Cell & Developmental Biology
ISSN: 2168-9296

Gilbert and Man, Cell Dev Biol 2014, 3:2
DOI: 10.4172/2168-9296.1000e124

Editorial Open Access

Translational Dysregulation in Autism

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Rec date: May 02, 2014, **Acc date:** May 05, 2014, **Pub date:** May 07, 2014

Editorial

Autism Spectrum Disorder (ASD) is one of the most common neurodevelopmental disorders. In the United States, as many as 1 in 166 individuals have ASD and it is estimated that more than 50% of those with ASD have intellectual disability [1]. ASD is among the most heritable neuropsychiatric disorders, and available evidence points to a complex genetic basis [2]. Whereas the genetic influences that cause ASD are heterogeneous, shared features are commonly observed in individuals, including impaired social relationships, augmented language and communication, and a limited range of interests and behaviors [3]. In most cases the cause is unknown, however genetically defined syndromes with increased prevalence of ASD can offer valuable insight into the underlying molecular pathways.

In the brain, neurons communicate via synapses, tiny specialized structures connecting an axon from one neuron to the dendritic spine, or shaft, of a receiving neuron. Formation and maturation of synapses constitute one of the most fundamental processes in brain development. In mature neurons, synapses are constantly regulated in their structure and function, and synaptic plasticity underlies higher brain functions, including learning, memory, cognition and behavior. Mouse models of ASD gene mutations discovered in humans have consistently revealed aberrant synaptic function, typically expressed as a disruption in plasticity [4-6] and alterations in the number and balance of excitatory and inhibitory connections [7,8]. Therefore, irregularities in the "autistic" neuron may manifest as an increased or decreased number of synapses, which are either too strong or too weak. Interestingly, most of the ASD-related genetic mutations seem to not directly affect synapse structure, indicating that another level of control is dysregulated in ASD. Recently, emerging findings show alterations in protein expression in ASD [9], implicating a dysregulation in protein synthesis in the pathology of ASD.

For the majority of mRNAs, the translation process begins with the involvement of the eukaryotic initiation factor 4F (eIF4F) complex. The eIF4 factors include the 5' cap-binding protein eIF4E, the scaffolding protein eIF4G that bridges the poly-A tail and the ribosome by circularizing mRNA, and the RNA helicase eIF4A for resolving mRNA secondary structures [10]. Under normal conditions, most cellular mRNAs require basal amounts of eIF4E for translation, however, eIF4E can preferentially enhance the translation of mRNAs that contain extensive secondary structure in their 5'-untranslated regions (UTRs) or other sequence components [10,11].

The eIF4E binding protein 2 (4E-BP2) acts to repress translation by disrupting formation of the eIF4F complex [12]. Phosphorylation of 4E-BP2 by mammalian target of rapamycin (mTOR) complex 1 (mTORC1) stimulates translation by releasing 4E-BP2 from the complex, while non-phosphorylated forms of 4E-BP2 bind to eIF4E and inhibit translation initiation [10]. 4E-BP2 is one of 4 mammalian homologues (4E-BP1-4) in which 4E-BP2 is predominantly expressed in the brain and plays an important role in long-term plasticity, learning and memory [13].

A recent study has demonstrated a strong link between protein synthesis and ASD. Santini et al. show that transgenic mice over-expressing eIF4E display exaggerated cap-dependent translation without compensatory changes in the levels of other translational control proteins [14]. Importantly, eIF4E-transgenic mice display repetitive and stereotyped behaviors, abnormalities in social interactions, cognitive inflexibility and patterns of behavioral abnormalities that are consistent with ASD. Additionally, spontaneous post-synaptic currents in layers II/III of the medial prefrontal cortex and hippocampus revealed an enhancement in excitatory input and postsynaptic sensitivity for inhibitory events, consistent with the hypothesis that autism may arise from an imbalance in the ratio of excitation to inhibition (E/I). Furthermore, eIF4E-transgenic mice exhibited enhanced metabotropic glutamate receptor-dependent LTD (mGluR-LTD) compared to wild-type mice, consistent with previous findings that showed changes in neuronal protein synthesis are accompanied by altered hippocampal mGluR-LTD [14-16]. Therefore, an increased expression of eIF4E in the brain leads to altered synaptic plasticity and behavioral abnormalities associated with ASD.

