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In This Issue

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Deriving therapeutic autologous disease-free stem cells It is hoped that individuals with inherited disorders such as β-thalassemia, which is caused by mutations in the beta-globin gene, might one day be cured by gene therapy and/or stem cell–based therapeutics. However, there are many obstacles preventing routine clinical use of such approaches. Eckardt and colleagues have shown that they can overcome some of these hurdles and use genetically repaired autologous stem cells to treat mice with β-thalassemia caused by dominant inheritance of disease-causing mutations (623–627). Their first step was to harvest unfertilized oocytes from affected female mice and use them to generate diploid uniparental zygotes. Development of these zygotes to the blastocyst stage enabled ES cell lines to be derived from them. Selection of ES cell lines lacking the disease allele provided a source of genetically corrected autologous stem cells that had not been genetically manipulated. These ES cell lines were differentiated in vitro into hematopoietic progenitor/stem cells, which were transplanted into mice with dominantly inherited β-thalassemia, leading to long-term reversion of the disease phenotype. The authors therefore suggest that their genetic correction strategy could potentially be applicable to any dominantly inherited disease. However, several obstacles to clinical use remain that are problematic for all human ES cells, including developing ways to efficiently differentiate the cells into transplantable tissue. Th17 cells […]

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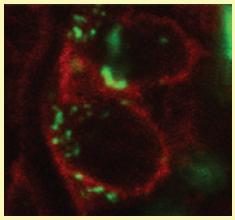
Propagating α-synuclein pathology

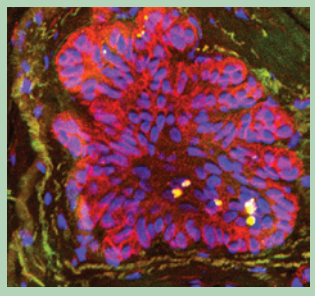


Parkinson disease (PD) is characterized neuropathologically by the presence of Lewy bodies — intracytoplasmic inclusions that are primarily composed of aggregated α-synuclein (α-syn) — in the cell body of affected neurons. Recent data, including the observation that Lewy bodies gradually appear in grafted neurons of patients treated with a fetal mesencephalic transplant, have suggested that α-syn can be transferred between neurons and that this propagates disease. Hansen, Angot, and colleagues, have now tested this hypothesis in several coculture systems and in vivo models (715–725). Initial analysis in coculture systems indicated that α-syn from one cell could be transferred to a second cell in the culture and that in the second cell the transferred α-syn interacted with endogenous α-syn and formed aggregates. Uptake of α-syn was mediated by endocytosis. Importantly, in vivo transfer of α-syn from host cells to grafted dopaminergic neurons in mice overexpressing human α-syn was also observed. The authors therefore suggest that intercellularly transferred α-syn displays a prion-like behavior and that this could play a role in the progression of neuropathology in PD.

Th17 cells keep systemic fungal infections at bay

Rates of systemic fungal infections have increased dramatically in recent years. Researchers are therefore intensively working to develop vaccines against the causative pathogens; in North America, the three major causative pathogens are *Coccidioides posadasii*, *Histoplasma capsulatum*, and *Blastomyces dermatitidis*. Determining the type of immune response that protects against infection with these pathogenic fungi is key to the development of an effective vaccine. In this context, Th1 cells are believed to be crucial. However, Wüthrich and colleagues have generated data in mice that indicate that Th1 cells are not required for vaccine-induced protection against lethal lung infection with *B. dermatitidis* (554–568). Instead, vaccine induction of Th17 cells was both necessary and sufficient to protect mice against all three of the fungi linked to the majority of cases of systemic fungal infection in North America. Further analysis revealed that the Th17 cells mediated protection by recruiting neutrophils and macrophages to the alveolar space, where they then activated them. The authors therefore suggest that vaccines developed to prevent systemic fungal infections in humans should be designed to induce Th17 cells.

Going bald without hair follicle progenitors



Androgenetic alopecia (AGA) is a frequent form of hair loss in both men and women. However, it is more common in men, in whom it is also known as male-pattern baldness. In this issue (613–622), Garza and colleagues set out to determine whether loss of hair follicle stem or progenitor cells could contribute to the pathogenesis of AGA. A reservoir of small quiescent stem cells is found in the region of the hair follicle known as the bulge. In humans, these cells are marked by expression of cytokeratin15 (KRT15) and CD200. Analysis of bald and non-bald scalp samples from men with AGA revealed that cells expressing high levels of KRT15 and with the stem cell properties of small size and quiescence were present in both samples. However, numbers of cells expressing high levels of CD34 and cells expressing high levels of CD200 and α6-integrin (ITGA6), both of which exhibited the characteristics of progenitor cells rather than stem cells, were substantially reduced in bald samples. As mouse cells analogous to these progenitors were capable of regenerating hair follicles, the authors suggest that loss of progenitor cells, and not stem cells, contributes to the pathogenesis of AGA.

Deriving therapeutic autologous disease-free stem cells

It is hoped that individuals with inherited disorders such as β-thalassemia, which is caused by mutations in the beta-globin gene, might one day be cured by gene therapy and/or stem cell–based therapeutics. However, there are many obstacles preventing routine clinical use of such approaches. Eckardt and colleagues have shown that they can overcome some of these hurdles and use genetically repaired autologous stem cells to treat mice with β-thalassemia caused by dominant inheritance of disease-causing mutations (623–627). Their first step was to harvest unfertilized oocytes from affected female mice and use them to generate diploid uniparental zygotes. Development of these zygotes to the blastocyst stage enabled ES cell lines to be derived from them. Selection of ES cell lines lacking the disease allele provided a source of genetically corrected autologous stem cells that had not been genetically manipulated. These ES cell lines were differentiated in vitro into hematopoietic progenitor/stem cells, which were transplanted into mice with dominantly inherited β-thalassemia, leading to long-term reversion of the disease phenotype. The authors therefore suggest that their genetic correction strategy could potentially be applicable to any dominantly inherited disease. However, several obstacles to clinical use remain that are problematic for all human ES cells, including developing ways to efficiently differentiate the cells into transplantable tissue.