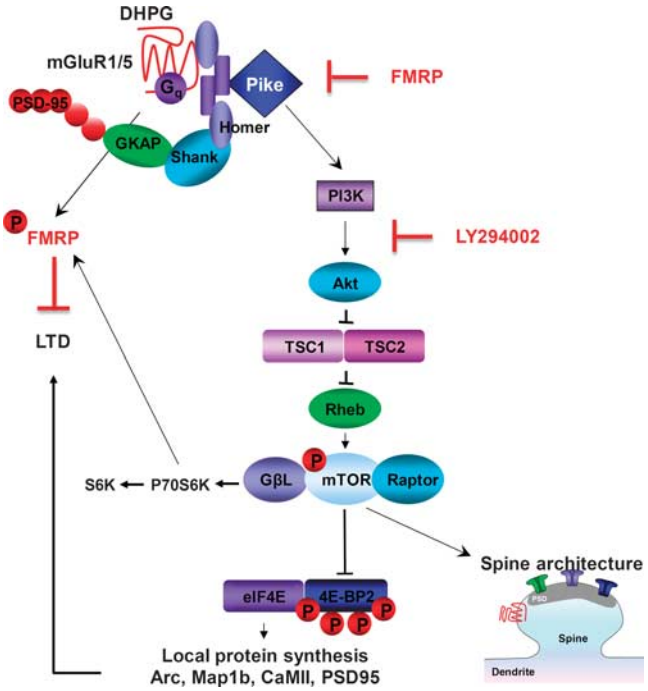

Figure 1. Scheme showing the link between deficits in FMRP and overactivated mTOR. Our findings support a model where, in WT mice, FMRP represses PIKE, an upstream activator of PI3K signaling and identified target of FMRP, and thereby inhibits mTOR signaling. Upon activation, group I mGluRs act *via* Gq and Homer to bind PIKE and engage PI3K signaling, which activates mTOR. mTOR drives cap-dependent translation and local synthesis of synaptic proteins such as Arc, Map1b, CaMII, and PSD-95, critical to mGluR-LTD. In addition, mTOR regulates LIMK and cofilin, which promote spine morphogenesis. In mice lacking FMRP, PIKE is derepressed, resulting in overactivation of mTOR, accumulation of synaptic proteins, and exaggerated, protein synthesis-independent LTD. The PI3K inhibitor LY294002 corrects p-mTOR and restores DHPG sensitivity. A prediction of the model is that dysregulation of mTOR signaling contributes to the cognitive and social interaction deficits observed in humans with Fragile X.

FMRP (Darnell *et al*, 2011) is elevated at the synapses of *Fmr1* KO mice (Gross *et al*, 2010; Sharma *et al*, 2010), providing a functional link between loss of FMRP and overactivated mTOR signaling (Figure 1). These findings identify dysregulation of mTOR signaling as a phenotypic feature common to FXS, TSC1 and 2, NF1, and PTEN-associated autism syndromes. Whereas other syndromic ASDs arise from mutations in components of the PI3K–mTOR pathway, FXS arises from silencing of the gene encoding FMRP, an RNA-binding protein that represses translation of a large array of RNAs including PIKE. This, in turn, results in elevation of PIKE and overactivation of PI3K–mTOR signaling. These observations raise the possibility that dysregulation of mTOR may be a unifying theme in a growing number of ASDs and ASD-associated syndromes.

On the basis of the clear link between overactivated mTOR signaling and autism, the mTOR pathway represents a promising therapeutic target for the treatment of ASDs. Treatment with the mTORC1 inhibitor rapamycin has shown promising results in PTEN knockout mice (Zhou *et al*, 2009) and TSC2 + /− mice (Ehninger *et al*, 2008). Thus, interventions that target mTOR signaling should be at the leading edge of future translational research in the autism field.