Upstream of mTOR, PTEN (phosphatase and tensin homolog) dephosphorylates phosphatidylinositol (3,4,5)-trisphosphate (PIP3) into the biphosphate product, PIP2. This dephosphorylation is important because it results in the inhibition of the Akt signaling pathway. Germline mutations in PTEN are present in about 1-5% of ASD patients [17] and PTEN knockout mice exhibit cognitive and social deficits [18], which are rescued by the mTORC1 inhibitor rapamycin [19]. Akt is an essential link between the PI3K pathway and mTOR through the inactivation of the Tuberous Sclerosis Complex (TSC). In line with the role of the PI3K/Akt/mTOR pathway, mutations in the two TSC genes (TSC1 and TSC2) have also been linked to ASD in a subset of patients [20]. $Tsc2^{+/-}$ mice display synaptic plasticity and memory deficits and knockout of Tsc1 in cerebellar Purkinje cells also leads to ASD phenotypes in mice. Both $Tsc2^{+/-}$ and $Tsc1^{-/-}$ mouse deficits are rescued by treatment with rapamycin [21]. These findings suggest that mutations in any of the upstream regulators of mTOR can disrupt eIF4F translation initiation and protein synthesis-dependent plasticity, leading to the pathological neurodevelopment of ASD (Figure 1).

