WHITE MATTER DISEASE

Successful gene therapy in X-linked adrenoleukodystrophy

Allogeneic hematopoietic stem cell transplantation (HCT) has been shown to have disease-modifying effects in the demyelinating cerebral form of X-linked adrenoleukodystrophy (X-ALD), but finding a tissue-matched stem cell donor can be difficult, and allogeneic HCT carries a high mortality risk (15–20% in children, and up to 40% in adults). To circumvent these problems, Patrick Aubourg and Nathalie Cartier at the Hospital Saint-Vincent de Paul, Paris, France and their colleagues have devised a new strategy in which patients are treated with their own genetically modified stem cells. As reported in *Science*, this approach has so far proved to be effective in two patients with X-ALD.

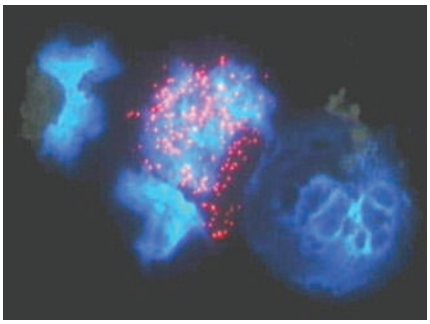
X-ALD is a CNS demyelinating disorder caused by loss-of-function mutations in the *ABCD1* gene, which encodes the adenosine triphosphate–binding cassette transporter ALD. The condition manifests in boys from the age of 6–8 years, most of whom die before adolescence. "In 1990, I obtained proof of concept that allogeneic HCT can arrest and even reverse cerebral demyelination of X-ALD when performed at an early stage of the disease," says Aubourg.

For the latest trial, the investigators used a self-inactivating lentiviral vector derived from HIV1, which, according to Aubourg, "has the unique property to allow penetration of DNA material into cells [such as neurons] that do not divide, and—at least *in vitro* and in mice—into the nucleus of hematopoietic stem cells." $CD34^+$ cells were isolated from the peripheral blood of two patients with X-ALD, and were transduced with a vector containing the wild-type *ABCD1* gene. The patients underwent myeloablation to remove resident hematopoietic stem cells, and then received infusions of their own genetically modified cells.

Between 24 and 30 months of follow-up, both patients showed expression of ALD in a substantial proportion of their peripheral blood leukocytes, indicating that the genetically corrected cells had engrafted successfully. By 14–16 months after transplantation, brain MRI scans revealed that demyelination had been halted in both cases. Concomitant stabilization or improvement of cognitive and motor function was observed, consistent with the clinical outcomes that were previously obtained with allogeneic HCT.

"This is the first time that a severe disease of the brain has been treated with success by gene therapy," says Aubourg. He points out, however, that "there is no real remyelination. To some extent, reversal is possible, but minimal."

Aubourg and colleagues achieved a transduction efficiency of ~15% in hematopoietic stem cells with their lentiviral vector, compared with the 0.01% recorded previously with murine γ-retroviral vectors. His team is currently working to increase the efficiency even further, and he believes that 60% transduction could be achievable. As well as increasing the therapeutic efficacy of the transplanted cells, improvements in transduction efficiency could enable the use of less-toxic conditioning regimens.



$CD34^+$ cells from the bone marrow of a patient with X-linked adrenoleukodystrophy, 24 months after hematopoietic stem cell gene therapy (nuclei are blue and red spots indicate ALD protein expression in peroxisomes). Image provided by Prof. Patrick Aubourg.

"Our data have important implications for all CNS diseases that can possibly be treated by bone marrow transplantation," says Aubourg. His team is now extending the X-ALD trial both within Europe and to the US, and a trial using the same strategy in metachromatic leukodystrophy is being planned by a team in Milan. Aubourg hopes that hematopoietic stem cell gene therapy could eventually become a first-line treatment option for all patients who develop the cerebral form of X-ALD.

Heather B. Wood

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