Translating autism

By Kai-Jye Lou, Staff Writer

Researchers at **McGill University** have mouse data showing a causal link between eIF4E-mediated translational dysregulation and autism-related deficits. The group also corrected the dysregulation—and the associated autistic phenotype—with a small molecule.¹

The McGill group, led by Nahum Sonenberg, has been studying the role of eukaryotic translation initiation factor 4E (eIF4E) in protein synthesis for over three decades and has primarily focused on the factor's relevance in cancer. eIF4E binds to the cap structure on mRNA and helps to initiate the translation of the mRNA. Sonenberg is a professor in the Department of Biochemistry and at the Rosalind and Morris Goodman Cancer Research Centre at McGill.

The team previously reported that eIF4E-mediated protein translation is modulated by the phosphoinositide 3-kinase (PI3K), protein kinase B (PKB; PKBA; AKT; AKT1) and mammalian target of rapamycin (mTOR; FRAP; RAFT1) pathway, which is commonly disrupted in cancer.²

He said the initial connection to autism came after other research groups showed that autistic children carry mutations in genes upstream of *mTOR*. These genes included *PTEN* (*MMAC1*; *TEP1*) and *tuberous sclerosis complex tumor suppressor 1* (*TSC1*).³⁻⁵

Separately, a 2009 study from a research group in the U.K. showed an association between mutations that increased eIF4E promoter activity and autism.⁶

With multiple studies pointing to eIF4E-dependent processes in autism, the McGill group sought to determine whether dysregulation of eIF4E activity itself could cause an autistic phenotype. Indeed, past studies suggested that dysregulated translation of mRNA could be an underlying cause of autism⁷ but never showed a causal relationship.

In a new study published in *Nature*, the McGill researchers showed that increasing eif4e activity in mice—by knocking out the gene encoding an eif4e repressor called eif4e binding protein 2 (eif4ebp2)—led to autism-associated electrophysiological abnormalities and behaviors.

In these mice, as well as mice that overexpressed eif4e, translation of neuroligin proteins was greater than that seen in wild-type controls. Alterations in neuroligin signaling occur in autism.^{8,9}

In the mouse models, a small molecule inhibitor of eIF4E signaling called 4EGI-1 reversed the electrophysiological abnormalities and decreased autistic behaviors compared with vehicle. Knockdown of neuroligin 1 (*Nlgn1*) had similar effects.

Importantly, inhibition of eif4e and *Nlgn1* activity did not affect electrophysiological and behavioral parameters in wild-type mice.

“The study is of particular interest for me because it provides strong evidence directly supporting the ‘troubled translation’ hypothesis that

Mark Bear and I proposed in 2008, where we suggested that dysregulation of translation may be a core pathophysiological mechanism in autism,” said Raymond Kelleher, an assistant professor of neurology at **Harvard Medical School** and a principal investigator at the Center for Human Genetic Research at **Massachusetts General Hospital**.

Kelleher said the new data also draw a direct link between translational dysregulation and the regulation of the balance of excitatory and inhibitory synaptic transmission by neuroligins, which is another candidate pathophysiological mechanism in autism.

Eric Klann, a professor in the Center for Neural Science at **New York University**, said the results are consistent with observations from ongoing work from his lab, which is investigating excessive eIF4E translation as a molecular mechanism underlying autism. He added that his group has been working with similar mouse autism models and with 4EGI-1.

Klann noted that his group has a complementary paper in the press that further solidifies the causal relationship between eIF4E-mediated translational dysregulation and autism.

“Our work and the Sonenberg data show that exaggerated eIF4E-dependent translation will cause synaptic and behavioral abnormalities consistent with autism,” he told *SciBX*.

Validation needed

The findings now need to be validated in mice carrying mutations in genes known to cause autism and with more drug-like inhibitors of eIF4E-mediated protein translation than 4EGI-1.

A group at Harvard Medical School first identified 4EGI-1 in 2007 as a small molecule that inhibits translation of mRNA by disrupting the association between eIF4E and eIF4γ (EIF4G).¹⁰ However, the researchers noted in their study that the compound does not have the potency necessary for development as a drug candidate.

Moreover, it is still unclear which subset of patients with autism should be targeted. Klann said fragile X-associated autism could be the place to start, as dysregulated mRNA translation also is seen in mouse models of fragile X syndrome.

About 15%–30% of patients with fragile X syndrome also have autism.⁷

Klann added that there already are multiple companies trying to target the eIF4E-regulated translational axis and related axes in cancer. “Some of the compounds these companies are developing could potentially cross the blood brain barrier and could thus be suitable for use in patients with autism,” he told *SciBX*.

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—Raymond Kelleher,
Harvard Medical School

At least two eIF4E inhibitors are in development. **Isis Pharmaceuticals Inc.**'s ISIS-EIF4ERx, a second-generation antisense compound targeting eIF4E, is in Phase II testing to treat non-small cell lung cancer (NSCLC) and prostate cancer. **Translational Therapeutics Inc.**'s TRX-201, a Lipid Vector Technology (LVT) derivative of ribavirin, is in preclinical development to treat thyroid cancer.

The generic antiviral ribavirin also inhibits oncogenic eIF4E activity and has been tested in an investigator-led Phase II trial in patients with acute myelogenous leukemia (AML).^{11,12} The researchers reported 5 responses and 4 cases of stable disease among 11 evaluable patients.

Kelleher wanted to see the McGill team's findings validated in other mouse autism models.

"It will be important to determine whether the mechanisms defined in this study apply to known genetic causes of autism—that is, whether known genetic causes of autism lead to dysregulation of cap-dependent translation and/or neuroligin expression," he told *SciBX*. "Similarly, it will be important to test whether partial inhibition of cap-dependent translation or knockdown of specific neuroligins can reverse synaptic and behavioral deficits in mouse models of known genetic causes of autism."

Sonenberg said his group is developing mice with eif4ebp2 knocked out in specific brain regions. His team also is trying to develop conditional knockout mice to determine whether loss of eif4ebp2 at different time points in early life would lead to the autistic phenotype.

Klann's group is now trying to determine whether targeting eif4e in fragile X mouse models would be able to correct the associated autistic behaviors. The team also is trying to develop a method to measure the translation of various proteins in the mouse autism models, which will

help to identify common dysregulated proteins across the multiple models.

Finally, Klann said his group has been contacted by companies interested in testing compounds that inhibit the eIF4E translational regulatory pathway in the mouse autism models being used by his group.

The findings reported in *Nature* are unpatented. The mouse models are available for licensing.

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