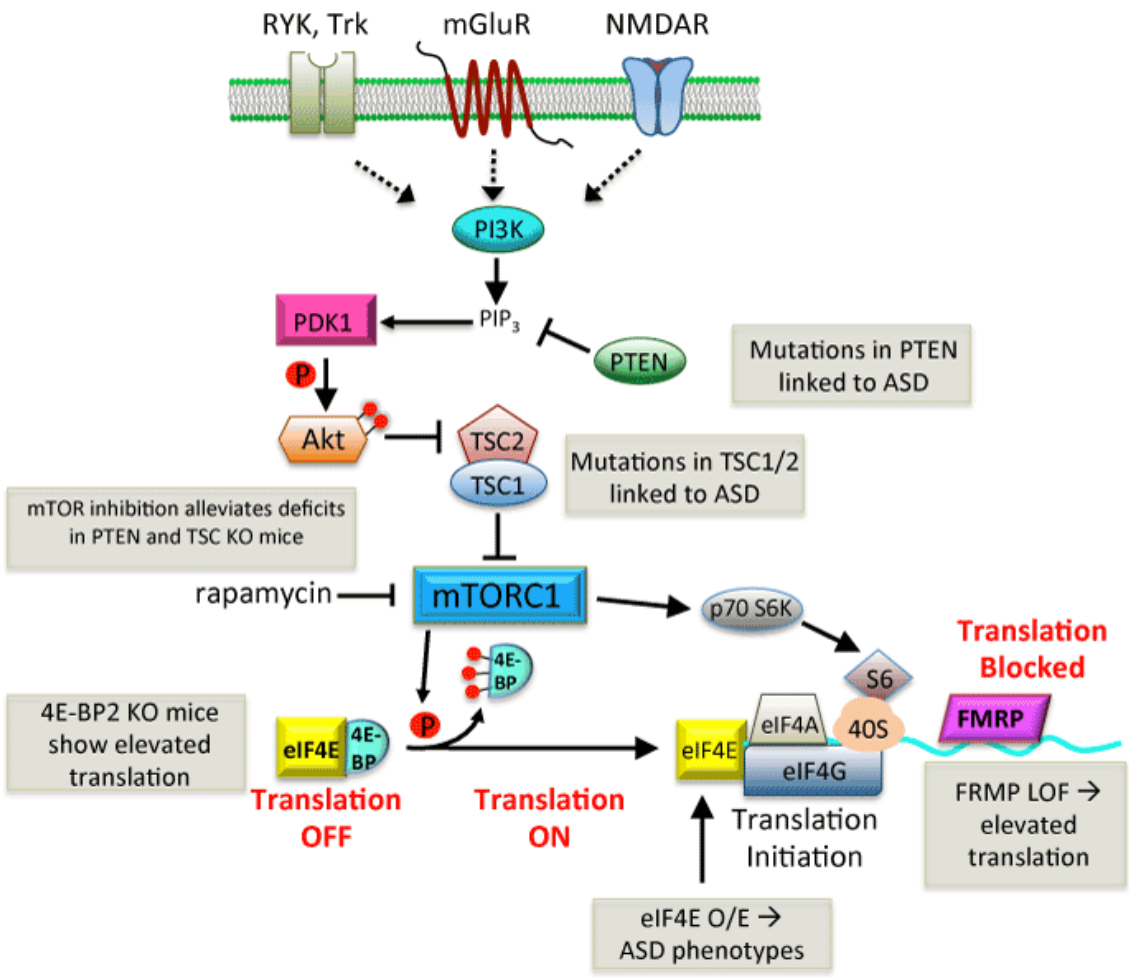

Figure 1: Dysregulation of the PI3K/Akt/mTOR pathway in ASD. The mTOR pathway integrates multiple inputs, such as RYK/ Trk receptors, NMDARs and mGluRs. Activation of PI3K phosphorylates and converts PIP2 to PIP3, leading to PDK1-mediated Akt activation. The Akt signaling cascade inhibits the TSC1/2 complex removing its inhibition on mTORC1. Activated mTORC1 phosphorylates 4E-BP, releasing eIF4E to form a 4E/4G complex to initiate protein translation. mTORC1 also stimulates translation initiation via p70 S6K-dependent phosphorylation. Mutations in PTEN and TSC1/2 cause hyperactivity of the mTORC1-eIF4E pathway and have been linked to ASD. 4E-BP2 inhibits translation by competitively binding eIF4G and preventing its interaction with eIF4E. Either loss of 4E-BP or over-expression of eIF4E enhances cap-dependent translation. Loss of function of FMRP, which binds to mRNA and inhibits translation, results in excess protein synthesis, while mTOR inhibition with rapamycin is sufficient to alleviate ASD phenotypes.

RYK: Receptor-like tyrosine kinase; Trk: Tyrosine receptor kinase; NMDAR NMDA receptor; mGluR: Metabotropic glutamate receptor; PI3K: Phosphoinositide-3 kinase; PIP2: Phosphatidylinositol biphosphate; PIP3: Phosphatidylinositol (3,4,5)-triphosphate; PTEN: Phosphatase and tensin homolog; PDK1: Phosphoinositide dependent kinase 1; Akt: Serine/threonine specific kinase; TSC: Tuberous sclerosis complex; mTORC1: Mammalian target of rapamycin complex 1; p70 S6K: p70 ribosomal kinase; 40S: Ribosomal subunit; eIF4: eukaryotic translation initiation factor; 4E-BP: eIF4E binding protein; FMRP: Fragile-X mental retardation protein; P: Phosphate group; O/E: Overexpression; LOF: Loss of function, ASD; Autism spectrum disorder.

Distinct from other cell types, neurons are highly polarized cells with a long axon and extensive branches of dendrites. It has become clear that in neurons protein synthesis is not limited to the cell body (soma), as it also occurs locally in the neurites. Local protein synthesis is crucial in neuron structural development, connectivity and synaptic function [22-24]. Current evidence indicates that, in addition to global changes in protein synthesis, ASD is also associated with disruptions in the control of local protein translation. Fragile-X Syndrome (FXS) is the most common monogenic cause for ASD and is identified in roughly 2-5% percent of cases, while approximately 15-30% of FXS patients meet the criteria for ASD [9]. FXS is caused by loss of function of the Fragile-X Mental Retardation Protein (FMRP), which is an RNA-binding protein involved in the control of local protein synthesis, as well as mRNA stability and trafficking [25]. FXS has been associated with elevations in rates of protein synthesis [26]. FMRP facilitates local translation within dendrites and spines in response to changes in

neuronal activity, while loss of FMRP results in aberrant protein synthesis-dependent forms of plasticity [27]. FMRP typically translocates from the nucleus to the cytoplasm to associate with polyribosomes through large messenger ribonucleoprotein particles to suppress translation of bound mRNA [28]. FMRP has also been shown to interact with components of the microRNA (miRNA) pathway, or miRNAs themselves [29,30]. Additionally, the cytoplasmic FMRP interacting protein 1 (CYFIP1) has been causally linked to ASD as an eIF4E binding protein, leading to an inhibition of eIF4F complex formation and translation [31]. Indeed, studies show that the mTORC1-eIF4E pathway becomes hyperactivated in FXS patients, further implicating dysregulation of eIF4E and translation initiation in FXS and ASD.

Dysregulation in protein translation is likely one of the fundamental pathologies in ASD. Future studies are expected to expand the list of specific proteins that are affected and their functional implications. Furthermore, understanding the preference and relationship of local vs. global changes in protein translation in ASD will be important in developing our understanding of ASD etiology.

Acknowledgement

We thank lab members for useful discussions. Research in our laboratory is supported by an NIH grant (HYM, MH079407).

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