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Animal models of gene-environment interactions in schizophrenia

Yavuz Ayhan[1], **Akira Sawa**[1,3,4], **Christopher A. Ross**[1,2,3,4], and **Mikhail V. Pletnikov**[1,4,*]

[1]Department of Psychiatry and Behavioral Sciences, Johns Hopkins University School of Medicine, Baltimore, MD 21287, USA

[2]Department of Neurology, Johns Hopkins University School of Medicine, Baltimore, MD 21287, USA

[3]Department of Neuroscience, Johns Hopkins University School of Medicine, Baltimore, MD 21287, USA

[4]Program in Cellular and Molecular Medicine; Johns Hopkins University School of Medicine, Baltimore, MD 21287, USA

Abstract

The pathogenesis of schizophrenia and related mental illnesses likely involves multiple interactions between susceptibility genes of small effects and environmental factors. Gene-environment interactions occur across different stages of neurodevelopment to produce heterogeneous clinical and pathological manifestations of the disease. The main obstacle for mechanistic studies of gene-environment interplay has been the paucity of appropriate experimental systems for elucidating the molecular pathways that mediate gene-environment interactions relevant to schizophrenia. Recent advances in psychiatric genetics and a plethora of experimental data from animal studies allow us to suggest a new approach to gene-environment interactions in schizophrenia. We propose that animal models based on identified genetic mutations and measurable environment factors will help advance studies of the molecular mechanisms of gene-environment interplay.

Keywords

schizophrenia; depression; gene-environment interactions; mouse models; DISC1

I. Introduction

Schizophrenia is a devastating disorder with a worldwide prevalence of 0.5-1.2% [62,132]. The disease generally presents in late adolescence and early adulthood [61]. As a disorder of youth and adulthood, schizophrenia leads to significant loss of daily activity, reduced productivity and increased unemployment rates [131]. The disease is associated with higher rates of violent behavior and higher rates of suicide, causing not only mental suffering for the patients but also significant difficulties for the caregivers. Schizophrenia poses a significant burden to the society, causing substantial excess of direct and indirect costs [131]. Although

*the corresponding author Mikhail V. Pletnikov, M.D.; Ph.D. Department of Psychiatry and Behavioral Sciences Johns Hopkins University School of Medicine 600 North Wolfe Street, CMSC 8-121 Baltimore, MD 21878 USA Phone: 410-502-3760 FAX: 410-614-0013 Email: mpletnik@jhmi.edu.

the efforts to treat the disease have led to significant success starting from the second part of last century, the current treatment options are palliative only [71].

For this chronic, debilitating disease known for thousands of years [114], no test exists to identify affected individuals beyond the signs and symptoms of the disorder. Various disease-associated alterations have been noted, including enlargement of lateral and third ventricles, reduced volumes of medial temporal lobe and superior temporal gyrus, sensorimotor gating deficit, impaired cognitive modalities such as attention and working memory [101]. However, neither *in vivo* nor postmortem examinations can identify a specific morphological, biochemical or electrophysiological phenotype. Indeed, the cause of the disorder remains unknown, possibly with multiple factors contributing to the disease generation. We believe that experimental models may help enlighten the etiology and pathogenic mechanisms of the disorder and ultimately facilitate new therapeutic treatments.

The etiology of schizophrenia is complex [78] [2,24,60]. The heritability estimates of schizophrenia are between 60-80% [1]. The variance is explained by both genetic factors and shared and unique environmental effects [70]. The early environmental factors most frequently associated with schizophrenia are maternal prenatal infections (CMV, influenza, rubella, toxoplasma), winter/early spring birth, preterm birth and obstetric complications (mostly related to hypoxia), urban living and adolescent cannabis use [123]. Although the associations with these factors were demonstrated to a various degree in different cohorts, no specific environmental factor is able to explain the majority of cases of schizophrenia. Thus, it has been proposed that interactions between genetic and environmental factors may play a leading role in the pathogenesis of this mental illness [20,118,123].

