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Pluripotent stem cell based gene therapy for hematological diseases

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ABSTRACT

Standard treatment for severe inherited hematopoietic diseases consists of allogeneic stem cell transplantation. Alternatively, patients can be treated with gene therapy: gene-corrected autologous hematopoietic stem and progenitor cells (HSPC) are transplanted. By using retro- or lentiviral vectors, a copy of the functional gene is randomly inserted in the DNA of the HSPC and becomes constitutively expressed. Gene therapy is currently limited to monogenic diseases for which clinical trials are being actively conducted in highly specialized centers around the world. This approach, although successful, carries with it inherent safety and efficacy issues. Recently, two technologies became available that, when combined, may enable treatment of genetic defects by HSPC that have the non-functional allele replaced by a functional copy. One technology consists of the generation of induced pluripotent stem cells (iPSC) from patient blood samples or skin biopsies, the other concerns nuclease-mediated gene editing. Both technologies have been successfully combined in basic research and appear applicable in the clinic. This paper reviews recent literature, discusses what can be achieved in the clinic using present knowledge and points out further research directions.

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1. Genetic correction of hematopoietic stem cells

In 2000, the Fischer group described the successful genetic correction of the most common form of severe combined immunodeficiency (SCID-X1) by using retroviral overexpression vectors (Hacein-Bey et al., 1996; Cavazzana-Calvo et al., 1996). The patients had an inherited defect in the interleukin 2 common gamma chain (IL2RG gene), leading to a non-functional receptor for IL-2, IL-4, IL-7, IL-9, IL-15 and IL-21. SCID-X1 patients have low to absent numbers of T cells and NK cells caused by a defect in IL-7 and IL-15 signaling, respectively. These defects lead to severe immunodeficiency with recurrent and life threatening infections. SCID-X1 patients are treated with allogeneic stem cell transplantation if a HLA identical sibling is available. However, patients without such a donor could be treated with genetically modified autologous hematopoietic stem and progenitor cells (HSPC). For this treatment modality, $CD34^+$ HSPC are isolated from bone marrow of the patient. These cells are subsequently transduced by using a retroviral vector to express the IL2RG receptor and re-infused (Fig. 1A). This therapy was successful in all patients treated and results similar to hematopoietic stem cell transplantation using matched siblings were obtained. Yet, it should be noted that 5 out of 20 patients developed T cell acute lymphoblastic leukemia.

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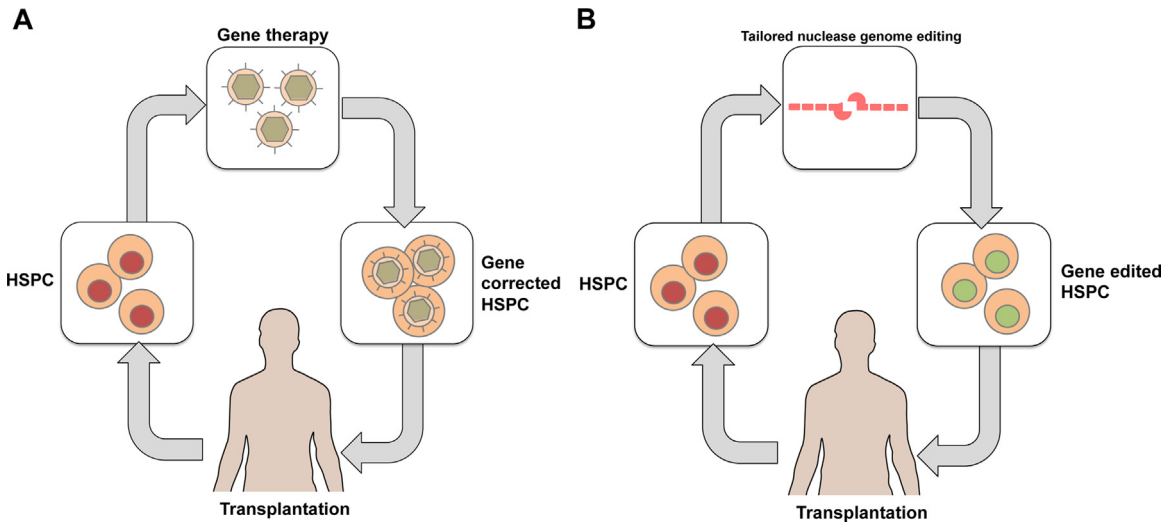

Fig. 1. Hematopoietic stem cell based gene therapies for hematological diseases.
(A) Standard gene therapy using retroviral or lentiviral transduction of hematopoietic stem progenitor cells (HSPC). Patient derived HSPC are transduced with an expression vector encoding the functional gene. Upon successful transduction, gene substituted HSPC are generated; (B) gene therapy using tailored nucleases to obtain gene edited HSPC.

