Adult neural stem cells and schizophrenia

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Abstract

Schizophrenia (SCZ) is a devastating and complicated mental disorder accompanied by variable positive and negative symptoms and cognitive deficits. Although many genetic risk factors have been identified, SCZ is also considered as a neurodevelopmental disorder. Elucidation of the pathogenesis and the development of treatment is challenging because complex interactions occur between these genetic risk factors and environment in essential neurodevelopmental processes. Adult neural stem cells share a lot of similarities with embryonic neural stem cells and provide a promising model for studying neuronal development in adulthood. These adult neural stem cells also play an important role in cognitive functions including temporal and spatial memory encoding and context discrimination, which have been shown to be closely linked with many psychiatric disorders, such as SCZ. Here in this review, we focus on the SCZ risk genes and the key components in related signaling pathways in adult hippocampal neural stem cells and summarize their roles in adult neurogenesis and animal behaviors. We hope that this would be helpful for the understanding of the contribution of dysregulated adult neural stem cells in the pathogenesis of SCZ and for the identification of potential therapeutic targets, which could facilitate the development of novel medication and treatment.

Key Words: Neural stem cells; Adult hippocampal neurogenesis; Schizophrenia; Risk genes; Signaling pathways; Behavior

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Core Tip: This review focuses on the role of schizophrenia risk genes and related signaling pathways in adult hippocampal neurogenesis, which has been shown to play an essential role in many psychiatric disorders. We summarize the outcome of adult neural stem cells and animal behavior when these risk genes or the key components in related signaling pathways are dysregulated. We hope this will shed light on the elusive pathogenesis of schizophrenia.

INTRODUCTION

Schizophrenia (SCZ) is a devastating brain disorder with a prevalence of 1% worldwide. Patients typically show a subset of positive symptoms including delusions, auditory and visual hallucinations, disorganized speech and thought disorder, negative symptoms including a lack of motivation, interest and emotional blunting, lack of thought and content of speech, and/or cognitive deficits[1-3]. Although SCZ has been extensively investigated in the past few decades, the underlying cellular defects and molecular mechanism of SCZ have not been clearly established. Considerable evidence supports the notion that SCZ is the behavioral outcome of neurodevelopmental disturbance long before the onset of clinical symptoms[4]. However, it is known that neurodevelopment is not confined to the embryonic stages, and is a prolonged process continuing in adults. On the basis that the first psychotic symptoms in most patients occur in late adolescence[3], abnormal adult hippocampal neurogenesis might facilitate the emergence of hippocampal-dependent cognitive and affective deviation.

Adult neurogenesis is a complex and complicated process, which occurs in the subgranular zone (SGZ) of the dentate gyrus (DG) in mammalian brain[5]. Quiescent neural stem cells in the SGZ become activated, proliferate, differentiate, mature into glutamatergic neurons and receive innervations from the entorhinal cortex while projecting axons to the cornu ammonis 3 (CA3) region[6]. The direct evidence that defective adult neurogenesis might be involved in the etiology of SCZ originates from studies on post-mortem samples, in which the number of cells expressing Ki67, the cell proliferation marker, was reduced by 50%-60% in the SGZ[7]. In addition, patients diagnosed with SCZ present with an immature DG with impaired maturation of adult-born neurons[8].

Recently, several risk genes associated with SCZ have been identified through genome-wide association studies (GWAS), some of which are components of important signaling pathways. Given the evidence that numerous genes are implicated in the etiology of SCZ, the disease is currently accepted as a polygenic disorder caused by the complex interplay between genetic and environmental factors[9-11]. In this review, we mainly focus on the roles of some risk genes and key signaling pathways implicated in SCZ, during the process of adult neurogenesis.