There have been numerous studies suggestive of interactions between environmental and genetic factors in schizophrenia [19,22,51,59]. However, epidemiological studies in humans have not been able to address the mechanisms whereby gene-environment interactions (GEI) occur. Several approaches to evaluate the GEI in animal models of schizophrenia have been proposed, although there is still a need for refinement and further development of animal models pertinent to the pathogenesis of schizophrenia and related mental diseases. Here, we will critically evaluate the most popular approaches to GEI animal models of schizophrenia, and propose that establishing animal and cell models based on interactions of the relevant mutant genes and measurable environments will likely stimulate mechanistic studies.

II. Strain models of gene-environment interactions

Interactions between genes and early environment have been successfully studied in several animal models. In macaques, for example, when compared with mother-reared animals, peer-reared offspring show increased neuroendocrine and behavioral responses to stress, and a common polymorphism in the serotonin transporter receptor gene has been shown to exacerbate or dampen specific aspects of this developmental programming [8,23]. Also in rodents, cross-fostering studies reveal that genetic background modulates susceptibility to the long-term behavioral and endocrine effects of different maternal environment [3,16,74].

Regarding schizophrenia, one of the most popular approaches to model GEI interactions has been comparing schizophrenia-like consequences of early developmental manipulations between different strains of rats and mice similar to the studies above. This approach is based on the hypothesis that schizophrenia most likely results from disturbances in the normal development [92,128]. The experimental manipulations included neonatal hippocampal lesions, isolation rearing and neonatal viral infection or immune challenges.

Rat strain studies

Lipska and Weinberger were the first to evaluate how the genetic background moderates the effects of early brain injury that leads to behavioral schizophrenia-like abnormalities in rats [73]. The authors have evaluated the effects of early (postnatal day (PND) 7) ventral hippocampal lesion in Sprague-Dawley (SD), Fisher 344 (F344) and Lewis rats. These strains were chosen because they exhibit substantial differences in responsiveness to stress, predisposition to inflammatory diseases, and preference for drug abuse. Novelty- or amphetamine-induced locomotor activity was measured after small or large ventral hippocampal lesions (SVH and LVH, respectively) at PND 35 and 56. LVH lesions led to increased novelty- and amphetamine-induced activity in F344 rats at PND 35 and PND56, and in SD rats at PND 56. In contrast, the same lesion produced no effects on novelty- or drug-induced activity in Lewis rats. It has been proposed that the observed strain differences can be at least in part explained by differential stress reactivity of the hypothalamus-pituitary-adrenal (HPA) axis, and/or the functional sate of the mesolimbic dopamine system, with Lewis rats having lower HPA axis and mesolimbic DA functions with lower emotional reactivity and higher sensitivity to the reinforcing effects of drugs compared to F344 rats. This study has demonstrated how two factors, one genetic (rat strain) and one environmental (neonatal damage to the hippocampus) affected behavioral changes associated with DA function abnormalities implicated in the pathophysiology of schizophrenia [73].

In addition to neonatal lesion of the hippocampus, another developmental manipulation that disrupts the normal neurodevelopment is rearing in social isolation [39]. Rearing adolescent rats in isolation has been found to lead to an “environmental lesion,” which produces perturbations in behavior and brain neurochemistry thought to resemble those of schizophrenia. In particular, isolation-reared rats display deficits in pre-pulse inhibition (PPI) of acoustic startle which is a sensorimotor gating abnormality that is associated with schizophrenia [32]. It has been also shown that isolation-induced neurochemical and behavioral abnormalities are suggestive of hyperactivity in mesolimbic DA systems, consistent with the pathophysiology of schizophrenia [9].

One study has assessed the effects of early postnatal social isolation on PPI between fawn-hooded and Wistar rats and has found that social isolation from PND21 and until adulthood differentially impairs PPI in these rat strains [45]. Mark Geyer and associates have performed a series of studies to assess the effects of strain-isolation rearing interactions on PPI. When the effects of social isolation on startle reactivity, habituation, and PPI were compared between male Lewis, SD and F344 rats, Lewis and F344 rats were found to exhibit lower startle reactivity than SD rats. In addition, Lewis rats displayed a more rapid habituation compared to two other strains of rats. Isolation rearing produced deficits in PPI in both SD and F344 rats but had no effect in Lewis rats [39]. In a separate study, 0.5 mg/kg of apomorphine disrupted PPI in Fisher but not in Lewis rats, suggesting that in contrast to SD and F344 rats, PPI in Lewis rats is relatively resistant to pharmacological or developmental manipulations [125].

