Schizophrenia Bulletin vol. 36 no. 2 pp. 243–245, 2010
doi:10.1093/schbul/sbq004
Advance Access publication on February 12, 2010

Mutant Mouse Models: Phenotypic Relationships to Domains of Psychopathology and Pathobiology in Schizophrenia

Colm M. P. O'Tuathaigh[1,*] and John L. Waddington[1]

[1]Molecular and Cellular Therapeutics, Royal College of Surgeons in Ireland, St Stephen's Green, Dublin 2, Ireland

*To whom correspondence should be addressed; tel: +353-1-402-2377, fax: +353-1-402-2453, email: cotuathaigh@rcsi.ie

The present series of review articles seeks to elaborate how current findings in mutant mice may inform on the relationship between candidate genes and individual psychopathological and pathobiological aspects of schizophrenia. Each of the authors focuses on an overlapping selection of both well-characterized and emergent candidate genes, as identified through association and linkage studies and/or via their involvement in putative pathophysiological mechanisms, particularly those relating to dopaminergic and glutamatergic processes.

Key words: mutant model/schizophrenia/positive symptoms/negative symptoms/cognition/endophenotype

Introduction

It has been argued that schizophrenia is a polygenic disorder for which risk is determined by a number of genes of small effect vis-à-vis a phenotype that shows considerable heterogeneity across patients; however, the extent to which diversity in age at onset of diagnostic symptoms, subsequent symptomatology, course of illness, and underlying pathobiology might each reflect single vs multiple independent genes and/or single vs multiple pathophysiological processes is far from clear.[1–4] Recognizing the ''disconnect'' between genotype and phenotype in psychiatry, Gottesman and colleagues pioneered the use of endophenotypes to improve genetic studies; endophenotypes are defined as stable, measurable, intermediate disease features that bridge the gap between the overt manifestations of schizophrenia and underlying risk genes.[5,6] There is considerable emphasis at present on refining the schizophrenia phenotype into separate, more readily discernible endophenotypes that may relate more closely to underlying genes and pathobiology. A thorough delineation of the relationship between schizophrenia risk genes and both individual domains of psychopathology and relevant pathobiological biomarkers has the potential to provide an important conceptual link toward understanding the nature of schizophrenia. Generation and characterization of mice mutant for genes either implicated in brain mechanisms relevant to putative pathophysiologies of the disorder or associated with risk for schizophrenia have provided an important translational stimulus to addressing these issues.[3,4]

Positive Symptoms

Van den Buuse (this issue) provides an analysis of phenotypic modeling of positive symptoms in relevant genetic model systems, with a particular focus on the ''proxy'' indices of baseline- and psychotomimetic drug–induced locomotor hyperactivity and disruption of prepulse inhibition (PPI). Given the primacy of dopaminergic hyperfunction and antagonism in relation to psychotomimetic and antipsychotic activity, respectively, it is unsurprising that validity for positive symptomatology is assessed using dopamine-linked behaviors such as exploratory activity and sensorimotor gating (PPI). The author stresses the importance of pharmacological characterization, together with study of the effects of the mutation on other neurotransmitter systems so as to exclude or identify the involvement of compensatory mechanisms. This article provides a comprehensive account of psychosis-related behavioral changes in mice mutant for dopaminergic and glutamatergic function, as well as genes associated with risk for psychosis. Such behavioral changes may inform on the circuitry underlying specific endophenotypes related to psychosis.

Negative Symptoms

O'Tuathaigh and colleagues (this issue) highlight several conceptual and methodological challenges associated with accurately capturing in mutant models the complexity of negative symptoms. The authors outline the difficulties in accessing fundamentally, perhaps uniquely, human characteristics. Validation of behavioral models of negative symptoms is complicated by their refractoriness to existing treatments and lack of understanding

concerning both their specificity and pathobiology. Additionally, the authors point out that similarity of a given behavioral feature in rodents to aspects of the human condition needs to be informed by understanding of the species-specific taxonomy of such behaviors and their underlying cellular/molecular bases. To this end, the importance of adopting a comprehensive phenotyping strategy capable of capturing several aspects within each domain, eg social interaction, is emphasized. The authors argue that the field of negative symptom modeling will be advanced by greater emphasis on the development and application of behavioral measures beyond the most widely studied domain of social behavior, to include anhedonia and avolition, together with studies to clarify the neuronal circuitry and cellular/molecular basis of these processes.

Cognitive Deficits

Arguello and Gogos (this issue) address inter alia the important issue of developing novel, targeted treatments for ameliorating the cognitive deficits of psychotic illness and affirm that model systems are essential tools to this end. Based upon Cognitive Neuroscience Treatment Research to Improve Cognition in Schizophrenia and the cognitive domains identified therein, these authors consider and evaluate the tasks used most commonly to measure specific psychosis-relevant cognitive constructs and their relative advantages vis-à-vis drug development. The importance of establishing a high degree of psychological and neuronal homology in these processes, as measured in both humans and rodents, is emphasized. The authors emphasize also the necessity for behavioral models of working memory processes to explicitly assess the executive control contribution to working memory, arguing that executive processes largely determine working memory performance and may be responsible for working memory deficits in schizophrenia. They call for increased precision in the selection of behavioral paradigms used to measure cognition, with a particular emphasis on working memory, in order to identify relevant disease processes and improved treatments.

Structural/Neuropathological Deficits

Jaaro-Peled and colleagues (this issue) focus on modeling structural and neuropathological alterations reported in brains of patients with schizophrenia. These include gross structural deficits, as reported in magnetic resonance imaging studies, and morphological abnormalities, as reported in studies of neuronal cytoarchitecture and cell biology in postmortem brain. While the lack of a prominent neuropathological signature has long been considered an obstacle to the development of accurate preclinical models of schizophrenia, growing evidence for more subtle neuropathological changes in brains of patients with schizophrenia provides a basis for validation of putative mouse models. Importantly, these authors summarize evidence for neuropathological changes in genetic vs nongenetic (pharmacological, environmental, and lesion-based) preclinical models of psychosis. The growing body of evidence implicating risk genes and/or their interacting molecular partners in the development of these neuropathological markers provides encouragement to further delineation of the mechanisms underlying the cellular/molecular characteristics of schizophrenia.

Concluding Remarks

Current theory posits that multiple genetic and environmental factors contribute to abnormal brain development and disruption to resultant lifetime trajectory that underlay the clinical phenotype of schizophrenia; recent advances in molecular technology and increasing refinements in behavioral assessment are facilitating elucidation of these processes via mutant models.[3,4] However, not only the increasing array of candidate risk genes but also emerging evidence for a large number of rare copy number variations (CNVs), and the apparent association of such risk genes and CNVs with dimensions of psychotic illness across conventional diagnostic boundaries,[7,8] present substantive challenges to future studies. Adopting a multitiered phenotyping strategy, which incorporates multiple levels of analysis from molecular to behavioral, is necessary to reveal the relationship of a specific risk gene and/or CNV to pathobiology and psychopathology. However, while gene-endophenotype relationships continue to be explored within a translational framework, there is increasing recognition of the necessity to develop mutant models that incorporate gene-environment and gene-gene (epistatic) processes because these possess a key to explaining how genetic factors interact with environmental adversities to determine the pathobiology of schizophrenia over its lifetime trajectory.

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