Gene Therapy in Rare Anemias

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Gene therapy is becoming a powerful tool for the treatment of inherited diseases. Clinical trials performed during last two decades have demonstrated its usefulness in the treatment of several genetic diseases, mainly immunodeficiencies. Hereditary hemolytic anemia exhibits a high molecular heterogeneity with a wide number of mutations involved in structural and metabolic genes of the erythrocyte. Despite of having a better understanding of their molecular basis, definitive curative therapy for red blood cell (RBC) defects still remains challenging. Conventional bone marrow transplantation allows the generation of donor-derived functional hematopoietic cells of all lineages in the host, and represents the standard care or, at least, a valid therapeutic option for many inherited diseases. However, complications associated to allogeneic transplantation, including severe infections, graft rejection and graft versus host disease can be life threating, being fatal in around 30% of the patients. The recessive inheriting trait of most of these erythroid diseases and the confined defect to the hematopoietic/erythropoietic system, make them suitable diseases to be treated by gene therapy. Correction by gene therapy requires the stable transfer of a functional gene into the autologous self-renewing hematopoietic stem cells (HSCs) from the patient and their transplantation back. Autologous BM transplantation of genetically corrected cells shows several advantages over the allogeneic procedure. First, it overcomes the limitation of human leukocyte antigen (HLA)-compatible donor availability, so it can be applied to every patient. Second, the reduction of morbidity and mortality associated with the transplant procedure, as there is no risk of GvHD and, consequently, no need for post-transplant immunosuppression. To date, gene therapy approaches for the treatment of inherited erythroid deficiencies are still limited, mainly because of the frequent lack of selective advantage of genetically corrected cells. This implies that high levels of transgene expression are required, as well as an efficient transduction of HSCs. This requirements have already been described and overcomed in some particular cases in different RBC diseases, such as β-Thalassemia, Sikle Cell Disease, or in deficiencies affecting the erythroid metabolic pathway, like erytropoieticprotoporphyria (EPP), caused by the deficiency of the last enzyme of the hemebiosintesis pathway, or the piruvate kinase deficiency (PKD), where there is an impairment in the final yield of ATP in RBC. Clinical trials are nowadays ongoing for the genetic correction of globin mutations, addressing the cure of β-Thalassemia, Sickle Cell Disease, with very good preliminary results. And preclinical data demonstrates the feasibility of this type of treatment for the other mentioned erythropaties. Subsequent clinical trials will confirm the feasibility of gene therapy for the treatment of inherited rare cell anemias.