Development of Drugs to Treat Fragile X Syndrome and Autism

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Technology description

Technical Summary

Fragile X syndrome (FXS) is an inherited neurologic disease caused by loss of fragile X mental retardation protein (FMRP). A prominent feature of FXS is exaggerated signaling through metabotropic glutamate receptors (mGluRs), and therapeutic strategies to treat FXS are targeted mainly at mGluRs. Recent studies, however, indicate that a variety of receptor-mediated signal transduction pathways are dysregulated in FXS, suggesting that FMRP acts on a common downstream signaling molecule. Dr. Gary Bassell has demonstrated that deficiency of FMRP results in excess activity of phosphoinositide 3-kinase (PI3K), a downstream signaling molecule of many cell surface receptors.

Remarkably, the researchers observed increased PI3K activity in FMRP-deficient non-neuronal cells which do not express mGluRs. They showed that FMRP regulates the synthesis and synaptic localization of p110b, the catalytic subunit of PI3K. In wild type, mGluR activation induces p110b translation, p110b protein expression, and PI3K activity. In contrast, both p110b protein synthesis and PI3K activity are elevated and insensitive to mGluR stimulation in Fmr1 knock-out. This suggests that dysregulated PI3K signaling may underlie the synaptic impairments in FXS. In support of this hypothesis, the researchers showed that PI3K antagonists rescue three FXS-associated phenotypes: dysregulated synaptic protein synthesis, excess AMPA receptor internalization, and increased spine density. The results indicated that targeting excessive PI3K activity may be a potent therapeutic strategy for FXS. Moreover, since a number of gene mutations in PI3K subunits or regulators can lead to autism, we anticipate that selective PI3K subunit inhibitors may have broader applicability for the treatment of autism.

Potential Market

FXS affects 1 in 4000 males and 1 in 6000 females; autism affects nearly 1 in 150 individuals. Currently, there are no treatments for FXS approved by the FDA.

Application area

PI3K inhibitors as therapeutics for FXS and Autism.

Advantages

A novel target and mechanism has been discovered that contributes to FXS.

Compounds that inhibit the catalytic subunit of PI3K have been demonstrated to rescue cellular and biochemical phenotypes in a mouse model of FXS.

Institution

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