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NEURODEVELOPMENTAL DISORDERS

TSCerebellar autism in mice

The cerebellum has recently been implicated in autistic spectrum disorders (ASDs), but much remains unknown about its contribution to ASD pathogenesis. Animal models of tuberous sclerosis, a genetic disorder that is characterized by autistic features and results from mutations in the genes tuberous sclerosis complex 1 (*TSC1*) or *TSC2*, have been used to study the pathogenesis of autistic symptoms, and a new study now shows that loss of TSC1 function in cerebellar Purkinje cells in mice induces an autism-like phenotype that can be prevented by rapamycin treatment.

Tsai and colleagues generated heterozygous and homozygous mutant mice in which *Tsc1* was selectively deleted in cerebellar Purkinje cells. They found morphological changes in the cerebellum of adult homozygous mutant mice starting at 1 month of age. Specifically, Purkinje cells were reduced in number and had enlarged somas compared with those of control and heterozygous mice. In addition, spine density on Purkinje cell dendrites was increased in homozygous and heterozygous mice.

The morphological alterations were accompanied by functional changes. Although synaptic transmission at Purkinje cell inputs was normal in mutant mice, heterozygous and homozygous mutant Purkinje cells showed a reduced spontaneous firing rate and fired fewer action potentials following current injection, which is indicative of decreased excitability. Thus, Purkinje cells lacking one or both copies of *Tsc1* appear to receive normal synaptic inputs but show reduced output owing to decreased intrinsic excitability.

Tsc1 mutant mice also had behavioural symptoms associated with autism. As pups, homozygous and heterozygous mice emitted a higher number of vocalizations — which is indicative of altered social communication — and in adulthood they showed impairments in social interaction tests. In addition, homozygous mutant mice showed less behavioural flexibility, and therefore reduced learning, in the reversal phase of a watermaze learning task, and both heterozygous and homozygous mice self-groomed more than control animals.

As TSC1 normally dimerizes with TSC2 to inhibit mammalian target of rapamycin (mTOR), the authors investigated whether treatment with the mTOR inhibitor rapamycin could compensate for the absence of TSC1 in Purkinje cells. Indeed, rapamycin treatment in homozygous mutant mice starting at postnatal day 7 prevented the development of morphological abnormalities in Purkinje cells, the reversal learning deficits and the abnormalities in social behaviour.

The finding that loss of TSC1 from Purkinje cells is sufficient to induce an autism-like phenotype in mice points to an important role for the cerebellum in the neural circuit that mediates ASD symptoms and provides a molecular basis for studying this role.

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ORIGINAL RESEARCH PAPER Tsai, P. T. *et al.* Autistic-like behaviour and cerebellar dysfunction in Purkinje cell *Tsc1* mutant mice. *Nature* 1 Jul 2012 (doi:10.1038/nature11310)