SCZ RISK GENES

Disrupted in SCZ 1

Disrupted in SCZ 1 (DISC1), one of the widely-studied risk genes for SCZ, was originally identified in a large Scottish family. A balanced chromosomal translocation t(1;11)(q42.1;q14.3) leads to disruption of the C-terminal region in DISC1 gene, which is co-segregated with mental disorders such as SCZ and depression[12-15]. Suppression of Disc1 expression perturbs neural progenitor proliferation during adult neurogenesis through the glycogen synthase kinase 3β (Gsk-3β)/β-catenin pathway. Furthermore, Gsk-3 inhibitors attenuate progenitor proliferation and behavioral defects caused by Disc1 suppression[16]. Various studies have shown that alteration of Disc1 expression impedes the maturation of newborn neurons including aberrant morphological development, mis-positioning of new DG granule cells, enhanced dendritic outgrowth and defects in axonal targeting[17-20]. In addition, Disc1 works as a scaffold protein and interacts with many signaling effectors to regulate adult neurogenesis. For example, Disc1 directly interacts with Girdin, which regulates the differentiation, maturation, migration, and cytoskeleton organization of adult neural progenitors and inhibits Akt activity[21,22]. Interestingly, the cellular defects and hippocampal-dependent behavioral deficits caused by Disc1 deficiency can be largely rescued by the administration of rapamycin, an inhibitor of mammalian target of rapamycin (mTOR), which is the Akt downstream effector[23]. In addition, an interplay between intrinsic Disc1 and extrinsic γ-amino butyric acid (GABA) signaling also contributes to dendritic growth and synapse formation in immature neurons via the Akt-mTOR pathway[24-26]. Collectively, DISC1 regulates multiple steps of adult neurogenesis through interaction with key effectors of various signaling pathways.

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pathways directly and indirectly.

**Neuregulin-1**

Neuregulin-1 (NRG1) was identified as a risk factor for SCZ more than a decade ago through a genome-wide scan of SCZ families in Iceland, which was later supported by many associated studies[27-29]. NRG1 binds to ErbB2-4, a family of epidermal growth factor-like tyrosine kinases, and defective NRG1/ErbB4 signaling is found in the prefrontal cortex and hippocampus of SCZ patients[30-32]. Moreover, multiple studies have proven that NRG1 is associated with affective behavior and the pathology of SCZ[33-36]. It has been reported that the administration of Nrg1 displays robust antidepressant-like behaviors accompanied by increased ventral DG cell proliferation and neurogenesis in the caudal DG without alteration of neuronal fate[37]. The finding that it interacts with molecules in the glutamatergic synapse implies a role of Nrg1 in adult plasticity[38,39]. These observations suggest that NRG1/ErbB4 signaling might participate in the process of adult neurogenesis.

**Synaptosomal-associated protein, 25 kDa**

Synaptosomal-associated protein, 25 kDa (SNAP-25) is a soluble N-ethylmaleimide-sensitive factor attachment protein receptor protein, which plays a crucial role in modulating synaptic exocytosis[40-42]. Genetic studies and genome-wide meta-analyses have revealed its close association with multiple mental diseases including SCZ[43-46]. Snap-25 mutant mice display histologically and electrophysiologically immature DG neurons, leading to a severe working memory deficit[47]. Interestingly, selective inactivation of Snap-25 in adult neural stem cells results in enhancement in proximal dendritic branching of new-born neurons in the DG and robust efferent mossy fiber output to the CA3 region[48]. So far, the immature DG phenotype and similar schizophrenic-like behaviors have been found in Shnurri-2 knockout[49], Snap-25 mutant[47], and calmodulin-dependent protein kinase II (CaMKII) knockout mice[49]. Importantly, this immature DG phenomenon has also been observed in the post-mortem brains from schizophrenic patients[8,50], suggesting a close link between disrupted maturation of adult-born cells and schizophrenic-like behaviors.

**Calcium voltage-gated channel subunit alpha1 C**

Calcium voltage-gated channel subunit alpha1 C (CACNA1C) encodes the Cav1.2 subunit of voltage-gated calcium channels, whose genetic variations have been reported to increase the risk of psychiatric disorders including SCZ[51,52]. GWAS have identified several single-nucleotide polymorphisms (SNPs) of the CACNA1C gene, which show a close link with SCZ[53-55]. Furthermore, large exome sequencing studies have defined disruptive mutations within calcium ion channels in schizophrenic patients[56]. With regard to the functions of CACNA1C, it has received a lot of attention and been studied extensively in animal models. The results obtained from mice have shown that reduced gene dosage of Cacna1c leads to behavioral impairments including reduced locomotion and fear learning as well as impaired spatial memory[57-59]. Cacna1c has also been found to mediate brain-derived neurotrophic factor production and thus might also play a role in regulating adult neurogenesis. Indeed, studies on mice with ablation of Cacna1c showed that adult neurogenesis was impaired as revealed by decreased proliferation of progenitors and survival of new-born neurons, which coincides with its cognitive deficits[60,61].