Strain-specific alterations following early brain injury were also studied in a rat animal model of autism and schizophrenia based on neonatal Borna disease virus (BDV) infection [95]. Despite comparable virus replication and weight gain inhibition, neonatal BDV infection was shown to produce greater thinning of the neocortex in F344 rats compared to Lewis rats. The differential virus-induced brain pathology could contribute to the observed greater novelty-induced hyperactivity and impaired habituation and PPI of the acoustic startle response in BDV-infected F344 rats but not in BDV-infected Lewis rats [95,96]. In addition, it was demonstrated that neonatal BDV infection produced regional and strain-related alterations in monoamine brain systems and differential responses to serotonin compounds. These studies have provided new insights into the pathogenic events that lead to strain-specific abnormalities following exposure to the same viral infection [94-96].

As a variant of the strain approach, Ellenbroek and colleagues have pursued a strategy of selective breeding of outbred Wistar rats [27,58]. The strategy has been based on the observation that there is a bimodal distribution in the response to novelty, the response to a resident-intruder test as well as in the stereotypy response to the dopamine agonist, apomorphine (APO). The breeding has resulted in two lines of rats, susceptible (APO-SUS) and unsusceptible (APO-UNSUS), with the APO-SUS rats showing a strong, stereotyped gnawing response, whereas APO-UNSUS exhibiting a weak gnawing response. Similar to Fisher 344 rats, APO-SUS rats had a hyper-reactive HPA axis. The differential susceptibility to the effects of APO can be modulated by stressful events. For example, cross-fostering (an early stress event) decreases APO susceptibility in APO-SUS rats while maternal deprivation (a late stress event) enhances APO susceptibility in APO-UNSUS rats. Subsequent studies have demonstrated that it is the timing rather than the type of stressful life events that ultimately determines this phenotype expression. Specifically, the early stress affects primarily APO-SUS rats, making them more similar to APO-UNSUS animals, i.e., less responsive to APO, while the later stressful event influences predominantly APO-UNSUS rats, increasing their susceptibility to APO [35]. Thus, interaction between these genetic factors (i.e., the strain genetic background) and the early environmental stressors shapes the phenotypical expression of the genotype [35]. Curiously, depending on the genetic background, stress can have both “protective” and “pathogenic” effects on the behavior under study.

Numerous neurochemical, neuroendocrine and neuroimmune strain-specific factors have been evaluated to explain strain-related differences [37,87,99,119]. As has been already indicated, the genetically distinct Lewis and F344 inbred rat strains differ in HPA axis function. Lewis rats have blunted diurnal corticosterone level variation compared to F344 rats [31,43,88] and show impaired ACTH and corticosterone responses to inflammatory agents [113] and stressors [31,112]. In addition, there are several strain differences in the mesolimbic DA system. Tyrosine hydroxylase protein levels are lower in the VTA and higher in the NAc of F344 vs. Lewis rats [7,44,88]. F344 rats show higher numbers of spontaneously active VTA DA neurons [84], higher basal DA metabolite levels in NAc but no differences in DA levels compared to Lewis rats [18,115]. An interesting approach in rat strain research includes analysis of expression of genes among different strains at different conditions according to their susceptibility to psychosis-like behaviors [108,130]. Genetic investigations of strain differences in behaviors have provided valuable information on anxiety and depression models of rodents [136]. This line of investigations is anticipated to identify the molecular mechanisms underlying strain differences in certain phenotypes that may be reminiscent of schizophrenia.

Mouse strain studies

There are many strains of mice available for GEI studies. Mouse strains have been extensively characterized behaviorally [28] and to some degree genetically [6]. Several groups have demonstrated that certain mouse strains differ in tests for anxiety- and/or depression-related behaviors and display dissimilar sensitivity to various environmental challenges (for reviews, see [25,53]). However, compared to studies on rat strains, there have been much fewer reports on using different mouse strains for modeling GEI relevant to schizophrenia. Instead, mouse studies have focused more on models for the specific genes. In addition, there have been some difficulties with the experimental manipulations found to be less efficient in mice, e.g., stress (e.g.[83]).

