Neuron–glia interactions clarify genetic–environmental links in mental illness

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How genes and environment interface to generate major psychiatric disorders such as schizophrenia has been puzzling, as are the relative roles of neurons and glia in such disturbances. Tomonaga and colleagues have recently reported striking neurobehavioral abnormalities in mice expressing Borna disease virus phosphoprotein (BDV-P) selectively in glial cells. The study provides a novel approach of linking environmental and genetic factors to behavior by producing genetically engineered mice. The key role for glial BDV-P implicates neuron–glia interactions in the pathogenesis of psychiatric conditions.

Psychiatric conditions such as schizophrenia and mood disorders reflect a combination of genetic and environmental factors [1]. Recent advances in human genetics have revealed candidate susceptibility genes for schizophrenia. Because even in identical twins the concordance for schizophrenia and mood disorders is only 40–50%, a contribution of environmental factors has been long considered likely and infection by viruses and other agents have been implicated in the etiopathogenesis of schizophrenia [2–6]. For example, cytomegalovirus, herpes simplex virus 1, influenza virus, poliovirus, Toxoplasma gondii, rubella and Borna disease virus (BDV) have been studied as candidate agents using epidemiological, immunological and neuropathological approaches [3–6]. Genetic factors in schizophrenia can be examined, at least in part, using genetically engineered mice. However, it has been difficult to pinpoint causal links between viral infections and neurobehavioral disturbances. Furthermore, lack of reactive astrogliosis, a sign of viral infection, in postmortem brains from schizophrenia patients has been an obstacle for accepting viral involvement in the pathogenesis of schizophrenia. In a recent study, Tomonaga and colleagues [7] have developed an approach to examine effects of viral infections in transgenic mice and have proposed a novel mechanism whereby virus infection might lead to developmental neural abnormalities without reactive astrogliosis.

In their study, selective glial expression of Borna disease virus phosphoprotein (BDV-P) in mice led to behavioral and neurological abnormalities, such as enhanced inter-male aggressiveness, hyperactivity and spatial reference memory deficit [7]. The mouse brains displayed significant reductions in brain-derived neurotrophic factor and serotonin receptor expression, as well as a marked decrease in synaptic density, without reactive astrogliosis. Involvement of BDV in some human neuropsychiatric conditions, as an environmental factor, has been indirectly suggested, although the current evidence does not unequivocally support conclusions concerning human BDV infection in the etiology of human psychiatric conditions [8–10]. BDV infection in rats usually leads either to significant brain injury after neonatal inoculation or to encephalomyelitis in adult animals [11,12], which are not relevant to study conditions similar to schizophrenia brains. The transgenic mice expressing BDV-P have overcome this experimental barrier. Furthermore, the results from BDV-P mice imply that ‘glial’ dysfunction during brain development that is caused by an environmentally derived factor leads to ‘neuronal’ dysfunction and abnormal behaviors in adults; thus, neuron–glia interaction could be a mechanism underlying psychiatric conditions.

Glia: not only supporting cells, but also key regulatory components to neurons

Glia, especially astrocytes, once seen only as supporting cells, are increasingly appreciated as regulators of neurons, for example in neuron generation, synaptic network formation and neuron electrical activity [13–16]. The signaling is bidirectional, as glia are modulated by neurotransmitters released from neurons, which act on glial receptors.

Astrocytes secrete many factors that can influence neural synapse formation, including cholesterol and tumor necrosis factor α (TNF-α) [14]. In response to neurotransmitters released from neurons, astrocytes release factors such as glutamate, ATP and D-serine [15]. In the context of psychiatric conditions, particular attention should be paid to D-serine, which is now recognized as an endogenous co-agonist at the glycine site of the NMDA subtype of glutamate receptor [17]. The psychotomimetic states elicited by NMDA antagonists such as phencyclidine (PCP) mimic certain features of schizophrenia, implying hypo-NMDA neurotransmission in brains of schizophrenia patients. Clinical trials of D-serine, as an agonist of the NMDA receptor, reveal partial amelioration of cognitive dysfunction in schizophrenia, especially when combined with classic neuroleptics.
Persistent glial expression of BDV-P could influence neural synapse formation and neurotransmission, which presumably result in the brain dysfunction and behavioral abnormalities observed in the BPV-P transgenic mice (Figure 1).

Schizophrenia: interaction of genetic and environmental factors during neurodevelopment
Combining classic linkage analysis with analysis of schizophrenia-associated single nucleotide polymorphisms within the linkage areas have revealed several promising candidate genes for schizophrenia, including dysbindin, neuregulin-1, G72, the regulator of G-protein signaling-4 (RGS4) and catechol-O-methyltransferase (COMT) [1,18]. Another promising candidate for psychosis, disrupted-in-schizophrenia-1 (DISC1), was identified by a cytogenetic approach. In a Scottish family, a chromosome translocation (1;11)(q42.1; q14.3) with disruption of DISC1 inside its open reading frame segregates with major psychiatric illnesses with a logarithm of the odds (LOD) score of 7.1 [19]. This translocation interrupts the coding sequence of DISC1 gene, leading to loss of the C-terminal 257 amino acids of the DISC1 protein. Recent association and linkage studies have indicated that DISC1 abnormalities could be involved in psychiatric conditions not only of the unique Scottish family but also in the general population with schizophrenia [20].

Interestingly, most of the susceptibility genes for schizophrenia that have recently been identified might have roles in neural development [1,21]. DISC1 is a cytoskeletal-associated protein and it could be involved in neurite outgrowth and neuronal migration, because the mutant DISC1 in the Scottish family inhibits neurite outgrowth when overexpressed transiently in differentiated PC12 cells [22]. Of note, BDV-P could, via interaction with high mobility group box protein 1 (HMGB1), interfere with neurite outgrowth or neuronal migration in the developing brain [23]. Furthermore, recent observations suggest DISC1 is expressed in glial cells as well as in neurons [24]. Mutation in DISC1 could also lead to glial dysfunction.

These candidate genes are in agreement with a ‘neurodevelopmental hypothesis’ for the pathogenesis of schizophrenia. The most reproducible observation in schizophrenia brains is that ventricles are enlarged and there are minor anatomical deficits in the prefrontal cerebral cortex and hippocampus even at the onset of the disease [25]. Neuropathological studies reveal variability of cell orientation and decreased synaptic structures in neurons, but no signs of glial proliferation (gliosis or astrocytosis).

One reasonable interpretation is that key pathological events in schizophrenia involve infectious processes in genetically susceptible individuals during brain development [1,2,6]. Viral infection in astrocytes can disturb...
neuron–glia communication, which can be further augmented by genetic risks. Many laboratories are currently producing mice genetically engineered for schizophrenia candidate genes such as DISC1. Crossbreeding studies of mice with genetic risk and mice with environmental risk, such as BDV-P transgenics, could clarify genetic–environmental interactions in mental illness.

Concluding remarks
Molecular mechanisms underlying psychiatric conditions such as schizophrenia might reflect a meshing of neuron–glia communication and genetic–environmental interactions. To verify these interactions, we would need to answer the following questions. (i) Which virus proteins are responsible for the effect? (ii) How does virus infection influence cellular mechanisms, such as alteration of gene expression, or signaling cascades via protein interactions? (iii) Which cells represent a meeting place of such cellular (genetic) and viral (environmental) interactions – astrocytes, or neurons, or other cells? Mice expressing specific viral proteins under cell-type-specific promoters should provide effective tools for such studies.

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