Finding a druggable target for schizophrenia

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Schizophrenia is a devastating brain disease that affects ∼1% of the population worldwide and is characterized by a complex array of positive (delusions and hallucinations), negative (apathy and social withdrawal), and cognitive (deficits in attention and working memory) symptoms. Clinical features of schizophrenia frequently arise during late adolescence or early adulthood, which places this disease as the most chronic of the psychiatric disorders and as one of the leading causes of disability and premature mortality (1). Increasing evidence suggests that cognitive impairment is at the core of schizophrenia and precedes the manifestation of psychosis (2). Furthermore, no pharmacological treatment is currently available for cognitive deficits, which are among the most debilitating symptoms of the disorder. The identification of novel treatments to ameliorate the cognitive symptoms of schizophrenia thus seems crucial to improve the quality of life in these patients.

Schizophrenia is thought to be a neurodevelopmental disorder with highly heritability (3). Genetics studies over the past few years have found a strong association between polymorphisms, common genetic variation, and structural deletions in the gene encoding for neuregulin-1 (NRG1) and its receptor ERBB4 with risk for schizophrenia (4–8). In particular, risk polymorphisms in ERBB4 that predict increased expression of the ERBB4 cytoplasmic isoform-1 (CYT-1) receptor isoform and GABA levels in human cortex have attracted a lot of attention (7, 9, 10). The CYT-1 isoform of ERBB4 contains a phosphatidylinositol 3-Kinase (PI3K)-binding site and triggers activation of the PI3K pathway (Fig. 1). Genetic manipulations of NRG1/ERBB4 signaling in animal models lead to abnormal GABA neural circuit development and plasticity (11–13) and cause behavior alterations associated with attention and cognitive deficits, such as prepulse inhibition (PPI) deficits, working memory impairment, and hyperactivity (11, 13). PI3K function has also been linked to neural circuit development, synaptic plasticity, and cognitive function (14, 15).

Thus, human genetics and experimental models point out the potential relevance of NRG1/ERBB4 signaling in the regulation of different aspects of schizophrenia, including cognitive function, but what we are still missing in the field is a more rationale use of this information to identify putative targets and design potential novel drugs to alleviate some of these symptoms.

In PNAS, Law et al. (16) provide unique insights into the mechanisms that link NRG1/ERBB4 signaling and schizophrenia. They first found that an ERBB4 risk haplotype (AGG; rs7598440; rs839523; rs707284) associated with elevated ERBB4 CYT-1 transcription in prefrontal cortex and hippocampus is expressed in patient-derived lymphoblastoid B-cell lines (LCLs). Using these cells, they searched for changes in downstream signaling partners of ERBB4-juxtamembrane isoform-a/CYT-1. They found that the expression of phosphatidylinositol 3-kinase isoform D (PIK3CD), which encodes one of the catalytic subunits of this enzyme (p110δ), changes in association with schizophrenia and ERBB4 genetic variation. PIK3CD transcripts were found to be increased in LCLs, prefrontal cortex, and hippocampus. In contrast, no changes were detected in the ERK-MAPK pathway, which is also linked to ERBB4 signaling. Surprisingly, increased PIK3CD levels did not enhance PI3K function but, instead, dampened PI3K signaling (16) (Fig. 1C). These results thus reveal a complex deregulation of the NRG1/ERBB4/PI3K pathway in schizophrenia that has a negative impact on PI3K signaling. These unexpected results raise the question of whether altered expression in NRG1/ERBB4 signaling in schizophrenia causes gain or loss of function, or even any specific deregulation, within this signaling pathway. It is worth mentioning that downregulation and overexpression of NRG1 cause similar behavioral phenotypes, including impaired recognition memory, hyperactivity, and enhanced exploratory phenotype (17–19). Some of these behavioral deficits are also found in ERBB4 loss-of-function experimental models (11, 13). These results draw our attention to the need to be cautious in our interpretation of the mouse models. Does any unbalance in the expression of NRG1 and ERBB4 have the same functional consequences? Detailed analysis of NRG1 and ERBB4 expression in human postmortem brains of subjects carrying these polymorphisms and functional analyses in mouse models with specific overexpression or deletions of the different isoforms of NRG1 and ERBB4 will improve our understanding of the consequences of disrupting the expression of these genes in the etiology of schizophrenia.

Antipsychotic drugs modulate positive symptoms but have many side effects, in addition to the lack of impact on negative and cognitive symptoms. To test whether manipulation of the PIK3CD cascade reverses some of the deficits of well-known schizophrenia experimental models, Law et al. (16) use a specific inhibitor of PIK3CD, the small molecule IC87114. Remarkably, this compound dramatically blocked amphetamine-induced hyperlo...
comotion in a mouse model of psychosis-like behavior (16). In addition, IC87114 reversed PPI deficits in a neurodevelopmental animal model of schizophrenia based on a ventral hippocampal lesion that causes deficits in sensorimotor gating. These deficits in sensorimotor gating have been associated with attention and cognitive deficits. The specific action of IC87114 on the PIK3 pathway also influences the activation of thymoma viral proto-oncogene 1 (AKT) (Fig. 1D).

PI3K signaling has been shown to be involved in neural circuit development and synaptic plasticity (14, 20). Because of this, one would intuitively expect that inhibition of PI3K signaling would result in decreased cognitive performance. In contrast, Law et al. (16) find that specific inhibition of the catalytical subunit of PI3K restores attention and cognitive impairment, as measured by PPI deficits. How do we reconcile these contradictory ideas? First, IC87114 function seems to be specific to the catalytical subunit in one of the PIK3 isoforms. Second, increased ERBB4/CYT-1 receptor expression may cause a molecular shift toward an attenuated NRG1/ERBB4/PI3K signaling system, perhaps acting as a dominant-negative form. In this context, inhibition of this alteration may restore the cascade to relatively normal signaling levels (Fig. 1D). It would be interesting to know the extent of the inhibition of p110δ, Law et al. provide unique insights into the mechanisms that link NRG1/ERBB4 signaling and schizophrenia.

and whether the alternative signaling cascades are decreased in humans carrying polymorphisms on ERBB4/CYT-1. Do we have a unique candidate target for the treatment of neuropsychiatric disorders? The IC87114 inhibitor seems very specific because it exerts its action only through the catalytical isoform of the PIK3. Moreover, when tested in experimental animal models, it does not show side effects; thus, it is a promising candidate. It would be interesting, however, to extend these initial observations to additional animal models. Furthermore, we ignore the mechanism of action through which inhibition of PI3K signaling improves cognition. Because this pathway has also been shown to be involved in neural circuit development and synaptic plasticity (14, 20), it is possible that chronic inhibition of this pathway has deleterious consequences, and this should be explored.

Further studies on the specific deregulation of ERBB4 signaling cascades in humans should contribute to increase our understanding of the role of NRG1/ERBB4 in schizophrenia. The development of new animal models based on these discoveries, and their subsequent analysis, should also fuel discoveries in this area. Together, these studies are beginning to pave the way for a more logical design of strategies for searching new druggable targets.

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5. Walsh T, et al. (2008) Rare structural variants disrupt multiple genes in neurodevelopmental pathways in schizophrenia. Science 320:539–543.