In a model of the immune etiology hypothesis of schizophrenia, Tsuda and colleagues have evaluated the effects of early neonatal administration of interleukin-1α (IL1- α) in four mouse strains, C3H/He, DBA/2, C57BL/6, ddY. Neonatal treatments with IL-1α have differentially altered adult behavioral/cognitive traits in a strain-dependent manner. IL-1α has decreased PPI in DBA/2 and C57BL/6 mice and had no effects on PPI in C3H/He and ddY mice. In addition,

this treatment elevated locomotor activity and startle responses in DBA/2 mice and has decreased startle responses in C3H/He mice. The authors have observed most profound behavioral alterations in DBA/2 mice. The behavioral changes correlated with a significant IL-1α -triggered Iκ-B degradation in the frontal cortex and an increase in p38 MAP kinase phosphorylation in the DBA/2 strain. Of note, a recent study found increased IL-1 and NF-kappaB levels in schizophrenics which were reversible with antipsychotic treatment [109]. The study has indicated that the mouse genetic background can modulate the IL-1α-triggered cytokine signaling pathway to produce the distinct effects on neurobehavioral traits in adult animals [120].

The effects of isolation rearing that produce PPI deficits in rats have also been evaluated in mice. For example, isolation rearing has been shown to produce PPI deficits in ddY mice [39]. Varty et al have examined whether isolation rearing induces locomotor hyperactivity and PPI deficits in the two mouse strains used for genetically engineered mice, 129T2 and C57BL/6. Male 129T2 and C57BL/6J mice were housed either in groups of three (socials) or singly (isolates) at weaning. Six and seven weeks later, PPI, startle reactivity, and locomotor activity (LMA) were measured. In both strains of mice, isolation-reared for 6-7 weeks produced PPI deficits but had no effect on startle reactivity or habituation [126].

Similar to rat strains investigations, numerous neurochemical, neuroendocrine and neuroimmune strain-specific factors have been evaluated to explain strain-related differences in mice [9,56,134]. In general, the strain approach has been anticipated to facilitate a quantitative trait loci (QTL) analysis of genetic vulnerability to eventually identify the chromosomal locations of several genes that may contribute to quantitative variations in a phenotype. However, the multitude of genes involved significantly decreases the utility of the strain methodology for studying the specific molecular mechanisms of GEI. The recent progress in mouse genetics has allowed for manipulation of a single gene in regional and/or temporal fashion and provided an opportunity to evaluate how specific genes can interact with environmental factors to produce schizophrenia-like neurobehavioral abnormalities in animal models.

III. Genetic mouse models of gene-environment interactions

Recent reviews have argued that putting the neurobiological pathways in the center of GEI studies will significantly aid mechanistic investigations with animal models [102,103,129]. We think that the progress in this field will also be facilitated by studying the combinations of environmental risk factors and candidate genes implicated in the causation of schizophrenia. For example, combining etiologically relevant genetic mutations with environmental factors such as stress [63,66], cannabis exposure [21,48] or viral infections [13,90] offers promising solutions in increasing the power and construct validity of GEI mouse models [4]. In this section we will summarize current studies investigating gene-environment interaction in some genetic mouse models and discuss possible new approaches.

Reelin

Recently, there have been several studies to model GEI in schizophrenia in genetic mouse models. Among candidate molecules, reelin (RELN) is a protein of the extracellular matrix playing a key role in brain development and synaptic plasticity [50]. The heterozygous (HZ) reeler mice were used to evaluate the effects of early adverse experiences on schizophrenia- and autism-like behavioral abnormalities [36]. Based on the acetylcholine-dopamine intreractions and long term effects of gestational chlorpyrifos- an organophosphate with acetylcholinesterase inhibition property- on dopamine turnover, homozygous reeler (RL), heterozygous (HZ), and wild-type (WT) mice were prenatally exposed to chlorpyrifos-oxon (CPF-O), the active metabolite of chlorpyrifos, or to vehicle (prenatal controls) on gestational

