NEURODEVELOPMENTAL DISORDERS

MeCP2 has a role in maintaining synaptic density but not in basal postsynaptic transmission

The importance of scaling up

Loss-of-function mutations in the gene encoding the transcriptional regulator methyl CpG binding protein 2 (MeCP2) are the leading cause of Rett syndrome — a neurodevelopmental disorder that almost exclusively affects females. How the loss of MeCP2 causes the neurological deficits observed in Rett syndrome is unknown. Now, however, Turrigiano and colleagues show that MeCP2 has an essential role in maintaining excitatory synapse number and in regulating whether synapses increase or decrease their strength in response to chronic changes in neuronal activity (termed synaptic scaling). These data raise the possibility that some of the deficits associated with Rett syndrome arise from a perturbation in homeostatic plasticity.

Previous studies in MeCP2-null mice (a model of Rett syndrome) showed that these animals had reduced numbers of glutamatergic synapses. To further investigate this observation, the authors acutely and selectively knocked down MeCP2 expression by RNA interference in cultured postnatal rat neocortical pyramidal neurons. Cell-surface immunostaining experiments revealed that these cells had a reduced number of puncta that were positive for GluA1 (a subunit of the AMPA receptor (AMPA)) and of puncta that showed colocalization of GluA1 and VGLUT1 (a label of presynaptic excitatory terminals). However, spared synapses showed

IMAGESTATE

no change in the intensity of GluA1 staining, and MeCP2 knockdown had no effect on the amplitude or frequency of AMPAR-mediated miniature excitatory postsynaptic currents (mEPSCs) in these cells. Together, these results show that MeCP2 has a role in maintaining synaptic density but not in basal postsynaptic transmission at the level of individual synapses.

Knockdown of MeCP2 did, however, affect the synaptic scaling capacity of neurons, as following treatment with an AMPAR antagonist, MeCP2-deficient neurons showed no increase in AMPAR-mediated mEPSC amplitudes to compensate for their reduced firing capacity. Synaptic scaling can also

be induced *in vivo* in response to sensory deprivation, but MeCP2-null mice that were placed in the dark for 4 days at postnatal day 20 or 21 showed no increase in the amplitude of AMPAR-mediated mEPSCs.

Together, these data show that MeCP2 has an important role in synaptic plasticity during postnatal development, and suggest that loss of MeCP2 causes dysfunction in synaptic scaling within neocortical circuits. Moreover, it seems that MeCP2 is also important for experience-dependent visual cortical plasticity.

Man Tsuey Tse

ORIGINAL RESEARCH PAPER Blackman, M. P. *et al.* A critical and cell-autonomous role for MeCP2 in synaptic scaling up. *J. Neurosci.* **32**, 13529–13536 (2012)