STEM CELLS TRANSLATIONAL MEDICINE®

PREVIEWS

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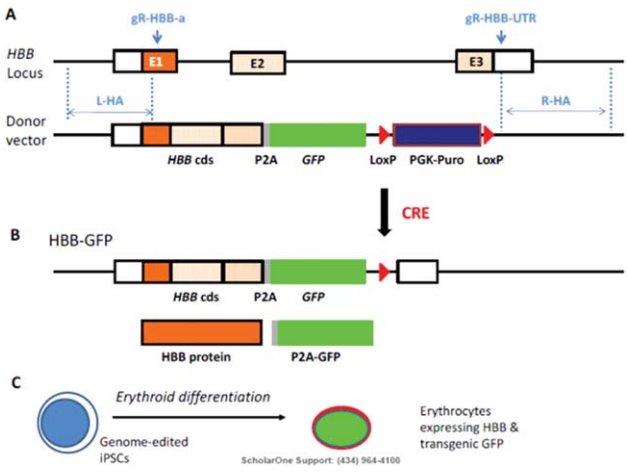
Genome editing of stem cells by zinc finger nucleases, transcription activator-like effector nucleases, or clustered regularly interspaced short palindromic repeats (CRISPR)/Cas systems holds great promise for the creation of disease models and reporter cell lines and the study of gene function. The combination of high-efficiency on-target editing and undetectable off-target editing has even led to the application of CRISPR/Cas9 genome editing in early human embryos as a potential means to cure genetic diseases such as beta-thalassemia and sickle cell disease. Two recent studies from Cai et al. and Sontag et al. exemplify the potential of CRISPR/Cas9 genome editing with two different approaches: the universal correction of *beta-globin* mutations and the creation of an *IRF8* knockout stem cell model.

Aging and unhealthy living can also take their toll on endogenous adult stem cells, leading to the development of vision loss, diabetes, and frailty, among other related maladies. Returning lost function to dysfunctional adult stem cells may reduce such pathologies and extend healthy lifespan and, other than genome editing, one potential means to achieve this goal is to supply, or indeed inhibit, factors that can boost stem cell function. Recent reports from Vergori et al. and Boregowda et al. describe two different tactics to return lost functionality to aging or "unhealthy" stem cells: supplying a nuclear receptor protein to endothelial progenitor cells (EPCs) via membranous microparticles (MPs) and inhibiting Ip6k1 signaling in mesenchymal stem cells (MSCs).

FEATURED ARTICLES

Universal Mutation Correction Strategy Takes Aim at Common Genetic Diseases



CRISPR/Cas9-mediated correction and subsequent erythrocytic differentiation of patient-specific induced pluripotent stem cells (iPSCs) represents an exciting therapeutic approach for patients carrying mutations in the *beta-globin* (*HBB*) gene. These mutations lead to common recessive genetic diseases such as beta-thalassemia and sickle cell disease. However, designing specific correction schemes for each of the more than 200 known mutations is a daunting task. To circumvent this vexing problem, researchers from the laboratories of Zhaohui Ye and Linzhao Cheng (Johns Hopkins University School of Medicine, Baltimore, MD) have validated a universal strategy that can correct all *HBB* mutations. The authors' approach uses two validated guide RNAs and Cas9 to insert a DNA template providing the entire *HBB* coding sequence, culminating in the restoration of HBB protein production in iPSC-derived erythrocytes [1]. Cai et al. hope that their universal strategy will do away with the need for interventions such as bone marrow transplants, chronic transfusion of red blood cells, or treatment with small molecules with potentially dangerous off-target effects, and will find use in the treatment of other genetic diseases.

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Microparticle-Based Approach Returns Lost Endothelial Progenitor Cell Function

Patients suffering from diabetes, obesity, and other related metabolic pathologies present with a compromised vascular system linked to inflammation and the dysfunction of bone marrow-derived EPCs. In an attempt to rectify these problems, a team of researchers from the Maria del Carmen Martinez laboratory at Université Angers, France has reprogrammed EPCs via small membrane vesicles known as MPs carrying the peroxisome proliferator-activated receptor (PPARα), which promotes EPC maturation and myeloid lineage differentiation [2]. While EPCs from mice fed on a high-fat diet (HFD) displayed reduced levels of circulating EPCs and impaired EPC and monocytic progenitor cell differentiation, treatment with MPs carrying PPARα restored the lost differentiation capacity and enhanced in vivo angiogenesis. Overall, this captivating new study proposes PPARα treatment as an exciting new therapeutic option for sufferers of various metabolic syndromes.

