SYNAPTIC PHYSIOLOGY

Making connections through MeCP2

Rett syndrome is caused by mutations or duplications in the gene that encodes methyl-CpG-binding protein 2 (MeCP2), which binds to methylated DNA, thereby suppressing gene transcription. *Mecp2* mutant mice and patients with Rett syndrome show defects in synaptic development, but the underlying mechanism is not clear. Writing in *Neuron*, Zhaolan Zhou and colleagues shed fresh light on the regulation of MeCP2 function by experience-dependent neuronal activity.

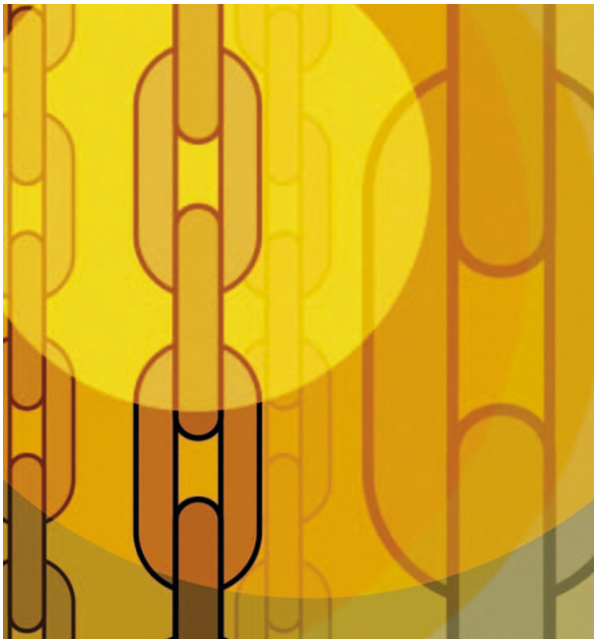
The researchers previously showed that membrane depolarization in cultured cortical neurons gave rise to a form of MeCP2 with a slightly higher molecular weight. In the new study, they found that this was due to the phosphorylation of serine 421 (S421) on MeCP2. Stimulation of cultured hippocampal neurons with neurotransmitters or neurotrophins also induced S421 phosphorylation on the protein.

Using a seizure model, Zhou *et al.* showed that synchronized synaptic activity induced by chemo-convulsants triggered MeCP2 phosphorylation at S421 in cortical layers II–VI and in all regions of the hippocampus. They went on to study the effect of a physiological stimulus, light exposure, on MeCP2 S421 phosphorylation. Exposure of circadian-entrained animals to light during the subjective night normally triggers a behavioural shift in the phase of circadian rhythm, which is mediated by a subset of retinal ganglion cells projecting directly to the suprachiasmatic nuclei (SCN). Using entrained mice, the team found that such light exposure triggered the phosphorylation of MeCP2 at S421 in the SCN.

Although MeCP2 is ubiquitously expressed in mammalian tissues, mutations in the gene only affect the nervous system. To tackle this puzzling phenomenon, the researchers analysed a wide range of tissues and found that S421 phosphorylation on MeCP2 occurred only in neural tissues. The mechanism underlying this specificity is not clear, but Zhou *et al.* suspect that calcium/calmodulin-dependent protein kinase II (CaMKII) has an important role. Furthermore, inhibitors of the enzyme abolished phosphorylation of MeCP2 at S421 in response to membrane depolarization, whereas elevation of CaMKII activity led to MeCP2 phosphorylation in the absence of neuronal activity.

What does MeCP2 do once phosphorylated? Previous studies showed that the phosphorylated protein had reduced binding to methylated DNA. The researchers conjectured that this might lead to the activation of genes that are important for synaptic development. To prove this, they used a lentivirus-mediated protein-replacement assay, which allowed them to substitute endogenous MeCP2 with higher levels of tagged variants in cultured hippocampal neurons. In neurons expressing wild-type MeCP2, the level of brain-derived neurotrophic factor (BDNF) transcript increased as a result of membrane depolarization, whereas the level of induction of BDNF was decreased in the MeCP2 variant in which the serine residue was mutated to alanine (S421A).

To establish a causal link between MeCP2 function and synaptic development, *Zhou et al.* adopted a similar approach to overexpress the wild-type or mutant gene in organotypic hippocampal slice cultures. They found that high levels of MeCP2 expression led to a decrease in the complexity of dendritic branches, mimicking the phenotypes that were due to duplications of the gene. Interestingly, the dendritic morphology of neurons expressing mutant MeCP2 was similar to the control, indicating that inhibition of dendritic growth might be mediated by S421 phosphorylation on MeCP2.



This elegant study provides evidence that experience-dependent phosphorylation of MeCP2 is crucial for the normal development and maturation of the brain. How this process is perturbed in patients with Rett syndrome remains to be seen. In addition, it will be interesting to test whether mice with a point mutation at S421 on MeCP2 have the neurological symptoms associated with this disorder.

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ORIGINAL RESEARCH PAPER Zhou, Z. *et al.* Brain-specific phosphorylation of MeCP2 regulates activity-dependent Bdnf transcription, dendritic growth and spine maturation. *Neuron* **52**, 255–269 (2006)

FURTHER READING Bienvenu, T. & Chelly, J. Molecular genetics of Rett syndrome: when DNA methylation goes unrecognised. *Nature Rev. Genet.* **7**, 415–426 (2006)

WEB SITE

Greenberg's laboratory: http://www.childrenshospital.org/research/greenberg/