**Reelin**

Reelin, an extracellular matrix glycoprotein which is mainly synthesized by Cajal-Retzius cells in the cortical marginal zone of the telencephalon at embryonic stages and in a subpopulation of GABAergic interneurons in adulthood, has been shown to play an essential role in embryonic and adult brains[62-66]. Reelin exerts its biological functions by binding to integrin receptors and then triggers phosphorylation of disabled-1 (Dab1). Phosphorylated Dab1 then recruits downstream molecules such as Crk/Crkl, phosphatidylinositol 3-kinase and Nckβ to their functional compartment[67,68]. It has been reported that Reelin mRNA and protein levels are reduced by almost 50% in cortical and hippocampal regions in post-mortem brains and serum of schizophrenic patients[69-71]. In the adult brain, Reelin is synthesized and secreted by GABAergic interneurons, and the reduction of glutamic acid decarboxylase 67 (Gad67), an enzyme which catalyzes the transition of glutamate to GABA, has also been observed in the same brains[72]. Thus, the authors postulate that decreases in neuritil and dendritic spines observed in the prefrontal cortex of post-mortem brains may be an outcome of disturbed GABAergic function and an associated decrease in Reelin secretion[73]. In addition, Li et al identified six SNPs located in Intron 29 of the REELIN gene, which have a significant association with the risk of SCZ in the Chinese population[74]. Similarly, other groups have reported a gender-specific (women) association between SNPs in REELIN and SCZ[75-77]. Studies on animal models have also found that heterozygous Reeler mice (Reelin mutant) display many neuroanatomic and neurochemical changes similar to those described in patients with SCZ. These changes include altered synaptic plasticity, decreased dendritic spine density, reduced Gad67 mRNA and protein levels in the frontal cortex and behavioral disturbances in associative memory and prepulse inhibition, whereas supplementation with REELIN can partially restore these abnormalities[78-83]. Inactivation of Reelin signaling
also leads to impaired adult neurogenesis as shown by decreased proliferation, aberrant migration and dendritic development of new-born neurons[84-86]. Taken together, these findings suggest that reduced REELIN expression in SCZ might have an impact on adult neurogenesis.

Other molecules
Apart from the susceptibility genes mentioned above, other molecules are also implicated in adult neurogenesis and SCZ, such as miR-19. A recent study revealed that miR-19 is enriched in adult hippocampal neural progenitor cells and regulates the migration of newborn neurons, highlighting its critical role in adult hippocampal neurogenesis[87]. Furthermore, miR-19 is found to be abnormally expressed in neural progenitor cells derived from induced pluripotent stem cells of schizophrenic patients[87], who show aberrant cell migration in brain. Thus, these data suggest that miR-19 may be a molecule associated with adult hippocampal neurogenesis and SCZ.

SCZ AND RELATED SIGNALING PATHWAYS CONTROLLING ADULT NEUROGENESIS

Wnt signaling
Wnt signaling, one of the most conserved molecular pathways, plays a vital role in the neurodevelopmental process and regulates the function and structure of the adult nervous system[88-90]. Wnts comprise a large cohort of secreted glycoproteins which interact with extracellular receptors, Frizzled or Low-density lipoprotein receptors 5/6[91]. Consequently, the activation of scaffold protein Dishevelled (Dvl) leads to inactivation of Gsk-3β. Normally, Gsk-3β promotes the degradation of β-catenin via phosphorylation. The inactivation of Gsk-3β finally causes the accumulation and translocation of β-catenin to the nucleus where it binds to the transcription factor Tcf/Lef family and activates target genes.

Wnt signaling is involved in brain development during the embryonic stages including cortical patterning, cell adhesion, migration, cell fate determination and proliferation[89,92,93]. In the adult brain, growing evidence indicates that components of Wnt signaling regulate multiple stages of adult neurogenesis including proliferation, fate commitment and synaptic plasticity[90,94,95]. For example, loss of Wnt7a expression dramatically reduced the neural stem cell population, increased the rate of cell cycle exit in neural progenitors and dramatically impaired dendritic development in the hippocampal DG of adult mice by modulating the β-catenin-cyclin D1 and β-catenin-neurogenin 2 pathway, respectively[96]. Knockdown of Wnt5a impaired neuronal differentiation and dendritic development of adult-born neurons by activating Wnt/c-Jun N-terminal kinase (JNK) and Wnt/CaMKII signaling[97].

