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Can the injection of the patient's own bone marrow-derived stem cells preserve cone vision in retinitis pigmentosa and other diseases of the eye?

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A significant step towards the general therapeutic use of adult stem cells has been taken in the field of ophthalmology. A recent study with mice raises the possibility that some forms of human blindness might be treated with cells from the patient's own bone marrow. Martin Friedlander at the Scripps Research Institute in La Jolla, California, and his team worked on retinitis pigmentosa (RP). In RP cells in the retina break down over time, causing gradual loss of vision and sometimes blindness. There is currently no good treatment, because RP has many different underlying causes.

Now, however, Friedlander's group has published in the current issue of the *Journal of Clinical Investigations* a novel and widely applicable approach to the treatment of RP and perhaps other eye diseases too [4].

From earlier work by this group [3, 5] and others [2] it is known that adult bone marrow contains a population of hematopoietic stem cells (HSCs) that can be divided into lineage-positive (Lin+) and lineage-negative (Lin–) subpopulations depending on their potential to differentiate into different blood cells. The Lin– HSCs contain a variety of progenitor cells that include those capable of becoming vascular endothelial cells [1]. These endothelial progenitor cells (EPCs) can be mobilized from the bone marrow in response to a variety of signaling molecules and can target sites of angiogenesis in ischemic peripheral vasculature and incorporate themselves into degenerating or newly forming vessels. In the retina they help to stabilize and rescue retinal blood vessels that would ordinarily completely disappear secondary to photoreceptor cell loss.

Now, in their new study,Friedlander's team has shown that adult bone marrow-derived Lin– HSCs can nearly completely prevent retinal vascular degeneration, as normally observed in the *rd1* or *rd10* mouse models of retinal degeneration, when injected intravitreally up to 2 weeks after birth. This vascular rescue correlates clearly with neuronal rescue. The rescue effect persists for 6 months after treatment and is most effective when the Lin– HSCs are injected before the retinal degeneration is complete. In mice this is up to 16 days after birth. These mice normally show practically complete outer nuclear layer degeneration by 30 days after birth.

In the retina of injected mice the inner nuclear layer remains nearly normal, and the outer nuclear layer containing the photoreceptors is significantly preserved. Surprisingly the rescued cells are predominantly not the rods but the cones. In addition,

electroretinogram (ERG) recordings are observed in rescued mice. They are low and severely abnormal but occur at times when they are never observed in control-treated or untreated *rd*/*rd* eyes. This rescue effect is also achieved when human bone marrow-derived Lin– HSCs are used to treat immunodeficient mice with retinal degeneration.

A microarray gene expression analysis of rescued and nonrescued eyes revealed a significant upregulation of antiapoptotic genes. Upregulation of these genes may play a role in the protection of the retina from vascular and neural degeneration by inhibiting the initiation of apoptosis that normally leads to degeneration in *rd*/*rd* mice. Since most neuronal death that is observed in retinal degenerations occurs by apoptosis, such protection may be of great therapeutic benefit in prolonging the life of photoreceptors and other neurons that are critical to visual function in these diseases.

The precise molecular basis of the neurotrophic rescue effect is unknown, but it is observed only when there is also vascular stabilization or rescue. The authors show that the presence of injected stem cells alone is not sufficient to generate a neurotrophic rescue. The clear absence of stem cell-derived neurons in the outer nuclear layer rules out the possibility that the injected cells are transforming into photoreceptors.

Extrapolating these data from mice to humans one could speculate that the patient's own bone marrow cells might provide effective cone neuroprotection. This is probably true, even for patients with a genetic defect, as long as vascular cells are affected. This effect might not only preserve central vision by preserving predominantly the cones but would also circumvent many of the unwanted potential side effects that are associated with the use of viral vectors in gene therapy, as well as avoiding rejection problems that may result from administration of embryonic stem cells.

It is widely appreciated in the clinic that a substantial loss of photoreceptors and other neurons can occur while still preserving functional vision, at least until a critical threshold is crossed and vision is lost. Nearly all of the human inherited retinal degenerations are of early, but slow, onset. From this a potential future procedure for patients can be drawn up: identify an individual with retinal degeneration, treat the patient intravitreally with an autologous bone marrow stem cell graft early enough, and delay retinal degeneration with concomitant loss of vision. If rescue of the cones occurred, as shown in the mouse model presented in the study of the Friedlander group, this treatment would be remarkably effective. In addition, if Lin– HSC-derived vascular endothelial cells achieve the observed neuronal rescue effect by induction of antiapoptotic factor synthesis in a paracrine fashion, it may even be possible to generalize the treatment to other visual neuronal degenerative disorders such as glaucoma, in which there is retinal ganglion cell degeneration. And, of course, bone marrow stem cells could also be used to treat other forms of blindness caused by diabetic retinopathy and age-related macular degeneration, as in both conditions blood vessels in the eye grow abnormally.

The technique presented here is surely one of the most promising treatments for blindness to have been unearthed in recent years. Clinical trials should be carried out in the near future.

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