GENE THERAPY FOR THE TREATMENT OF MUSCULOSKELETAL DISEASES

An Essay

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Abbreviations

A	Adenine
AAV	Adeno associated virus
ADV	Adenovirus
APC	Antigen presenting cell
BMP	Bone morphogenetic protein
C	Cytosine
cDNA	Cyclic DNA
CIA	Collagen induced arthritis
CNS	Central nerves system
DCs	Dandritic cells
DNA	Deoxyribonucleic acid
G	Guanine
GAM	Gene activated matrix
H.S.V	Herpes simplex virus
HIV	Human Immuno deficiency virus
ICF	Insulin like growth factor
IL	Interleukin
MHC	Major histocompatibility antigen
mRNA	Messenger Ribonucleic acid
NK	Natural killer cell
NPC	Nuclear pore complex
OA	Osteoarthritis
OI	Osteogenesis imperfecta
RA	Rheumatoid arthritis
RNA	Ribonucleic acid
SF	Synovial fibroblast
T	Thymine
TGF	Transforming growth factor
TNF	Tumor necrosis factor
tRNA	Transfer Ribonucleic acid
U	Uracil

Introduction

Gene therapy involves the insertion of laboratory manufactured or controlled genes into the body, to reach a target tissue or organ with the aim of curing or preventing disease, through the production of a certain proteins by process of transgene expression, in which gene transfer need a carrier called vector which may be viral or non viral [١]. The most common vector is viral because its ability to infect living cells and it's ease to be manipulated genetically [٢]. Controlling of gene therapy is an important factor in treatment of diseases, in which diseases need its specific control of gene therapy as regard of level and optimal duration of transgene expression. Orthopaedic application of gene therapy has resulted in progress toward managing acute and chronic, genetic and non-genetic diseases, also in bone healing and in bone tumours. These development, leads to treatments that are less invasive, more effective and less expensive [٣].

Gene therapy can be classified according to cell altered into somatic-cell therapy and germ-cell therapy. Somatic cell therapy manipulating the somatic cells that cause a disease, germ cell therapy alter gametes [٤].Also Gene therapy can be classified according to mode of vector delivery into systemic

and local, systemic gene therapy has the potential to target all cells, local gene therapy divided into two types: direct and indirect. Direct method by injecting gene directly into target tissue, while indirect method by removing target cells from body and exposed to vector in vitro so its called ex-vivo strategy [٥].

Genetic Basis

Gene structure

Genes are composed of deoxyribonucleic acid (DNA), which are codes for the production of specific polypeptide chains which are then joined in specific orders to produce proteins that make up living organisms.

The human genetic material contains ٢٣ pairs of chromosomes comprised of DNA, which consists of two complementary chains twisted about each other in the form of a double helix or twisted ladder model (Fig.١).

Figure ١.Twisted ladder model.[٦]

Each DNA chain is composed of four types of nucleotides that contain a deoxyribose residue, a phosphate, and a pyrimidine or a purine base. The pyrimidine bases are thymine (T) and cytosine (C); the purine bases are adenine (A) and guanine (G).

The sides of the ladder consist of the deoxyribose residue linked by phosphates. The rungs of the ladder are made up of pyrimidine and purine bases. The two strands of DNA are joined together by hydrogen bonds existing between the pyrimidine and purine bases: Adenine is always paired with thymine (AT), and Guanine is always paired with cytosine (GC). (fig.٢)

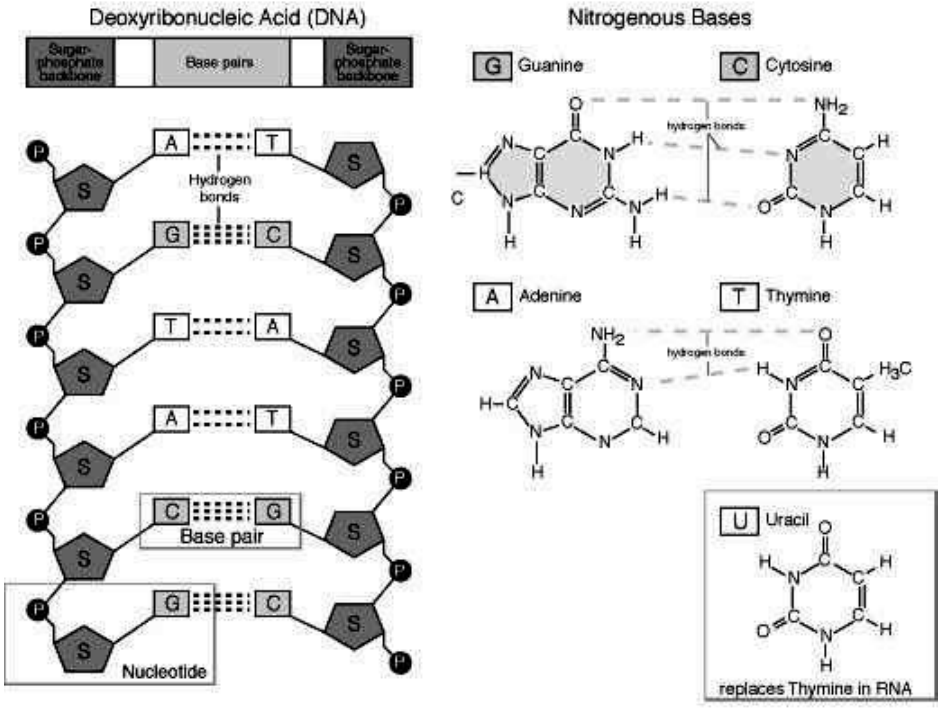

Figure ٢.DNA Structure [٦]