Disturbances in components of the Wnt signaling pathway have been reported in post-mortem brains of patients diagnosed with SCZ. These abnormalities include: (1) Reduced GSK-3β levels in the prefrontal cortex, hippocampus and cerebrospinal fluid of patients[98-100]. It is noteworthy that medications which may treat symptoms of SCZ in clinical use, also modulate the levels and activity of AKT, GSK-3 and WNT-related intracellular signaling[101,102]; (2) A reduction in Dickkopf WNT signaling pathway inhibitor 3 (DKK3) mRNA, a suppressive factor of WNT signaling, in the cerebral cortex and an increase in the Adenomatous polyposis coli (APC) expression, acting as an antagonist of the WNT signaling pathway, is found in schizophrenic brain[103]; and (3) The expression of WNT-related genes in canonical WNT signaling was attenuated in whole blood in a sample of SCZ patients using an enzyme immunoassay. Furthermore, plasma levels of soluble DKK1 and SCLEROSTIN were downregulated in patients[104]. Wnt signaling in SCZ was further confirmed in animal studies. One of the first animal models included Dvl knockout mice, which exhibited reduced social interaction and deficits in prepulse inhibition of acoustic and tactile startle[105]. In addition, Disc1 exerts its function through Wnt signaling directly or indirectly[17]. Subsequent studies have shown that Apc and β-catenin knockout mice also display behavioral deviations related to SCZ[106,107]. In addition, the component of Wnt signaling, T-cell factor 4 (Tcf4), has received increased attention as the SNPs in its non-coding regions are associated with an increased risk of SCZ in GWAS[108-111]. Tcf4 also plays an important role in adult neurogenesis. Tcf4 heterozygous mice showed a decreased hippocampal neuronal stem cell pool, and impaired maturation and survival of adult-born neurons[112]. Thus, it is likely that dysregulation of the WNT signaling pathway contributes to adult neurogenesis deficits observed in SCZ patients.

Notch signaling
The Notch signaling pathway plays a crucial role in a wide array of neurodevelopmental processes and adult neurogenesis. Notch receptors are single-pass transmembrane heterodimers and four isoforms (Notch1-4) have been identified. In mammals, there are several types of Notch ligands including three Delta/Delta-like molecules (Dll/Dlk-1, -3, and -4) and two Serrate/Jagged molecules (Jag-1 and Jag-2). The heterodimeric Notch receptor undergoes proteolytic cleavage after binding to one of its ligands. This process liberates the Notch intracellular domain (NICD) which later translocates to the nucleus and interacts with the DNA-binding protein RBPJ. The NICD-RBPJ conjugation in turn works as a transcriptional activator and stimulates the expression of basic helix-loop-helix transcription factors, such as the
Table 1 Studies of schizophrenia risk genes and related signaling pathways in adult neurogenesis

