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Review article

A short communication on therapeutic importance of sirna induced gene silencing

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ABSTRACT

Small interfering ribonucleic acid (siRNAs) are small interfering molecules which are messenger ribonucleic acid (mRNA) specific have many potential therapeutic role and by approaching techniques like microarray make possible of genome wide study. Small Interfering RNA have short 20-24 bp double stranded deoxyribonucleic acid (dsDNA) with phosphorylated 5' ends and hydroxylated 3' ends with two overhanging nucleotides. siRNA can also be introduced by transfection. Introduction of too much small interfering ribonucleic acid (siRNA) can results in nonspecific events due to activation of innate immune response.

Keywords: SiRNA, microarray, Helicase, mRNA, Therapeutic.

INTRODUCTION

For all living organisms gene expression has fundamental and functional importance as they express themselves via proteins synthesized in the cells. Rosalind Elsie Franklin's invention of X-ray crystallography made major contribution in the understanding of fine molecular structure of DNA, RNA and Viruses. The genetic material was identified as deoxyribonucleic acid (DNA) in 1944 and the double-helical nature of DNA was revealed in 1953 by Francis Crick, James Watson and Maurice Wilkins. It was proposed that another nucleic acid, single- stranded ribonucleic acid (RNA), acts as an intermediary in the process, Central Dogma genetic information is transcribed from DNA to RNA and then translated from RNA into protein for several years the hypothesis was formulated as "one gene-one ribosome- one protein". In 1961, Francois Jacob and Jacques Monod presented a visionary gene control model, for which they received the Nobel Prize in Physiology or Medicine in 1965 together with André Lwoffn. The discovery that RNA can act as a catalyst gave a radically new perspective on the roles of RNA (Nobel Prize in Chemistry to Sidney Altman and Thomas Cech in 1989) [1].

RNA world" is believed to have existed before DNA genetic material, and RNA was relegated to the role of messenger between DNA and protein, discovery of catalytic RNA have evolutionary implications but it also suggested that RNA could play a more active role in gene expression than earlier realized Within a year, the presence of RNAi had been documented in many other organisms, including fruit flies, trypanosomes, plants, planaria, hydra and zebrafish. It was proposed that short dsRNA, siRNA (small interfering RNA), guided the cleavage of mRNA. Subsequently, Fire and Mello were able to follow the process in vivo when siRNA is introduced into the cell experimentally to inhibit the activity of specific genes. In mammalian cells and physiological fluids it has been shown that siRNAs are more stable than antisense oligodeoxyribonucleic acids (AS-ODNs). Accuracy and potency of RNA interference (RNAi) in gene silencing was first experimentally documented in 1998 in Caenorhabditis elegan. Attempt to prolong the gene – silencing activity of siRNAs by introducing various chemical modifications has been done and increase the stability of molecules while maintaining their gene silencing potency e.g. 29-O- methylation [2]. Inducing gene silencing

using siRNAs has enormous potential for the understanding and indentifying the functionality of gene that may eventually could be used as a therapeutic strategy. In vitro siRNA production requires enzymatic synthesis, chemical synthesis and DNA- based expression vectors as well. Retroviral system (pSilencer adeno 1.0-CMV System) with Ambion's offers an adenoviral- mediated approach to deliver the siRNA into cells and animals. siRNA expression to transfect cells and in animal tissue it is proven that the pSilencer adeno vectors are ideal. In siRNA induced gene silencing there are many experimental concepts which demonstrates the siRNA efficacy which depends on multiple factors e.g. GC content, an adenosine base preference not a cytosine at the 19th or 20th base position of the sense strand which required for the unwinding/activation step in RISC complex which reduces the silencing ability, thermodynamic stability of the duplex at the 59 antisense end, ability to form a internal hairpins in the RISC complex. siRNAs are unwound by helicase which an ATP – dependent enzyme, the synthetic RNA which are 21-30 bp in length incorporated into the RNA-induced silencing complex for the specific cleavage of the target mRNA species [3].

Role of siRNA in disease

To design and synthesis of target-specific siRNAs (mRNA specific) mainly two approaches can be possible one is by computational and another is conventional methods. In Nasopharyngeal carcinoma silencing of hyluronan receptor (CD44) gene expression by RNai (in CNE-2L2 cell lines) results in reduction of malignanat potential of cells, in vitro colony formation and metastasis of tumor cells in nude mice and Desmoglein 3 which serve as molecular therapeutic marker in head and neck cancer cancer, inhibition of desmoglein 3 by RNAi as differentially expressed at RNA and protein level results in significant reduction in cell growth and colony formation to 57- 21 % in 3 head and neck cancer cell lines [4]. In oral squamous cell carcinoma the association of basal transcription of p53- inducible ribonucleotide reductase small – subunit 2 with its sensitivity to anticancer agents reduced expression of p27 was observed in oral squamous cell carcinoma due to an enhancement of its protein degradation, over expression of S phase kinase-interacting protein 2 in oral squamous cell carcinoma had been observed, siRNA mediated gene of S phase kinase-interacting protein 2 can be a novel modality of cancer [5].

It is demonstrated that in tooth development silencing of homobox, msh-like 1 in the dental mesenchyme results arrest of tooth development at bud stage. Whereas involvement of siRNA in the pathogenesis of osteoarthritis has been proved role of CD24 play an important in modulating expression of genes that regulate epithelial differentiation in periodontium. In animal model RNAi in Neurodegenerative disorders slows amyotropic lateral sclerosis (ALS) by knockdown of mutant. In preliminary studies, the RNAi therapy was found to be well-tolerated in the brain after direct CNS administration. Recently in mouse model of disease silencing of sphingosine kinase-1 isoform have been shown that results in the amelioration of C5a-induced acute peritonitis, and allergic asthma [6].

siRNA in clinical trials

Many clinical trials approaching siRNA are under process e.g Age related Mascular Degeneration (AMD), Respiratory Syncytial Viral Infections (RSV) and some are under pre-clinical studies e.g. chronic obstructive pulmonary disease, Dyslipidemia and Acute hearing loss [7].

CONCLUSION

In this short communication we tried to provide a brief role of different approaches with siRNA that have potential role in treating various diseases. Recent advancement of RNAi microarrays promises genome wide RNAi screening into a robust therapeutic approach.

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