Virus through Gene Therapy

Anila Jaleel,Saeeda Baig (Biochemistry Department, Ziauddin Medical University, Karachi.)

During the last 15 years biology and life science underwent a dramatic development. The identification of new genes, which are responsible for different phenomena: Cancer genes, adipositas genes and suicide gene lead to accelerated research in gene therapy[1]. Progress of molecular biological technology has brought about great advances in gene therapy. The establishment of DNA recombination and transfection techniques in 1980 allowed the scientists to study the cell at molecular level by manipulation of nucleic acids (RNA + DNA), including nucleic acids and isolation and characterization, which in turn were subject to therapeutic use. Since the initial clinical trials of gene therapy in 1990, over 250 of clinical protocol have undergone security in United States and over two thousand patients have been enrolled in gene therapy worldwide[2]. With over 220 investigational new drug applications currently in action, gene therapy represents one of the fastest growing areas in biotherapeutic research. Initially conceived for replacing defective genes in diseases such as a cystic fibrosis or inborn errors of metabolism with genes encoding the normal, or wild type, gene product, gene therapy has expanded into other novel applications such as treatment of cancer or cardiovascular disease where the risk: benefit profiles may be more acceptable, in relation to the severity of the disease.

Mechanism of Gene Therapy

Different types of vectors including modified retroviruses, adenoviruses, adenovirus-associated viruses and herpes viruses and plasmid DNA are used to transfer foreign genetic material into patients cell or tissues[3]. The virus life cycle involves taking over many normal cellular processes, that is why treatment of viral infections continues to be problematic, thus exclude the viruses as therapeutic targets. Chronic viral infections are particularly difficult as these viruses have excluding strategies to persist within the host and avoid elimination.

A viral infection of a cell equates to presence of an abnormal gene or genes within the cell and hence a genetic approach to treatment is of considerable interest. Gene therapy is usually classified into protein or RNA based strategies. Genes coding for proteins which interfere with viral assembly or transcription/translation, are introduced into the cell and expressed to protect the cell against infection.

a) RNA approaches are antisense i.e., the expressions of RNA complementary to the viral RNA to bind it. Ribozymes: RNA based enzymes, which clear target RNA molecules and Decoys which are RNA mimics of viral sequences which will sequester away viral proteins ligands from virus's own RNA. Candidate effectors have been introduced into viral vectors and delivered to cells by transduction and replicate their inhibitory effect in these[4].

b) Expression of viral protein themselves in appropriate combination can be used as genetic vaccine approach. Intracellular immunization with RevM10, a transdominant negative form of Rev protein efficiently inhibits human immunodeficiency virus (HIV) replication in vitro and gene therapy protocols that use this modality are currently being evaluated in human clinical trials. RevMIO resistant HIV (Type I) variants are selected by in vitro passage of HIV in a T lymphoblastoid cell line constitutively expressing RevMIO. Selected variant show changes in Rev response element (RRE) but no changes in Rev, replacement of wild type RRE with a mutated RRE can result in a virus that will show increase resistance to Rev Mio. After reported passages of the resistant variant in cells expressing Rev MIO, a virus with an additional mutation in the viral vpu gene was selected[5].

Gene therapy for persistent viral infection is an addition to the armamentarium that is already present. It is unlikely to be a monotherapy but it can target parts of lifecycle which other methods cannot. In addition it might be administered less frequently than conventional drugs and is almost certain to have

fewer side effects. The human genome project, which will soon identify all of the expected 100,000 genes in human DNA and determine the sequences of the 3 billion chemical bases that make up that DNA, has the potential to radically alter the way medicine will be practiced in 21 st century. According to Dr. Eric Lauder, “we are in the midst of one of the most remarkable revolution in the history of mankind, a revolution whose consequences will be so far reaching that they will touch every aspect of the society.

Genomic research will lead to the treatment and prevention of common disease such as Alzheimers and breast cancer. We will look back on cancer as a treatable and often preventable disease, a distant scourge much like we today regard Polio”.

This is the time when young scientists in Pakistan should be provided with the opportunity to engage themselves in such research projects and come up with the possible treatment of the diseases that are common in Pakistan and are responsible for high morbidity and mortality.

Reference

1.Hanselman R. Mutschler W. Relevance of life sciences for traumatologic and orthopedic unfallchirurg, 1999;102:250.66.

2.Tito Y , Niitsn Y. The advances of genes therapy in this quarter center. Gab—To-Kagaku-Ryolto, 1999:51-57.

3.Pilaro AM, Snrabaya MA. Preelinical development stragies for novel gene therapy Trop. Pathol., 1999:24:4-7.

4.Lever AML. Gene therapy for persistent viral infection. Workshop on Molecular biology and infectious diseases September, 21-25, 999.

5.II atntn TE, Rekosh D, Hammers-Kjolld ML. Seieetioit and characterization of human immunodeficincy virtts type I mutants that are resistant to inhibition by the transdotninant negative RevM10 protein. i. Virol.. 1999:73:5741-47.