days 14-16, that is, during a peak period of neurogenesis in the cerebral cortex. The results were consistent with complex interactions between genetic mutation (reeler genotype) and environmental insult (prenatal exposure to CPF-O). Unexpectedly, exposure to CPF-O paradoxically reversed the effects of the absence of reelin. Importantly, the authors have also shown that prenatal CPF-O unmasked previously unseen genotype dependency [65]. In a follow-up study, Laviola et al evaluated the effects of early maternal separation on brain and behavioral development in reeler mice [65]. Homozygous reeler (RL), heterozygous (HZ) and wild-type (WT) mouse pups underwent maternal separation or handling on PND 2-6. On PND 7, compared to other genotypes, RL mouse pups from the control group, showed reduced levels of ultrasound vocalization (USV) which may be a measure of social communication in mice [104] and of locomotion. Surprisingly, this deficit in RL mice was fully reverted by maternal separation. Maternal separation per se reduced social motivation in the homing test at PND 9 in WT mice, with no effects on HZ and RL ones. The present results have provided evidence that stress and ensuing hormonal stimulation during early postnatal development may interact with a genetic make-up to substantially modify the existing phenotype in mutant mice. We believe that the findings with reeler mice have also illuminated what one can anticipate from future GEI models, i.e., emerging new previously unseen phenotypes as a result of synergistic GEI interactions.

Nurr1

Another study has addressed interactions between Nurr1 mutation and a stressful experience such as postnatal isolation [34,85]. Nurr1 is a transcription factor which has a critical importance for the terminal differentiation of midbrain DA neurons [135]. Nurr-1 knock-out mice have been proposed as a model for schizophrenia-like phenotype [100]. HET Nurr1 knockout mice displayed increased locomotor activity, increased immobility in forced swim test, decreased passive avoidance retention latency in females, and gender specific alterations in dopamine and serotonin metabolism [100]. Isolation was applied via separating pups at PND 19 through PND 21. The behavioral effects of isolation were analyzed with PPI. Non-isolated Nurr1 HET mice did not differ from WT animals in PPI. However, social isolation impaired PPI in mutant mice and did not affect PPI in WT animals. In addition, social isolation decreased tissue content of DA and DOPAC in prefrontal cortex in heterozygous mice only. The authors have suggested that Nurr1 mutation could be an important factor for susceptibility to isolation-induced PPI deficits [34].

Neuregulin-1

Among interesting environmental factors suitable for GEI mouse models, one can select drugs of abuse because much is known about their mechanisms of action on the brain and human epidemiologic data have suggested a contribution of some drugs to the development of psychosis in vulnerable individuals [15,75,121]. For example, cannabis use is considered a contributory cause of schizophrenia and psychotic illness. However, only a small proportion of cannabis users develop psychosis. Genetic factors, in particular, are likely to play a role in the effects cannabis may have on psychosis outcome. In this context, the study that has evaluated interactions of cannabis with Neuregulin-1 (NRG-1) represents a promising direction in GEI mouse models. NRG-1 is an important candidate gene that was first identified in an Icelandic linkage study [110,111] . Association of this gene with schizophrenia has been replicated in many studies, although some contradicting reports exist [86]. Nrg1 KO mice have been tested for interactions between Nrg1 dysfunction and cannabis. 6-7-month-old wild-type (WT) and heterozygous (HET) Nrg1 animals have been assessed in open field (OF), elevated plus maze (EPM), hole-board test (HB), light-dark test (LD), social interaction (SI) test and PPI before and 30 minutes after acute injections of 5 or 10 mg/kg tetrahydrocannabinol (THC), an active ingredient of cannabis sativa, or vehicle administration. When compared with WT mice, Nrg1 HET mice displayed an anxiolytic-like phenotype in light-dark test and elevated-

