Review article/Artykuł poglądowy

Modeling the genetics of schizophrenia – the curse of plentitude?

Modelowanie genetyki schizofrenii – nadmiar możliwości?

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Abstract

Rapidly growing knowledge about the neurobiology and genetics of schizophrenia has stimulated new interest in animal models, which are used to dissect the molecular mechanisms of pathophysiological abnormalities in schizophrenia and create more effective therapies. The concepts about how to approach animal modeling of this complex, multifactorial (i.e., involving multiple genes and a variety of epigenetic causes) neuropsychiatric disorder have been evolving over years and reflect the changing ideas about the etiology and the mechanism of the illness (Lipska and Weinberger 2000; Chen et al. 2006). These past approaches included pharmacological manipulations of dopamine and glutamate systems, thought to be in the center of the neurotransmitter imbalance in schizophrenia and the main culprits in the psychotic symptoms and cognitive impairments (Costall and Naylor 1995). Subsequent concepts focused on disruptions of early brain development to address the evidence that the disorder has a neurodevelopmental origin; the onset of schizophrenia is typically in adolescence or early adulthood and early childhood is not normal in many cases (Lipska and Weinberger 2000; Moore et al. 2006). Manipulations of the psychosocial environment and induction of stressful conditions have also been considered as model targets due to the evidence that stress is involved in precipitating the illness (Jones et al. 1992). Most recently, however, a new generation of models based on the breakthroughs in the discovery of human schizophrenia susceptibility genes have yielded the most fascinating results. Although they brought us a bit closer to understanding the functions of some "faulty" genes, they have also raised more questions about the functions of the putative susceptibility genes and their role in the human disorder.

Key words: modeling the genetics schizophrenia, DISC1

Streszczenie

Szybki rozwój wiedzy w zakresie neurobiologii i genetyki schizofrenii spowodował znaczny wzrost zainteresowania zwierzęcymi modelami używanymi do badania molekularnych mechanizmów patofizjologii schizofrenii oraz opracowywania bardziej efektywnych metod leczenia. W ostatnich latach idee dotyczące opracowywania zwierzęcych modeli w tej złożonej, wieloczynnikowej (m.in. wiele genów i różnorodne przyczyny epigenetyczne) choroby neuropsychiatrycznej znacznie się zmieniały, co odzwierciedlało zmiany w rozumieniu etiologii i mechanizmów choroby (Lipska i Weinberger 2000; Chen i wsp. 2006). Poprzednie opracowania dotyczyły farmakologicznych manipulacji w układach dopaminergicznym i glutaminergicznym, uznawanych za główne układy neuroprzekaźnikowe zaburzone w schizofrenii, odpowiedzialne za objawy psychotyczne i upośledzenie funkcji poznawczych (Costall i Naylor 1995). W kolejnych podejściach skupiono się na zakłóceniach wczesnego rozwoju mózgu, ze względu na dowody, że schizofrenia jest chorobą neurorozwojową. Początek choroby zwykle następuje w okresie adolescencji lub wczesnej dorosłości, a zmiany zachowania mogą pojawiać się już w okresie wczesnego dzieciństwa (Lipska i Weinberger 2000; Moore i wsp. 2006). Innym obiektem modelowania stały się zmiany w obrębie środowiska psychospołecznego i czynniki stresowe, w związku z dowodami na rolę czynników stresowych w wyzwalaniu choroby (Jones i wsp. 1992). Ostatnio jednak nowa generacja modeli jest oparta się na najnowszych odkryciach dotyczących genów podatności na schizofrenię i rokuje uzyskanie fascynujących wyników. Prowadzi to do nieco lepszego zrozumienia funkcjonowania *nieprawidłowych* genów, ale rodzi też kolejne pytania dotyczące czynności domniemanych genów podatności na schizofrenii i ich roli w powstawaniu choroby.

Słowa kluczowe: modelowanie genetyki schizofrenii, DISC1

Many of the recently discovered schizophrenia candidate genes [e.g., COMT, GRM3, PPP3CC (calcineurin), DARPP32] have been associated with cognitive dysfunction, a symptom relatively resistant to current antipsychotic treatments and viewed as a core symptom of schizophrenia. The genetic animal models with mutations in the genes involved in brain development (e.g., DISC1, NRG1, DTNBP1) have provided insights into molecular mechanisms of abnormal neurodevelopment in schizophrenia. In particular, several recent studies on disruptions of the DISC1 gene in mice illustrate the great potential of the new genetic approaches but also signal the vast complexity of the problem.

The initial rationale for studying the effects of mutations in DISC1 came from the discovery of the chromosomal translocation resulting in a breakpoint in the DISC1 gene that co-segregated with major mental illness in a Scottish family (reviewed by Porteous et al. 2006). These clinical findings were followed by a number of association studies, which reported that numerous single nucleotide polymorphisms (SNPs) across the gene were associated with schizophrenia and mood disorders and a variety of intermediate phenotypes, including hippocampal function and structure, prefrontal gray matter volume, memory and cognition, suggesting that other problems in the DISC1 gene may exist in other subjects/populations.

Animal models constructed to mimic partial loss of DISC1 function suggested that DISC1 is necessary to support development of the cerebral cortex as its loss resulted in impaired neurite outgrowth and the spectrum of behavioral abnormalities characteristic of major mental disorders (Kamiya et al. 2005; Koike et al. 2006; Clapcote et al. 2007; Hikida et al. 2007). Unexpectedly, however, another DISC1 knockdown model, achieved by RNA interference in single cells of the dentate gyrus, has recently demonstrated that DISC1 may also function as a brake on neuronal development, and that its loss could lead to the opposite effects: dendritic overgrowth and accelerated synapse formation and maturation of newly generated neurons (Duan et al. 2007). Other emerging studies continue to reveal the highly complex nature of the DISC1 gene with multiple isoforms exhibiting different functions, perhaps depending on localization, timing and interactions with a multitude of other gene products, some of which appear to confer susceptibility to mental illness in their own right, independently of DISC1 (Hennah et al. 2007; Hodgkinson et al. 2007; Kakiuchi et al. 2007; Lipska et al. 2006; Millar et al. 2005; Pickard et al. 2007). Similar molecular complexity has also emerged in other susceptibility genes for schizophrenia, GRM3 (Sartorius et al. 2006), NRG1 (Tan et al. 2007) and COMT (Tunbridge et al. 2007). With the growing knowledge of transcript complexity, it becomes increasingly clear that subtle disturbances of isoform(s) of susceptibility gene products and intricate interactions between the susceptibility genes may account for the etiology of neuropsychiatric disorders. Research in animals will have a critical role in disentangling this web of interwoven genetic pathways.

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