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NEURODEVELOPMENTAL DISORDERS

A contagious deficit

The impaired brain function in patients with Rett syndrome, an X-linked neurodevelopmental disorder, is thought to be due to a loss of methyl-CpG-binding protein 2 (MECP2) in neurons. Now, Maezawa *et al.* show that astrocytes also express *MECP2* and can spread MECP2 deficiency through gap junctions, and so potentially contribute to Rett syndrome.

MECP2 is highly expressed in neurons and had previously not been detected in astrocytes. Here, however, immunofluorescence assays revealed MECP2 expression in astrocytes of wild-type mice, albeit at lower levels than in neurons. The authors also tested mice with a deletion of *Mecp2* exons 3 and 4. Mosaic heterozygous (female) *Mecp2*$^{+/-}$ mice, which provide the most suitable model for human Rett syndrome as it typically affects girls, had both MECP2-positive and -negative astrocytes.

Primary astrocytes cultured from *Mecp2*$^{+/-}$ mice expressed a 50–50 mixture of wild-type and mutant *Mecp2* transcripts, as established using reverse transcription PCR. Intriguingly, however, MECP2 expression in these cultures decreased from ~50% of wild-type values to 10–30% after 2–4 weeks in culture. Moreover, when *Mecp2*$^{+/-}$ astrocytes were co-cultured with wild-type astrocytes, MECP2 expression in the wild-type astrocytes also decreased in a time-dependent manner. Together, these data suggest that MECP2 deficiency can spread throughout astrocytes in culture.

Astrocytes are typically connected to one another by gap junctions; this spurred the authors to investigate whether these connections might mediate the transmission of MECP2 deficiency. Indeed, addition of gap junction inhibitors or downregulation of the gap junction component connexin 43 with small interfering RNA reduced the transmission of MECP2 deficiency.

Compared with wild-type astrocytes, astrocytes from *Mecp2*$^{+/-}$ mice grew slowly, released less interleukin 1β and interleukin 6 in response to an immune challenge, and expressed aberrant levels of *Bdnf*, a target gene of MECP2. In addition, the authors found reduced dendritic outgrowth in hippocampal neurons that were co-cultured with MECP2-deficient astrocytes. These findings indicate a role for astrocytic MECP2 in the regulation of both astrocytic and neuronal development.

The factor that passes though gap junctions to cause the reduction of MECP2 in astrocytes is yet to be identified. Nevertheless, these findings suggest that astrocytes might contribute to Rett syndrome: the time-dependent spread of MECP2 deficiency through astrocytes could explain why Rett syndrome symptoms typically appear after an initial period of normal development.

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ORIGINAL RESEARCH PAPER Maezawa, I. *et al.* Rett syndrome astrocytes are abnormal and spread MeCP2 deficiency through gap junctions. *J. Neurosci.* **29**, 5051–5061 (2009)