plus maze and hyperactivity in open-field test. THC administration resulted in differential behavioral effects based on genotype in locomotor activity, anxiety related tests and PPI. THC reduced activity only in Nrg1 hypomorphic mice in OF test at low dose and in LD test in both doses. In EPM and LD tests, THC produced anxiety-related responses only in Nrg1 HET mice. Similarly, THC had the significant effects on PPI in Nrg1 HET mice only and did not change PPI in WT animals. The results demonstrate increased sensitivity of Nrg1 hypomorphic mice to acute cannabinoid administration [10]. The same group has also evaluated neuronal activity induced by acute THC administration in Nrg1 hypomorphic animals by measuring numbers of cells that express *c-fos*. Adult male mice were given 10mg/kg i.p THC and *c-fos* expression in the brain was analyzed 90 minutes later. More *c-fos* expressing cells were found in various brain regions in Nrg1 HET mice compared to WT mice [11]. While acute treatments with THC may not reflect the human pattern of drug-taking, this study has provided the first evidence for interactions between a strong candidate gene for schizophrenia and cannabis which is implicated in the precipitation of some cases of schizophrenia [26,30,123]. Future studies with this model can uncover how the molecular pathways activated by THC may interact with Nrg and its protein partners to produce the observed phenotype.

COMT

Another interesting combination of the candidate gene and cannabis may include Catechol-O-Methyl Transferase (COMT). COMT is an enzyme responsible for metabolism of extracellular DA, and thus contributing to its clearance from synapses, particularly in the cortex [67]. The most studied functional polymorphism of COMT is the val/met in 108^{th} position at s-COMT and at 158^{th} position in MB-COMT [116]. COMT with the methionine allele is structurally less stable, making this variant of the enzyme less active [116]. Although most studies on the normal populations have shown that val carriers have a poorer cognitive performance compared to met carriers, the relation between these alleles and the risk of schizophrenia remains unclear [41] In a study evaluating the possible interaction between cannabis use and COMT genotype, cannabis users who have the COMT valine158 allele have been found to be more likely to exhibit psychotic symptoms and develop psychosis compared to drug users with two copies of the methionine allele [21]. This interaction has been confirmed in several human populations under different experimental conditions [49,124]. Nevertheless, the neurobiological basis of this interaction remains obscure. Using available genetic mouse models to investigate this particular interaction may yield important data relevant to schizophrenia. For example, one can propose to evaluate the effects of cannabis on the phenotype in COMT mutated mice to see if this combination may exacerbate the phenotype observed in these mice [42] [54,55].

Immune Mutant Models

One of possible types of GEI in schizophrenia may include genetic predisposition to abnormal immune responses to environmental challenges. For example, certain HLA haplotypes may predispose to influenza, or result in an excessive or inappropriate inflammatory response, which could produce prenatal brain damage and ensuing behavioral disorders. The well-known role of cytokines in the innate immune response makes them attractive candidates for studying their functions in disruption of fetal brain development in vulnerable individuals [29,40]. This notion has been supported by the epidemiological findings of an association between elevated cytokines in maternal serum and schizophrenia in the offspring [14]. It has been demonstrated that the maternal immune response to a microbe, rather than direct infection of the fetus, may account for the increased incidence of schizophrenia and related diseases [90].

There have been several studies on a role of prenatal immune activation in causation of neurodevelopmental schizophrenia-like abnormalities rats and mice [5]. In the context of GEI, there is one interesting study that has evaluated interplay between genetically enforced expression of the anti-inflammatory cytokine interleukin (IL)-10 by macrophages and prenatal

immune activation by polyinosine-polycytidylic acid (poly IC). Poly IC has been shown to mimic aspects of prenatal viral infections [38,107,137]. It has been found that over-expression of IL10 attenuated the long-term behavioral and pharmacological consequences of prenatal activation in the adult offspring. In the absence of prenatal immune challenge, enhanced levels of IL-10 by itself led to behavioral abnormalities in the offspring. These findings highlight that activation of both pro-inflammatory and anti-inflammatory pathways can similarly affect cognitive and behavioral development. Thus, it is the balance between pro- and anti-inflammatory cytokines that may be critical for normal neurodevelopment [81]. This study presents a unique approach that combines a mouse model, which tries to mimic genetic vulnerability to immune challenges, with an environmental insult mediated by the host immune system.

