intervention. Genetic susceptibility factors may work in concert with environmental insult to disrupt neuronal network formation and brain function, leading to disease manifestation. While the fundamental mechanisms underlying the action of genetic risk factors on neural functions remain largely unknown, a longstanding hypothesis of the pathogenesis of schizophrenia holds that disrupted neurodevelopmental processes causally precede the onset of cognitive symptoms in late adolescence and early adulthood.[1] Recent advances in genome-wide analysis have identified a large number of susceptibility genes for schizophrenia and other major mental illnesses.[2] Currently, a major challenge is to understand the role of these genes in neural development and how they contribute to pathogenesis of these mental disorders.

It is well established now that there is continuous neurogenesis from neural stem cells in discrete regions of the adult mammalian brains, including humans.[3,4] Adult hippocampal neurogenesis confers several unique advantages as a cellular model to understand signaling pathways involved in the etiology of mental disorders. First, adult neurogenesis recapitulates the complete process of neuronal development, from proliferation and fate specification of neural progenitors, to migration, axon/dendritic development, and synapse formation and maturation of newborn neurons[5] (**Fig. 1**). Under normal conditions, adult mammalian neurogenesis occurs primarily in two regions of the central nervous system—the olfactory bulb and the dentate gyrus of the hippocampus, thereby providing an anatomically constrained neurogenic environment.[3] Second, every critical milestone of early development recurs during the postnatal process but, importantly, the time course of these events is significantly prolonged.[5] This temporal expansion in combination with spatial restriction facilitates high resolution analysis of each developmental stage and its associated molecular components. Third, adult neurogenesis is dynamically regulated by many physiological, pathological and pharmacological stimuli.[3] Thus, the system allows examination of interactions between genes and environment. Finally, technical advancement permits the engineering of novel transgenic mice at a system level or retrovirus-mediated genetic manipulation at a "single-cell" level to reversibly regulate genes and proteins of interest in specific neuronal and stem cell populations. All of these factors support the viability of using adult neurogenesis to explore how regulatory control of susceptibility genes contributes to the pathology underlying psychiatric disorders. The best example is the study of molecular and cellular mechanisms involving schizophrenia susceptibility genes, which regulate both embryonic and postnatal neurogenesis.[6]

One such gene is Disrupted-in Schizophrenia 1 (DISC1), which was originally identified at the breakpoint of a balanced (1;11) chromosomal translocation and co-segregates with schizophrenia and mood disorders in a large Scottish family.[7] At least three key pathways, including NDEL 1,[8,9] GSK-3β[10] and AKT-mTOR,[11] have since been identified related to neurodevelopmental deficits arising from altered expression of this gene (**Fig. 1**). Disruption of DISC1 function in the adult hippocampus has been shown to dysregulate neurogenesis in the dentate gyrus, resulting in hypertrophy of cellular somas and processes, aberrant neuronal positioning and precocious maturation of pre- and post synaptic integration of newborn neurons.[8,12] Mechanistic studies suggest that DISC1 exerts an influence on the proliferation of adult neural progenitors through inhibition of GSK-3β.[10] On the other hand, DISC1 regulates development of adult born neurons by modulating AKT signaling through a direct interaction with KIAA1212.[11] AKT is a central mediator of intracellular pathways including initiation of protein synthesis and diverse neuronal developmental processes. It is suppressed by PTEN activation, a lipid phosphatase that appears functionally convergent with DISC1, in that blocking the expression of either PTEN or DISC1 can lead to a phenotypically similar effect on neurogenesis.[11] Critically, pharmacological inhibition of mTOR, a downstream effector of the AKT pathway, prevented the defects in neuronal morphogenesis and dendritic development from DISC1 suppression during adult neurogenesis. DISC1 has also been shown to interact with NDEL1 to synergistically regulate neuronal positioning during adult neurogenesis,[8] which is consistent with a reported epistasis between DISC1 and NDEL1 for the risk of schizophrenia in patients.[13] Given the large number of potential DISC1 interactors,[14] identifying the key effector pathways of DISC1 on different aspects of neuronal development in both the embryonic and adult brain

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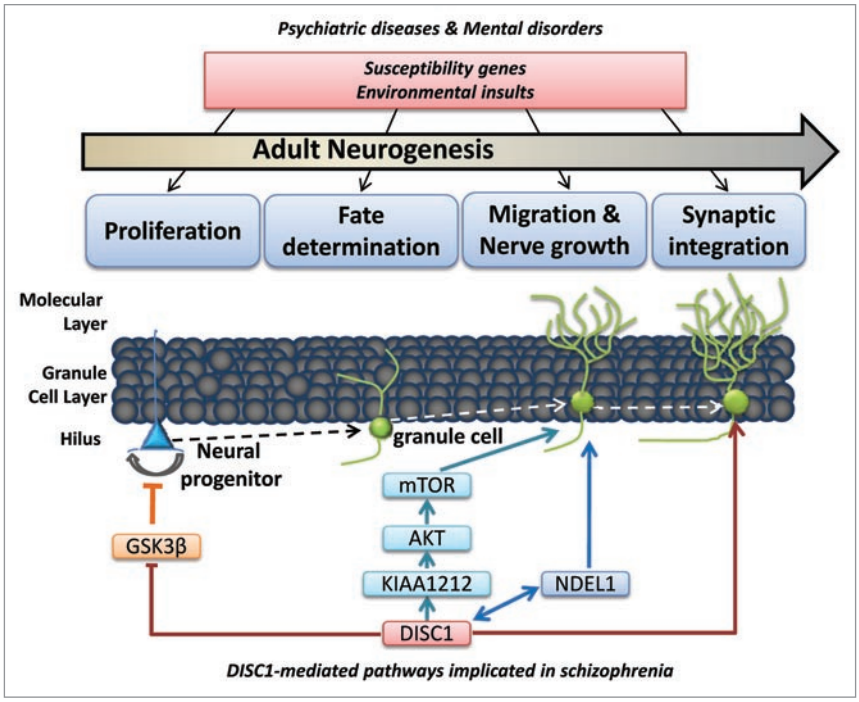

Figure 1. A simplified schematic diagram illustrating developmental stages of adult neurogenesis and DISC1-related pathways in regulating different aspects of adult neurogenesis.

should reveal novel targets for therapeutic intervention.

As a cellular model system, adult neurogenesis can be effectively used to explore developmental mechanisms that contribute to psychiatric diseases. Moreover, accumulating data suggest an interaction between adult neurogenesis and mood and anxiety disorders as well as addictive behaviors.[15] Levels of adult neurogenesis are also inversely correlated with acute and chronic stress, factors that have been implicated in triggering disease onset in adulthood.[16] And, remarkably, there are suggestive data on the necessity of intact neurogenesis to mediate the behavioral effects of antidepressants.[17] Interestingly, a decrease in cell proliferation within dentate gyus[18] and reduced volume of the olfactory bulb and hippocampus[19,20] have been reported in some schizophrenic patients. These studies suggest that adult neurogenesis itself may play a role in psychiatric symptomatology. Therefore, exploiting this cellular model to understand not only the molecular basis of neuronal development but also the factors regulating the postnatal neurogenic environment can lead to additional insights into disease etiology. Much work remains to be done, but the promise of this model to further our understanding of neurodevelopmental risk factors in order to treat and potentially prevent some of the most debilitating psychiatric illnesses is clear.

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