RNA Interference Therapeutics and Human Diseases

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INTRODUCTION

Humans have more than 20 thousand genes that are protein coding. Proteins are essential building blocks of our body as they perform a variety of functions in human body (Pines, 2007). They produce hormones, enzymes and hemoglobin (Hoffman & Falvo,2004). As proteins are important, their accurate production is also essential. Diseases are caused either by formation of defective protein or by over production of protein or less production of protein (Shenoy, & Jayaram, 2010; Selkoe, 2003). Diseases like Alzheimer's and Parkinson's disease, Huntington's disease, Creutzfeldt–Jakob disease, cystic fibrosis, Gaucher's disease, Uremia as well as other neurodegenerative disorders, heart disease, some cancers, stroke (Chaudhuri & Paul,2006) are caused by inappropriate synthesis of protein. Proteins in association with RNA form Ribonucleoprotein (RNP) which relates to diseases like influenza A virus, inherited motor neuron disease spinal muscular atrophy (SMA) (Pellizzoni,2007), premature aging, cancer (Blasco, 2005), aplastic anemia (Yamaguchi, Calado, Ly, Kajigaya, Baerlocher & Chanock, 2005), Alzheimer (Diner, Hales, Rabenold, Bishof & Duong, 2004) etc. In short, RNA and protein is linked with an outsized figure of diseases.

As gene expression (Alberts et al., 2007) is the process of formation of proteins, wherein DNA acts as a template for mRNA which further gets converted into proteins. So, altering the gene expression process may prevent from some disease to occur. More precisely, it is altering gene coding at mRNA level. This is the concept adapted by RNA Interference Therapeutics. RNAi Therapeutics (Aagaard & Rossi,2007) is the branch of science that focuses on control of gene activity at RNA level to cure diseases.

This chapter is organized as follows: RNA, DNA and gene expression are discussed in Introduction and Background section followed by RNA types, RNA interference process and RNA Therapeutics. Table 1 mentions some of the RNA Therapeutics companies. Further RNAi Therapeutics techniques PMO, LUNAR, RNA upregulation and Gene Silencing are discussed. It is concluded by RNAi Therapeutics' challenges and issues and lastly its future research directions.

BACKGROUND

Cells are the building blocks of life. Inside nucleus of a cell, DNA and RNA molecules reside. Ribo-NucleicAcid (RNA) molecule is a single stranded sequence consisting of four bases Adenine (A), Guanine (G), Cytosine (C) and Uracil (U). This single stranded sequence is known as the primary structure of RNA (Tinoco & Bustamante,1999).

The backbone of RNA contains ribose as sugar. Phosphate groups are also attached to ribose. RNA can be synthesized from DNA. DNA is another molecule which is double stranded molecule. DNA consists of nucleotides that contain a phosphate group, a sugar group and a nitrogen base. Nitrogen bases are Adenine (A), Guanine (G), Cytosine (C) and Thymine (T).

DNA molecule contains a number of genes. Some genes code for protein and others do not. The process of production of protein is called gene expression. Precisely, Gene Expression process involves two sub processes- Transcription and Translation. Gene expression process is initiated by making a copy of DNA to produce a complimentary strand called messenger RNA (mRNA) (Anfinsen,1972) as shown in Figure 1. mRNA is one of the types of RNA. Thymine of DNA is replaced by Uracil of RNA. This step is called Transcription. Proteins are made up of sequence of amino acids. 20 amino acids exist. The bases of mRNA in sets of three, code for a specific amino acid and forms a codon as shown in Figure 1. As the number of bases is four, so 64 (4*4*4) possible codons are there. Consequently, more than one codon may code for a specific amino acid. The amino acid is meshed together with codon by another type of RNA which is transfer RNA (tRNA). tRNA contains a complementary sequence of bases on the other side called anti codon as shown in Figure 1. A sequence of amino acids is called a protein. This process is called Translation. Together these processes transcription and translation are termed as gene expression. Each protein consists of a unique sequence of amino acids. Ribosomal RNA (rRNA) links the amino acids so that specific protein is formed.

TYPES OF RNA

Gene Expression is catalyzed by majorly three types of RNAs, namely, messenger RNA, transfer RNA and ribosomal RNA.

- **Messenger RNA (mRNA):** mRNA is responsible for transfer of genetic information from DNA to the ribosome and is the biggest family of RNA molecules. The structure of mRNA is shown in Figure 2.
- **Transfer RNA (tRNA):** Suppose we need to bake a cake. We need a kitchen, a recipe and raw materials. In the gene expression process, kitchen correlates to the cell, recipe is with mRNA and raw materials are supplied by tRNA. It brings together RNA nucleotides and amino acids.
- **Ribosomal RNA (rRNA):** rRNA links the amino acids into specific sequence for translation into particular protein.

Other types of RNA are non-coding RNA, transfer-messenger RNA, small-nuclear RNA, micro RNA, small interfering RNA, small nucleolar RNA, antisense RNA and Signal recognition particle RNA. The details of these types are out of the scope of this chapter. Additional readings section can referred for the same.

RNA INTERFERENCE

Decades ago, an experiment was conducted to increase the color of petunias flower wherein color producing gene was injected to the flower. Instead of increase in color, it was observed that color was lightened and even white petunias were produced in generations of flower (Jorgensen, Cluster, English, Que & Napoli, 1996). This was how the concept of gene expression suppression was coined. Further experiments revealed that introduction of sence and antisence RNA together forming double stranded RNA (dsRNA) leads to gene silencing (Fire et al., 1998).

The mechanism of RNA Interference (RNAi) involves treating the disease causing gene with specific small interfering RNA (siRNA) that targets the specific messenger RNA (mRNA). This mRNA is involved in production of protein that leads to the disease in question. The motive

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