Oncogenic transformation was caused by transactivation of LMO2 or CCND2 proto-oncogenes. Transactivation was induced by viral integration in close proximity of these latter genes (Hacein-Bey-Abina et al., 2003, 2008; Howe et al., 2008). In fact, most of the oncogenic events upon retroviral transduction could be traced back to insertion of the retroviral vector near proto-oncogenes. Disease related increase in susceptibility for oncogenic transformation could be detected in treated SCID-X1 patients and Wiskott–Aldrich syndrome (WAS) patients but not in Adenosine Deaminase (ADA)-SCID patients (Salavoura et al., 2008).

To alleviate problems related to transactivation of neighboring genes, self-inactivating (SIN) retroviral vectors were used for the treatment of SCID-X1. These SIN vectors lack the retroviral promoter and enhancer activity in their 3′ long terminal repeat (LTR), which is responsible for activating neighboring oncogenes. In a recent study by Hacein-Bey-Abina et al. (2014) patient derived $CD34^+$ HSPC were transduced with a SIN vector to express the IL2RG receptor. Successful engraftment of HSPC was observed and peripheral blood T cells expressing the IL2RG receptor were found in the blood. The results show that use of SIN retroviral vectors is an adequate alternative to the use of conventional viral vectors and that it may reduce the risk of oncogenic transformation compared to the use of regular retroviral vectors. Alternatively, SIN lentiviral vectors are used. The advantage of lentiviral vectors is that they can readily integrate into the genome of non-dividing cells, whereas retroviral vectors must rely on actively cycling cells for efficient transduction. In addition, although SIN lentiviral vectors predominantly integrate in gene encoding regions, they tend to leave the promotor region unaltered. In patients with WAS, such vectors were used for the correction of mutations in the WASP gene and no malignant transformations were observed (Astrakhan et al., 2012).

Clinical studies using these safer vectors are actively recruiting patients with primary immunodeficiency syndromes such as chronic granulomatous disease, ADA-SCID, WAS, SCID-X1, with lysosomal storage diseases and with hemoglobinopathies (Cartier et al., 2009; Cavazzana-Calvo et al., 2010).

In addition, expression levels of the corrected gene are generally not dynamically regulated during differentiation. The inserted cDNA sequence, lacks untranslated 5′ and 3′ regions. These regions are important in post-transcriptional regulation of the gene of interest, such as translation initiation and miRNA regulated mRNA processing. Constitutive gene expression in the absence of mechanisms regulating physiological levels of the encoded protein thus may enhance in itself malignant transformation. This especially applies to cases where the overexpressed corrected gene is a growth receptor such as the IL2RG.

Although patient follow up is still limited, it can be concluded that gene therapy using SIN LTR vectors seems less likely to induce oncogenic transformation. However, safety concerns remain at large. While the LTR used in current generation gene therapy vectors are self-inactivating, the viral vector still predominantly integrates into intragenic regions. When the viral vector is integrated in regulatory sequences of proto-oncogenes, insertional mutagenesis is still likely to occur. In combination with clonal selection that occurs during the development of some cell lineages such as T cells, malignant transformation remains a threat. Thus, while SIN vectors have been successfully applied in the clinic (Hacein-Bey et al., 1996; Astrakhan et al., 2012; Cartier et al., 2009; Cavazzana-Calvo et al., 2010; Gaspar et al., 2004; Boztug et al., 2010; Aiuti et al., 2013), possible adverse effects cause a major concern for patient safety.

2. Use of tailored nucleases for genetic repair of HSCs

The ideal gene therapy replaces *in situ* the functionally defective gene by a functional copy. Over the past years, different technologies have been developed allowing us to repair effectively the defective gene. These strategies all rely on a similar basic approach: sequence-specific DNA binding functional unit guides an engineered DNA nuclease to the defective gene with high sequence specificity. The nuclease induces a double stranded break (DSB) that is subsequently repaired by the endogenous homologous recombination (HR) machinery of the cell. For HR, the cell uses a template provided by a donor plasmid carrying the functional gene/DNA sequence. To this end cells are co-transfected with both the nuclease encoding sequences and the donor plasmid. Currently, three types of targetable nucleases are available: Zinc Finger nucleases (ZFN) (Hockemeyer et al., 2009), transcription-activation-like effector nucleases (TALEN) (Hockemeyer et al., 2011) and Clustered Regulatory Interspaced Short Palindromic Repeats (CRISPR)/Cas9 (Hou et al., 2013) (Fig. 2) (for an comprehensive review of these methods we see Gaj, Trends in Biotechol., 2013).

ZFN use multiple zinc-finger domains for recognition of specific DNA sequences. A single zinc-finger consists of 30 amino acids and

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