The ends of the DNA strands are designated ٥` and ٣`. The ٥` end indicates the sequence closer to the beginning of the gene; the ٣` end indicates the sequence closer to the end of the

gene. DNA is synthesized and read in the ٥` to ٣` direction (٥`& ٣` = number of carbon atom in deoxyribose residue).

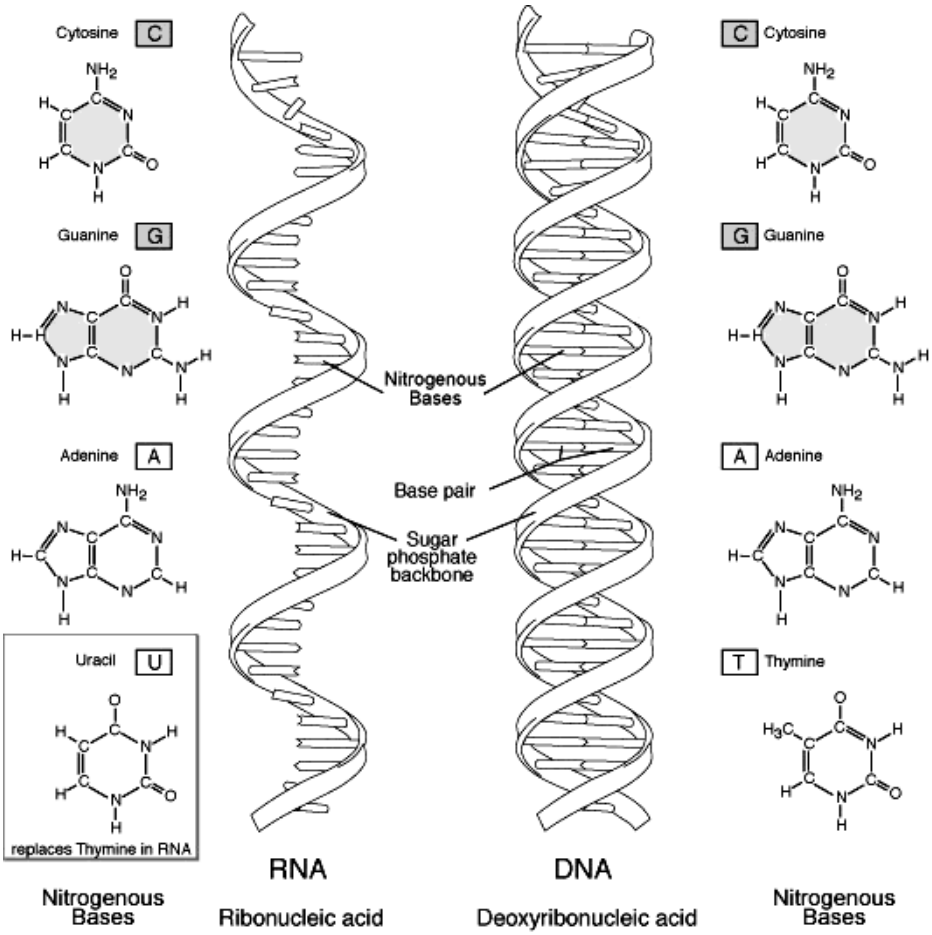

Figure ٣. RNA & DNA Structure[٦]

Two chemical differences exist between DNA and ribonucleic acid (RNA) in which, Ribose is the sugar in the structure of RNA rather than deoxyribose in DNA, also RNA has the pyrimidine base uracil (U) instead of thymine as in

DNA. So, in RNA, the connected purine and pyrimidine bases are GC and AU (fig.٣).

During cell division, the DNA content of the parent cell is replicated by separation of the two strands of the double helix and synthesis of two new complementary strands according to the rules of base pairing.

DNA acts as a template for messenger RNA (mRNA) Which transports the information contained in human DNA from the nucleus to the cytoplasm (Transcription), Less than ١٠٪ of human DNA is transcribed into mRNA, which is translated into amino acids – the "building blocks" of protein.

Translation is a process that occurs on the ribosomes, which translate the information coded by the mRNA into a chain of particular amino acids.

Amino acids are coded for by three base pairs. There are ٢٠ naturally occurring amino acids, which are the building blocks for proteins. With four different bases, and amino acids specified by groups of three bases, there are ٦٤ possible coding triplets so most amino acids are coded for by more than one triplet. (fig.٤)