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Habenular Signaling in Nicotine Reinforcement

Tobacco dependence is a complex genetic trait, with greater than 50% of the risk of developing dependence attributable to genetic factors (Li *et al*, 2003). Nicotine, the major psychoactive component in tobacco smoke responsible for dependence, functions in the brain through neuronal nicotinic acetylcholine receptors (nAChRs). A major breakthrough in understanding the genetics of tobacco dependence was the finding that allelic variation in the *CHRNA3-CHRNA5-CHRNB4* gene cluster, which encodes the $\alpha 3$, $\alpha 5$, and $\beta 4$ nAChR subunits, respectively, increases vulnerability to

tobacco dependence and smoking-associated diseases (Bierut *et al*, 2008; Thorgeirsson *et al*, 2008). In particular, a polymorphism in *CHRNA5* (rs16969968) that results in an aspartic acid to asparagine substitution at amino-acid reside 398 (D398N) more than doubles the risk of tobacco dependence in those carrying two copies of the risk allele. Little was known about how nAChRs-containing $\alpha5$, $\alpha3$, and/or $\beta4$ subunits may contribute to tobacco dependence. However, recent findings suggest that nAChRs containing these subunits play a key role in regulating nicotine reinforcement.

The $\alpha3$, $\alpha5$, and $\beta4$ nAChR subunits are densely expressed in the medial habenula (MHb) and its major site of projection, the interpeduncular nucleus (IPN) (Salas *et al*, 2009). Our laboratory has recently shown that mice with null mutation in the $\alpha5$ nAChR subunit gene intravenously self-administer significantly greater quantities of nicotine than their wild-type counterparts, particularly when higher unit doses of the drug are available for consumption (Fowler *et al*, 2011). This enhanced intake in the mutant mice was ameliorated by virus-mediated re-expression of $\alpha5$ nAChR subunits in the MHb–IPN tract. In addition, we found that IPN neurons were insensitive to nicotine in the mutant mice, reflected in greatly diminished induction of Fos immunoreactivity in response to nicotine injections. Moreover, lidocaine-induced inactivation of the MHb or IPN increased nicotine self-administration in rats, particularly at higher units doses of the drug. Finally, virus-mediated knockdown of $\alpha5$ nAChR subunits in the MHb–IPN tract did not alter the reward-enhancing properties of lower nicotine doses, but greatly attenuated the reward-inhibiting (ie, aversive) effects of higher nicotine doses in rats (Fowler *et al*, 2011). In keeping with these findings, overexpression of $\beta4$ nAChR subunits in the MHb–IPN tract enhanced aversion to nicotine and reduced consumption of the drug in mice (Frahm *et al*, 2011). Moreover, virus-mediated expression in the MHb of a major risk allele of the $\alpha5$ subunit gene (D398N allele), which decreases the function of $\alpha5$-containing nAChRs incorporating this risk allele and increases vulnerability to tobacco dependence in humans, reduced aversion to nicotine and enhanced nicotine intake in the $\beta4$ subunit-overexpressing mice (Frahm *et al*, 2011). Hence, nAChRs-containing $\alpha5$ and/or $\beta4$ subunits regulate the activation of the MHb–IPN tract in response to nicotine, which signals aversion to the drug. Deficient nAChR signaling in the MHb–IPN tract, which likely occurs in humans carrying risk alleles in the *CHRNA3-CHRNA5-CHRNB4* gene cluster, reduces nicotine aversion and results in greater consumption of the drug. As such, these finding reveal fundamental new insights into the mechanisms of nicotine reinforcement and the neurocircuitry of tobacco dependence.

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Circuits, Cells, and Synapses: Toward a New Target for Deep Brain Stimulation in Depression

Understanding the pathophysiology of depression requires knowledge of the anatomical pathways that malfunction in this disorder. The anatomy of depression involves limbic and hypothalamic activation mediating stress and anxiety. These interact with cortical areas, primarily the medial prefrontal cortex (mPFC), which appears to mediate the cognitive aspects of depression. The mPFC in turn innervates the thalamus and lateral habenula (l. habenula). The anatomy of melancholia has recently been advanced through an understanding of the role of the l. habenula and incorporation of this structure between the cortical and limbic inputs and the monoaminergic nuclei. The l. habenula controls the midbrain monoaminergic nuclei, whose output pathways interact with each other, as well as providing strong modulatory control of limbic and cortical areas. Recently understanding of how the dopamine system is regulated by the l. habenula in normal (Matsumoto and Hikosaka, 2009) and affectively disturbed states (Li *et al*, 2011) has been investigated. Over activity in the l. habenula is seen in both the learned helplessness model (Li *et al*, 2011) and in patients who express depressive symptoms following tryptophan depletion (Roiser *et al*, 2009). This over activity causes decreased dopaminergic stimuation, suppressing reward signals (Matsumoto and Hikosaka, 2009). It also depresses 5HT signals (Wang and Aghajanian,