Gene Darning for Gene Therapy

Editorial

With the invention of recombinant technology and the ability to cut/ paste genes, the immediate goal was to correct genetic defects at the gene level. In the early 1990s, we started showing hope of gene therapy to families with thalassemia major. Beta globin gene is one of the smallest genes and was considered easy to insert in the genome; but studies showed that it requires well controlled, sustained and a large amount of expression to cure thalassemia major. The hope of gene therapy thus began to appear to be a distant dream. The first real success for gene therapy has been for severe combined immunodeficiency (SCID) in the early 21st century. Till 2012, gene therapy had been attempted for 20 cases of X-SCID and 40 cases of SCID due to adenosine deaminase deficiency (ADA). However 5 of 20 cases with X-SCID developed one type of leukemia, confirming the risk of malignancy due to gene therapy to be true. The malignancy occurred due to insertion of the normal gene into an oncogene disrupting its function, due to the fact that the correct gene was not targeted to a specific location but was supposed to get randomly integrated. This complication of cancer was not reported in mouse models.

Insertion of a large gene, along with controlling regions and continued expression continues to be a challenge. The search for the perfect vector which can carry a large gene and can deliver it to all cells of the required type without causing any adverse effects has still not been successful. The death of a young man, Jesse Gelsinger due to a severe immune reaction to the adenovirus used for a gene therapy trial for ornithine transcarbamylase deficiency was a setback and the norms of Ethics Committees with regards to gene therapy trials became very stringent following this unfortunate episode. Insertion of the beta globin gene leading to stoppage of blood transfusion requirement in a poorly managed, splenectomised thalassemia major patient was first reported in 2010.

The last few years have seen newer developments which can facilitate and speed up the gene therapy trials. These include novel gene editing tools like CRISPR-Cas9 (clustered regularly interspaced short palindromic repeats – Cas9), development of an unlimited number of induced pleuripotent cells (iPCs) from patients' fibroblasts and the ability to transform iPCs into various lineage of cells. CRISPR-Cas9 technology uses a segment of RNA which helps to make a cut at a required site and efficiently replace the defective / mutated part of the gene. This method of homologous recombination is efficient and can replace the defective gene at its normal location and will maintain its relation with gene expression controlling regions of the gene like enhancers and suppressors. This system has been successfully used in a number of gene therapy experiments in cell lines. One such experiment on the 'Seamless gene correction of b-thalassemia mutations in patient-specific iPSCs using CRISPR/Cas9 and piggyBac' was reported in 2014. This is a really exciting development and such targeted correction reminds me of darning. The continuity of the newly added correct sequence is established with sequences before and after. CRISPR has brought new excitement and hope to scientists working on gene therapy as well as to clinicians waiting for a gene therapy option for patients with monogenic disorders. In this issue, the details of CRISPR technology are given in GeNeViSTA and GeNeXpeSS highlights the recent CRISPR-based publications. Though identification of genetic defects by prenatal genome sequencing and correction by gene therapy still looks a distant dream, CRISPR definitely appears a big step towards gene therapy in clinical practice.

Genetic Clinics aims to bring these latest developments in the field of medical genetics closer to the clinicians. Application of recently available genetic technologies in clinical situations has resulted in a paradigm shift in the care of patients and families with genetic disorders. Learning genetics in this era of molecular medicine sure is exciting and enjoyable!

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