

NEURODEVELOPMENTAL DISORDERS

Transplantation therapy in a mouse model of Rett syndrome

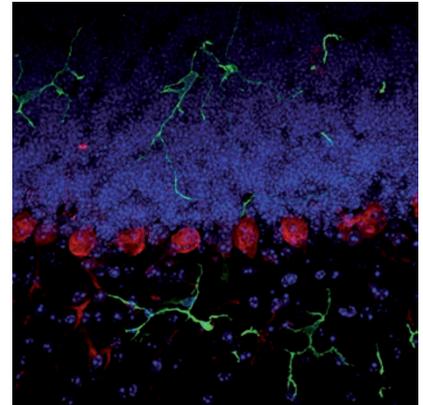
Transplantation of bone marrow cells might offer a new approach to the treatment of Rett syndrome, an X-linked autism spectrum disorder caused by mutations in the *MECP2* gene. Researchers at the University of Virginia, USA, have demonstrated that transplantation of wild-type bone marrow into *Mecp2*-null male mice brought about increased lifespan, a normalized breathing pattern, reduced apnoea episodes, and increased body weight and locomotor activity. Similar benefits were also observed in female *Mecp2*^{+/-} mice, which develop a milder form of the disease.

The researchers initially expected T cells to have a protective role in Rett syndrome. As Jonathan Kipnis, who led the study, explains: “we previously showed that elimination of T cells results in impaired cognitive function in mice, along with reduced synaptogenesis and reduced levels of brain-derived neurotrophic factor. Rett syndrome possesses some of the aspects that we see also in immune-deficient mice.” However, their observations instead highlighted a key role for microglial cells in Rett syndrome, as beneficial effects on the disease process were only

observed when functional microglial cell populations in the brain parenchyma were repopulated by the transplanted cells.

The *Mecp2*-null male mice were irradiation-conditioned prior to transplantation, to promote engraftment of the microglia-like cells that ameliorate the disease process. In mice that were head-covered to prevent irradiation of brain parenchyma, no engraftment or arrest of disease pathology occurred. The researchers also demonstrated that targeted expression of *Mecp2* in myeloid cells attenuated the Rett disease process in mice.

Blockade of the phagocytic activity of microglial cells—by using annexin V to mask crucial phosphatidylserine residues on apoptotic cells—also diminished the beneficial effects associated with expression of wild-type protein in myeloid cells. “We would like to better understand the phagocytic role of microglia in Rett syndrome and other autism spectrum disorders,” Kipnis comments. Moreover, the results of their study suggest that modulation of the immune response could be a potential new therapeutic avenue for patients with some neurodevelopmental disorders. “We



Microglia-like cells (green) invading brain tissue and interacting with Purkinje cells (red). Image courtesy of James Cronk (Kipnis laboratory).

want to see whether immune therapies could reverse as well as arrest the disease, and we are trying to find approaches that would boost the immune activity of myeloid cells in Rett patients,” he explains.

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Original article Derecki, N. C. *et al.* Wild-type microglia arrest pathology in a mouse model of Rett syndrome. *Nature* doi:10.1038/nature10907

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Further reading Liyo, D. T. *et al.* A role for glia in the progression of Rett's syndrome. *Nature* doi:10.1038/nature10214