DISC1

The Disrupted in Schizophrenia 1 (DISC1) gene was first identified as overlapping a balanced chromosomal translocation [t(1;11)] in a Scottish pedigree with high load of major mental disorders. The LOD ratio for this translocation is 7.1 for all mental disorders and 3.6 for schizophrenia [82]. The breakpoint is in the middle of the open reading frame for the gene. The disrupted gene either fails to express normal DISC1 protein or possibly produces a truncated protein that interferes with the function of normal DISC1. Either way, loss of DISC1 function is believed to be the outcome.

[82]. The existence of a clear, identifiable mutation with high LOD scores has put DISC1 in a unique position in schizophrenia research. In addition to the familial mutation of DISC1, multiple studies of associations of different DISC1 haplotypes or SNPs with mental disorders have stimulated studying the biology of DISC1. Numerous investigations have implicated DISC1 and interacting proteins in neuronal differentiation, migration, synaptogenesis and adult neurogenesis in the hippocampus [12,33,57]. Recently generated DISC1 mouse models [52, 64,69,93,105]have advanced our understanding of the putative mechanisms whereby this protein and its interacting partners may be involved in abnormal neurodevelopment relevant to schizophrenia.

We have generated a mouse model of inducible expression of mutant human DISC1 in forebrain neurons using the Tet-off system [77]. In this model, expression of mutant DISC1 is regulated by the CAMKII promoter and can be turned off by adding tetracycline or a related compound, doxycycline, to food or water. Similar to other DISC1 mouse models, expression of mutant DISC1 produced no gross developmental defects but significantly increased spontaneous locomotor activity in male but not female mice, decreased social interaction in male mice, enhanced their aggressive behavior and was associated with poorer spatial memory in Morris water maze task in female mice. The behavioral alterations have been accompanied by the lateral ventricle enlargement in adult mice and reduced dendritic arborization in primary cortical neurons and decreased expression of a synaptic protein, SNAP-25, consistent with human post mortem studies that show decreased dendritic length and dendritic arborization in frontal cortical areas. The findings also suggest that binding of mutant human DISC1 to endogenous mouse Disc1 might lead to altered expression of endogenous Disc1 itself and its binding partner, Lis1. These molecular disturbances might contribute to the observed neurobehavioral abnormalities. An interesting feature of the model is that expression of mutant DISC1 is associated with the relatively mild neurobehavioral abnormalities, consistent with the hypothesis that a genetic risk factor or a mutation is likely to interact with other genes and/or environmental pathogen(s) for a full-blown disease to develop (e.g., [91]). In addition, there have been several reports at the meetings of using other DISC1 mouse models in combination with various types of stress and/or immune activation during both prenatal and postnatal development [46,72]. Thus, we are using our DISC1 model to evaluate the effects of prenatal

immune activation on the neurobehavioral phenotype produced by expression of mutant DISC1.

Compared to previous studies, we are using a new paradigm based on the identified genetic mutation and measurable adverse environmental events. As an environmental factor, we are utilizing prenatal injections of poly IC to induce the immune response in the pregnant dams and/or fetal brains. This approach is anticipated to help evaluate the specific mechanisms of potential interactions since the brain targets of pro-inflammatory cytokines and the intracellular pathways that mediate effects of cytokines on neuronal cells have been extensively studied [80]. Similarly, the DISC1 protein interactome has been recently published [17]. This background information allows for testing the specific hypotheses as to what molecular mechanisms may mediate putative interactions between poly IC-induced pro-inflammatory molecules and proteins that are affected by mutant DISC1. Importantly, we think that putative mechanisms can be addressed in parallel in vivo and in vitro using primary neuronal cultures from embryos that express mutant DISC1 in differentiating neurons. In addition, the ability to regulate the timing of expression of mutant DISC1 provides an opportunity to identify the critical prenatal and postnatal periods in gene-environment interactions, a feature unavailable in other DISC1 models.

