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PI3Kδ turns schizophrenic

By Tim Fulmer, Senior Writer

A team of **NIH** researchers has linked phosphoinositide 3-kinase-δ to neuregulin signaling and shown that inhibiting the kinase improved behavior in rodent models of schizophrenia.[1] The findings could offer a way to target the neuregulin pathway, which has been associated with schizophrenia for more than a decade but has eluded drug discovery efforts because of a lack of validated targets.

Neuregulin 1 (NRG1) and its receptor, epidermal growth factor receptor 4 (EGFR4; HER4; ErbB4), are expressed in regions of the developing brain. The molecules mediate the proliferation of neuronal progenitor cells and drive neuronal migration, axon outgrowth and synapse formation.[2]

Over the past decade, several labs have independently identified genetic mutations in the *NRG1* and *ErbB4* genes of patients with schizophrenia, suggesting that signaling through the NRG1-ErbB4 pathway may be altered in the disease.[3–6] Moreover, *Nrg1* and *Erbb4* mutant mice show behavioral alterations that are similar to the behavior of some standard schizophrenia mouse models.[7,8]

Although those findings suggested targeting NRG1-ErbB4 signaling could help treat some forms of schizophrenia, researchers avoided going after NRG1 or ErbB4 directly because those proteins play an essential role in a variety of CNS cell types.

The NIH team, led by Amanda Law and Daniel Weinberger, decided to look for targets downstream of NRG1 and ErbB4. In particular, they noted that the ErbB4 isoform CYT-1 had a binding site for phosphoinositide 3-kinase (PI3K). That finding suggested that PI3K signaling might also be dysregulated in cells expressing mutant forms of ErbB4 and that PI3K inhibitors could be used to target NRG1-ErbB4 signaling downstream.

Law is a senior research fellow in the Clinical Brain Disorders Branch of the NIH's **National Institute of Mental Health**. Weinberger is a senior investigator in the same department.

The researchers first studied lymphoblastoid B cell lines (LCLs) to determine whether genetic mutations in *ErbB4* indeed correlated with alterations in PI3K signaling. Peripheral LCLs from patients with schizophrenia express some of the same *ErbB4* mutants that occur in the brain and are useful systems for studying dysregulated NRG1-ErbB4 signaling.

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> —Chang-Gyu Hahn, Perelman School of Medicine at the University of Pennsylvania

In LCLs from patients with schizophrenia, mRNA levels of the catalytic subunit of the PI3Kδ isoform were significantly greater than those in LCLs from healthy controls ($p=0.002$). The higher PI3Kδ mRNA levels were significantly correlated with an ErbB4 mutant that is associated with risk for schizophrenia ($p=0.01$).

Based on those findings, the researchers hypothesized that lowering PI3Kδ activity could help restore NRG1-ErbB4 signaling and treat schizophrenia.

The team treated two rodent models of schizophrenia with IC87114, a small molecule research compound that is highly selective for the PI3Kδ isoform.

In a mouse model of amphetamine-induced psychosis, intraperitoneal delivery of IC87114 significantly decreased psychotic hyperlocomotion compared with vehicle delivery ($p<0.05$). In a rat model of neurodevelopmental schizophrenia, IC87114 reversed sensorimotor deficits, whereas vehicle had no effect ($p<0.009$).

Finally, genetic analysis of two schizophrenic families revealed SNPs in the promoter and intronic regions of the *PI3Kδ* gene. That analysis suggested that disruptions in the neuregulin signaling pathway may be caused not only by mutations in the *NRG1* and *ErbB4* genes but also by mutations in genes encoding downstream effectors such as PI3Kδ.

The findings were published in the *Proceedings of the National Academy of Sciences*.

Many more steps

The researchers now need to see whether the changes in PI3Kδ activity they observed in human LCLs are replicated in a more disease-relevant tissue such as human postmortem brain samples, said Chang-Gyu Hahn. PI3Kδ inhibition could also be directly tested in those samples, he said.

Hahn is associate professor of psychiatry at the **Perelman School of Medicine at the University of Pennsylvania**. In 2006, Hahn and colleagues published in *Nature Medicine* that NRG1-ErbB4 signaling suppressed activation of NMDAR in schizophrenia.[9]

Hahn said more mechanistic work in mice should improve understanding of how altered PI3K activity contributes to the schizophrenia phenotype. "Genetic variation in a single gene, whether it be *ErbB4* or *PI3Kδ*, is not the underlying cause of schizophrenia. Rather, the disease is caused by variation in many genes encoding proteins involved in multiple pathways. Thus, they need to map out and understand how the NRG1-ErbB4-PI3K pathway interacts with proteins in other pathways to give rise to the complex schizophrenia phenotype," he said.

Such work "could not only identify other druggable proteins PI3Kδ interacts with, such as AKT or GSK3B, but also suggest additional ways of blocking the effects of PI3Kδ signaling in schizophrenia," Hahn told *SciBX*.

Corresponding author Law said her team is now "investigating the role of PI3Kδ in brain development and function using approaches in humans and rodents."

She added that the group also is "examining how modulation of the protein either pharmacologically or genetically impacts neuronal development, brain maturation and behaviors related to schizophrenia."

Law and colleagues are also determining which PI3Kδ-selective inhibitors would be most suitable for additional preclinical studies and trials in schizophrenia. She declined to provide additional details.

The lead PI3Kδ-selective inhibitor in clinical development is GS 1101 (CAL-101) from **Gilead Sciences Inc.** The compound is in Phase III testing to treat relapsed chronic lymphocytic leukemia (CLL). GS 1101 resulted from the chemical and pharmacological optimization of IC87114, the research compound used in the paper.

Gilead did not respond to requests for comment.

The *PNAS* findings are patented and available for licensing from the NIH.

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   Contact: Amanda J. Law, National Institutes of Health, Bethesda, Md.
   e-mail: lawa@mail.nih.gov
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COMPANIES AND INSTITUTIONS MENTIONED

Gilead Sciences Inc. (NASDAQ:GILD), Foster City, Calif.
National Institute of Mental Health, Bethesda, Md.
National Institutes of Health, Bethesda, Md.
Perelman School of Medicine at the University of Pennsylvania, Philadelphia, Pa.