| Genes or signaling pathways | Effects on adult neurogenesis | Behavior deviations |
|-----------------------------|------------------------------|---------------------|
| DISC1                       | Suppression of Disc1 expression results in accelerated neuronal integration, mispositioning of new DG granule cells, accelerated dendritic development, premature cell cycle exit and differentiation | Hyper-locomotion, depressive-like behavior, cognitive deficits (object place recognition test, Morris water maze test) |
| NRG1                        | NRG1 treatment induces increased ventral DG cell proliferation and neurogenesis. NRG1 regulates both excitatory and inhibitory synaptic transmission in the adult brain and abnormal neurotransmission and/or synaptic plasticity have been observed in the schizophrenic brain | Nrg1 hypomorphs showed hyperactivity in a number of tests, including the novel open-field test and the alternating-Y maze, impaired social behavior and increased aggression |
| SNAP-25                     | Snap-25 mutant mice display histologically and electrophysiologically immature DG neurons. Inactivation of Snap-25 in adult neural stem cells results in enhancement of proximal dendritic branching of new-born neurons in the DG and robust efferent mossy fiber output to the CA3 region | Working memory deficits, impaired contextual fear-discrimination learning |
| CACNA1C                     | Cacna1c deletion results in decreased progenitor proliferation and reduced survival of new-born neurons | Cacna1c heterozygous mice display reduced locomotion, fear learning, and impaired spatial memory |
| Reelin                      | Adult Reeler mutants show decreased proliferation, aberrant migration and dendritic development of new-born neurons | Heterozygous Reeler mice show a significant reduction in contextual fear conditioned learning and an age-dependent decrease in prepulse inhibition of startle |
| Wnt signaling               | Overexpression of stabilized β-catenin leads to enlarged brain and expanded neural precursor population. Wnt7a knockout mice show fewer neural stem cells. Wnt5a knockout decreases the number of immature neurons. Tcf4 heterozygotes show reduced size of neural stem cell pool and impaired maturation and survival of adult-born neurons | Dvl knockout mice display social interaction and deficits in prepulse inhibition of acoustic and tactile startle. Forebrain-specific β-catenin knockout mice show a depression-like phenotype. Apc heterozygote shows hypoactivity and a severe performance deficit in working memory |
| Notch signaling             | Inactivation of Notch1 blocks self-renewal of neural stem cells, reduces mitotic progenitors and neurogenesis. Adult deletion of Rbpj leads to depletion and exhaustion of neural stem cells | Notch1 heterozygote displays deficits in spatial learning and memory |

APC: Adenomatous polyposis coli; CA3: Cornu ammonis 3; CACNA1C: Calcium voltage-gated channel subunit alpha1 c; DG: Dentate gyrus; DISC1: Disrupted in schizophrenia 1; Dvl: Dishevelled; NRG1: Neuregulin-1; SNAP-25: Synaptosomal-associated protein, 25kDa; Tcf4: T-cell factor 4.

Hairy-Enhancer of Split[113-115]. A number of NOTCH4 variants and haplotypes have been found to be associated with SCZ[116,117]. This finding was subsequently confirmed by large GWAS[118]. Recent studies showed that the plasma levels of secreted NOTCH ligands (DLL1 and DLK-1) were elevated, whereas the levels of PRESENILIN-1, CREB-binding protein and RBPj were decreased in microarray analyses of whole blood from a large sample of SCZ patients[119]. In the study by Xue et al[120], Risperidone, one of medications used to treat SCZ, ameliorated cognitive deficits and cell proliferation by modulating the activity of Notch signaling in a murine model of SCZ. Mice deficient in Notch signaling have been shown to display spatial learning and memory impairment[121,122].

Notch signaling has long been identified as a factor that plays a primary role in adult neurogenesis. Notch receptors are expressed in neural stem cells and progenitors in the SGZ (Type-1 cells)[123,124]. In neural stem cells, the components of Notch signaling mainly work together to maintain an undifferentiated, proliferative state and therefore preserve the neural stem cell pool[125-127]. Indeed, inactivation of Notch1 leads to reduced mitotic progenitors and neurogenesis[128], whereas activation of Notch1 signaling increases neural stem cell proliferation and restoration of the glial cells at the expense of neurons[129]. Adult deletion of Rbpj results in depletion and exhaustion of neural stem cells[129]. Therefore, NOTCH signaling might be involved in the etiology of SCZ and especially cognitive deficits.

CONCLUSION

Accumulating evidence shows that impaired adult neurogenesis in the hippocampus is implicated in the pathogenesis of SCZ (Table 1). Decreased proliferation of adult neural stem cells in the DG and reduced hippocampal volume often coincide with impaired cognitive and affective functions, which are
commonly identified in animal models and schizophrenic patients. The question of how dysregulation of neurogenesis in the adult brain participates in the progression of SCZ arouses more and more interests. As SCZ is a neurodevelopmental disorder, many risk genes have an impact on both early brain development and adult neurogenesis. Thus, adult neurogenesis provides an attractive model to study the neurodevelopmental process, as it generalizes each step of neuronal development, including proliferation, specification, migration, dendritic branching and synapse formation. Although numerous susceptibility genes/molecules have been uncovered by genetic analysis and high-throughput sequencing, their functions still remain elusive. The studies on the roles of these susceptibility genes/signaling pathways in adult neurogenesis might shed some light on the understanding the etiology of SCZ and identifying potential therapeutic targets, which could facilitate the development of novel medication and treatment.

**FOOTNOTES**

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