In our preliminary studies, we compared the neurobehavioral effects of poly IC treatment between mice that expressed mutant hDISC1 protein throughout the entire life span and single transgenic tTA mice that did not express mutant hDISC1. Our preliminary experiments provided the initial support for the proposed hypothesis that mutant hDISC1 and prenatal immune activation synergistically affect the neurobehavioral development of the offspring. Curiously, poly IC-treated DISC1 mutant mice also exhibited the behavioral alterations that had not detected in these mice without additional prenatal immune stimulation [93]. Conversely, some behavioral alterations such as anxiety or depression-like responses we saw in poly IC treated mutant mice have not been previously reported for non-transgenic mice prenatally challenged with poly IC only [79]. In other words, our experiments demonstrated the significant interactions between prenatal immune stimulation and mutant hDISC1. The behavioral effects of interactions on emotionality, sociability and “depression”-like activity in DISC1 mice may resemble aspects of affective disorders in psychiatric patients [101]. Intriguingly, among the members of the Scottish family with the chromosomal translocation there are patients with both schizophrenia and mood disorders. It is tempting to speculate that the differential clinical manifestations of the chromosomal translocation in the patients may be due to adverse environmental events [97,101].

Several possible mechanisms of gene-environment interactions in this model could be suggested for future studies. At systems level, mutant hDISC1 and immune activation can have synergistic effects on maturation of neurons by affecting proliferation, migration, early dendritic development and axonal outgrowth, as well as synapse formation and maturation. In addition, activation of the hypothalamus-pituitary-adrenal axis by poly IC and/or released cytokines can produce stress hormones that could affect maturation of cortical and hippocampal neurons in hDISC1 mice. It is conceivable that neurons that express mutant hDISC1 might be more susceptible to adverse effects of stress hormones. At intercellular level, one can anticipate that released cytokines can have direct effects on maturing neurons that express mutant hDISC1. As expression of mutant hDISC1 may be responsible for attenuated neurite outgrowth [93], one can hypothesize that there would be synergistic effects of two factors to affect neurite development. At cellular level, one can envision multiple interactions between the pathways that mutant DISC1 is involved in and cytokines and/or poly IC itself via cytokine receptors or TLR3, respectively [47,76,133]. Although the described above scenarios are hypothetical and have not received any experimental confirmations, we think they provide initial mechanistic hypotheses to be pursued in future studies.

IV. Future directions

Animal models have been instrumental in advancing our understanding of the biology of psychiatric conditions. Recent discoveries in human genetics of mental illnesses have facilitated development of genetic mouse models that more accurately mimic the etiologic factors and will help elucidate the underlying pathogenic mechanisms. It is also hoped that these new mouse models will stimulate research in GEI that play a crucial role on the pathogenesis of schizophrenia. Although still in the infancy, the initial GEI studies have already demonstrated some issues important for future research. It has been found that while combining with environmental challenge certain genetic mutations can be both protective and pathogenic depending on the type of environmental factor and the time of interaction with genetic vulnerability. The available results also seem to indicate that in addition to much anticipated synergistic effects of genes and environments, their combinations can produce a completely new phenotypes previously unobserved in unchallenged mutant mice or wild-type mice exposed an environmental insult.

Despite the limitations to the mouse genetic strategy, including possible confounds related to background strain, and possible influences of flanking regions around mutant genes, gene targeted mutant mice are providing important tools for the genetic and cellular basis of GEI. Nonetheless, development of new approaches is clearly needed. As the diagnostic criteria are not set in stone, and patients with the same diagnoses may present distinct symptom profiles, it is often difficult to study the underlying mechanisms of subtle and variable behavioral alterations in mice. Thus, the use of stable and quantifiable phenotypes called intermediate phenotypes has been proposed in an attempt to provide more reliable functional readouts and better experimental targets as sites of biological synergism between genes and environments [89,98,117]. For example, transgenic DISC1 mice have been found to have lateral ventricular enlargement, a pathological feature that has been consistently reported for schizophrenia [52, 93,106,122]. Such a neurobiological construct appears more stable, and, thus, likely more amenable to mechanistic studies compared to behavioral alterations that are known to be sensitive to the housing and testing conditions [68,127].

At present, animal models of GEI in schizophrenia are just emerging and more research on this issue is needed. It has been suggested that the convergence of environmental and genotypic effects within the same neural substrate will stimulate true mechanistic GEI studies [20]. Future investigations will undoubtedly generate new GEI animal models, with more genetic mutations and functional variants becoming available.

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