Pathways to Cure

Editorial

The endpoint of research in human biology is cure of diseases and improvement in the quality and longevity of life. DNA, the basic molecule of life, has been the target of study and treatment over the last few decades. Techniques to correct the gene defect underlying Mendelian disorders are being pursued along with various forms of gene modifications for the treatment of cancers and autoimmune diseases. Success of gene therapy in immunodeficiency disorders is yet to be replicated for many other diseases, but trials are going on. The GenExpress in this issue mentions a study about successful gene therapy for Sanfilippo disease in mice model, wherein significant enzyme levels were reported in the cerebrospinal fluid. There was reversal of the behavioral phenotype in the treated mice along with improvement in the lifespan. Gene therapy is an important modality for lysosomal storage disorders with neurological involvement as currently available enzyme replacement therapies are unable to improve or prevent the neurological phenotype.

As many issues with gene therapy are yet to be sorted out, many other modalities of treatment are being explored. These include mRNA-based gene silencing of a disease modifier gene and use of ultrasonographic energy to take care of toxic aggregated material, as mentioned in the GenExpress in this issue. One of the interesting modalities, which appears relatively easy and is showing promise, is the use of molecules that work at the level of the mutant protein and molecules affecting the downstream pathways. Analogue of C Natriuretic Peptide (CNP) which is an antagonist of Fgfr3 in mouse models was recently used in children with achondroplasia, a disease caused by gain of function mutation in the *FGFR3* gene and improvement in growth was reported over a short period of time. Such types of novel drug therapies have been found to be effective in some other groups of disorders also. Inhibitor of mTOR, Sirolimus, has been found to be useful in the treatment of subependymal giant cell astrocytomas (SEGA) and renal angiomyolipomas (AML) related to Tuberous Sclerosis.

The functions of protein products of disease-causing genes are being understood. Better understanding of biochemical pathways has led to the development of molecules which can work at various levels of molecular pathways and can modify the course of disease. Noonan syndrome and other group of disorders with overlapping phenotypes have been discussed in this issue. The similarities and overlap of phenotypes of this group of disorders (known as RASopathies) is due to the proteins of the causative genes being involved in a common signaling pathway. The Ras/MAPK pathway has been well studied in cancer and is an attractive target for small-molecule inhibition to treat various malignancies. Trials to evaluate the effect of the MEK inhibitor MEK162 (Novartis) on adults with Noonan syndrome who have hypertrophic cardiomyopathy and the use of Simvastatin for improving cognitive function in Neurofibromatosis are underway. Phenotypic similarity is also observed in many groups of disorders due to commonalities in the pathogenesis at various level. The article on leukodystrophies in this issue gives an overview of genetic white matter disorders. Identification of the causative gene and understanding about the normal function and abnormal pathophysiology at the molecular level are important steps towards the development of drugs and that is increasingly happening these days. The publications on various strategies for treatment of genetic disorders have definitely raised our hopes for more definitive treatments for currently untreatable genetic disorders. Better understanding of the molecular pathology for the so-called non genetic disorders is also leading to development of newer drugs e.g. for the prevention of vascular complications in diabetes. The Human Genome Project has ushered the world into a new era of therapies.

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