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Correcting the aberrant Fanconi anemia transcriptional program by gene therapy

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Fanconi anemia (FA) is a multisystem disorder, but hematopoietic derangements are the most common causes of morbidity and mortality, which include bone marrow failure or leukemic transformation. FA is a genetically diverse disorder with twenty-two associated genes[1]. FANCA is the most commonly mutated gene, and about 60% of the patients have mutations in this gene.

All FA genes are involved in DNA-repair (Reviewed by Fajardo and Colleagues)[2]. FANCA is part of nine FA genes that are recruited to fork-like DNA structures, and form a single large nuclear protein called “core complex”. The core complex functions as a ubiquitin ligase that monoubiquinates a downstream heterodimer composed of two FA proteins, FANCI and FANCD2, which bind to an arrested replication fork at an interstand DNA crosslinks. The monoubiquitinated FANCI and FANCD2 forms a binding interface for single and double stranded DNA and downstream effector complexes with additional FA and other proteins to cleave DNA interstrand crosslinks, resulting in DNA adducts and dsDNA breaks. The later aberrant DNA fragments are resolved by exonucleases and by homologous recombination, both involve additional FA proteins.

Currently, the only curative treatment for the hematopoietic failure in FA is hematopoietic stem cell transplantation (HSCT). However, short-term and long-term complications (e.g., serious infections, organ failure and graft versus host disease) and not uncommon [3]. Further, HSCT significantly increases the risk of solid tumors in this patient population[4].

Due to the limited treatment options and their associated risks, gene therapy provides attractive alternative therapeutic option. However, there are several challenges with gene therapy that are specific for inherited bone marrow failure syndromes such as FA. For example, although mobilization, collection and cryopreservation of enough peripheral blood CD34+ cells from FA patients by administration of G-CSF or plerixafor are feasible[5]; this process is challenging for most of FA patients. The reason is that most patients are diagnosed when they have substantial cytopenia and their hematopoietic stem cells are depleted[6].

Several gene therapy trials have been conducted in FA and several others are currently being conducted in Europe and United States of America. Preliminary data showed that FANCA gene therapy without conditioning therapy is safe in FA and corrected cells are engrafted and manifest proliferative advantage[5, 7, 8]. Further, reasonable blood counts were sustained for several years[5]. However, long-term follow-up studies are lacking. Therefore, we do not know whether gene therapy can abrogate the FA phenotype of gradual depletion of hematopoietic stem cells (HSCs) and a decline in blood cell counts. Furthermore, we do not know whether gene therapy can provide HSCs with long-term ability to maintain normal or sufficient molecular and functional properties. We also do not know how long corrected HSC can generate hematopoietic stem and progenitor cells (HSPCs) with normal or sufficient molecular and functional properties.

In the current issue of Haematologica, Dr. Miren Lasaga and colleagues aimed to address some of the questions above. They studied four FA patient with FANCA mutations, who successfully underwent gene therapy using PGK-FANCA-WPRE lentiviral vector and had been previously published[5]. The vector contains phosphoglycerate kinase (PGK) promoter, woodchuck hepatitis virus posttranscriptional regulatory element (WPRE) sequence that enhances expression, and FANCA. Bone marrow CD34+ cells were harvested from the patients, transduced with the vector, and then infused back into the patient without conditioning.
The analysis in this work was performed 2-5 years after gene therapy. The corrected cells were estimated to constitute 26-77% of bone marrow CD34+ cells. Using single cell RNA sequencing, the authors demonstrated that lentiviral-mediated gene therapy resulted in substantial correction of the transcriptional program in HSPCs of patients with Fanconi anemia and brought it closer to the transcriptional program of normal hematopoietic stem and progenitor cells[9]. Importantly, the expression of several genes that had been shown to be upregulated and mediate bone marrow failure in FA, such as p21[10] and TGF-beta[11], were normalized after gene therapy. The authors also showed that gene therapy improved cellular properties that include reduced chromosomal breakage of peripheral blood T cells in response to diepoxybutane, and slow rate of telomere length reduction in peripheral blood cells by quantitative PCR compared to a control patient group who were not engrafted after cell transduction. Further, gene therapy improved cellular function, specifically survival of hematopoietic progenitors plated in cultures with mitomycin C and their ability form colonies; which likely facilitates a progressive increase in the number of bone marrow and peripheral blood gene-corrected cells.

The work described in this paper is important and documents positive effects of gene therapy. Although the results are very promising, there are still questions that need to be addressed. For example, the ability of gene therapy to provide sufficient HSPC numbers and blood cell counts for the full life span of the patient needs to be documented. Also, the sustainability of transcriptional program, DNA integrity and telomere length are still to be shown.
REFERENCES