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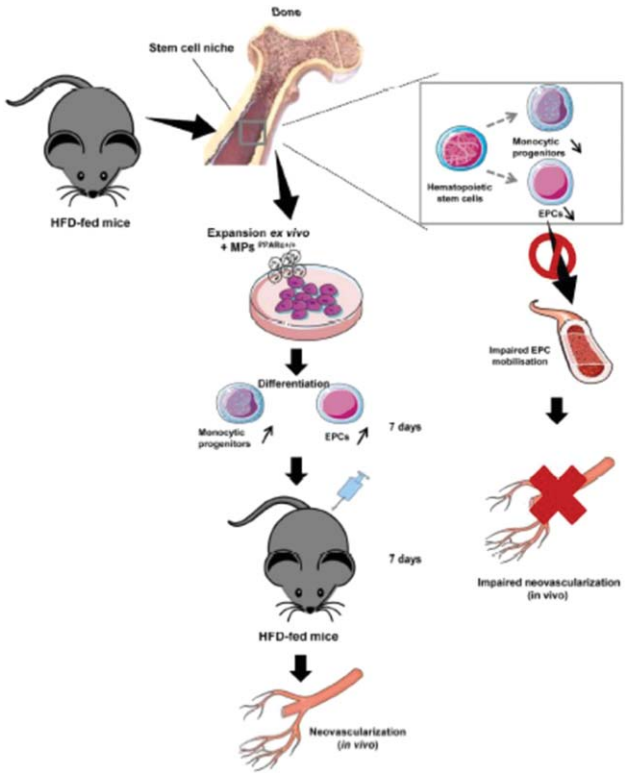
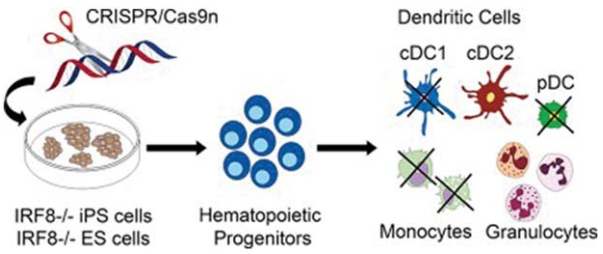


Related Publications

CRISPR/Cas9-Engineered Stem Cells Model Loss of IRF8 During Immune System Development



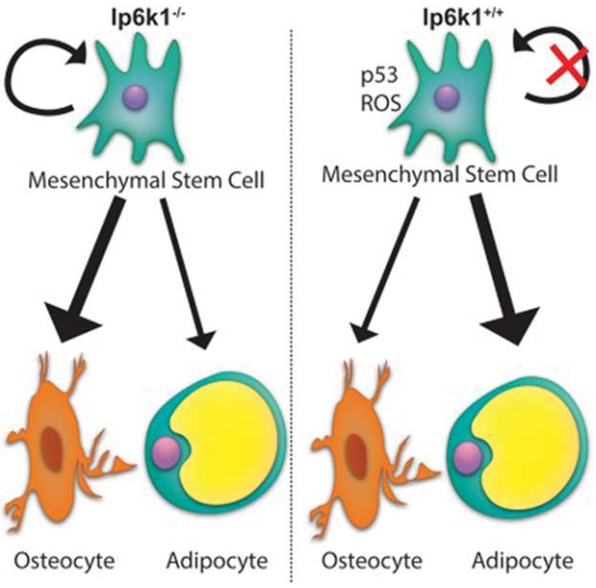
Mutations leading to the loss of function of the interferon regulatory factor 8 (IRF8) transcription factor lead to deficits in monocytes and dendritic cells, the antigen-presenting cells of the mammalian immune system. To investigate the consequences of IRF8 loss to human hematopoiesis and immune system development, researchers from the group of Martin Zenke (RWTH Aachen University Hospital, Germany) engineered *IRF8*-null iPSCs and embryonic stem cells (ESCs) via CRISPR/Cas9 genome editing [3]. While IRF8 loss did not affect pluripotent stem cell differentiation into hematopoietic progenitors, the lack of this transcription factor compromised the development of specific dendritic cell subsets and monocytes and enhanced granulocyte frequency. Overall, this new approach overcomes previous problems associated with primary cell and mouse model studies and may aid the description of the molecular mechanisms behind human immunodeficiencies.

DOI: 10.1002/stem.2565

IP6K1 Influences Mesenchymal Stem Cell Fitness and Differentiation Fate

Boosting the overall fitness of MSCs may provide a means to counteract age-related decreases in osteogenesis, increases in adipogenesis, and associated skeletal problems. A study from the laboratory of Donald G. Phinney (The Scripps Research Institute, Jupiter, FL) discovered that deleting the inositol hexakisphosphate kinase 1 (*Ip6k1*) gene enhanced MSC growth and survival and reversed age-related changes to MSC differentiation fate [4]. Interestingly, treatment with a pan-Ip6k inhibitor also retarded decreases in bone volume observed in mice fed on a HFD. Encouragingly, Boregowda et al. note that Ip6k1 inhibition represents a potentially safer strategy compared with other therapeutic interventions used to combat age-related MSC alterations, which increase fracture risk and alter feeding behavior.

DOI: 10.1002/stem.2645



References

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