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RNA Interference as a Therapeutic Tool

Archana Mahadev Rao and Divyashree MS*

Department of Biotechnology, Manipal Institute of Technology

Introduction

RNA interference is a technique in which the introduction of a dsRNA sequence into cells causes interference in the function of the endogenous genes that is complementary to the introduced RNA. RNA induced silencing was first noticed in the petunia plants and it was seen that the introduction of a transgene to enhance the expression of purple color led to the silencing of both the endogenous gene and the transgene [1]. The possibility to develop viral specific resistance due to this RNA silencing method was also realized in plants [2]. The regulation of gene expression due to RNA silencing was described in *C. elegans* [3]. Similar mechanisms are present in the fungi [4] and mammalian cells [5], which help in regulation of cellular functions. RNA interference is a novel method that can be used for controlling various disease conditions by targeting certain key genes that are vital to disease progression.

RNA interference can be brought about by microRNA (miRNA), small interfering RNA (siRNA) or by short hairpin RNA (shRNA). miRNA belongs to a class of non-coding RNA that are involved in the gene regulation activity in the normal cellular activities whereas the siRNA and shRNA are introduced in the cell to help in the gene expression.

The biogenesis of microRNA (miRNA) and siRNA generation are slightly dissimilar; however, their activity is similar in many aspects [6]. Dicer, a member of the RNase III family of ATP-dependent ribonucleases, binds to the dsRNA with 2 nucleotide 3' overhangs and cuts it to produce siRNA [7]. siRNAs are 21-23 nucleotide dsRNA duplexes with 2 or 3 nucleotide 3' overhangs [5]. These siRNAs incorporate into RNA-induced silencing complexes (RISC), where the siRNA duplex is unwound. The passenger strand is cut and escapes the complex, while the guide strand directs the RISC to the complementary site on the target mRNA [8]. Argonaute protein catalyzes the cleavage of target mRNA and the cleaved mRNA is released and the active strand containing RISC can direct the cleavage of additional target mRNAs [9].

RNA interference has emerged as a promising therapeutic technique. The short length synthetically produced siRNA can escape from the interferon response by the cell [10]. The higher interest in siRNA as a therapeutic can be contributed to the following points: Higher flexibility of siRNA in reaching the target and sequence-specific and stable inhibition, targeting multiple areas of same gene, the low levels of siRNA required to produce the response, capacity of silencing similar mRNA in different species, and minimal effect on other cell control mechanisms. There are around a thousand patents filed for siRNA as an antiviral agent, and it stands only second to siRNA as an anticancer agent. Several clinical trials have also been initiated using siRNA therapy with promising results [11]. The hurdles faced by this technique is majorly in the delivery of the siRNA to the cells. This problem can be solved using several oligonucleotide modification strategies [12] and using nanocarriers made of polymeric materials [13].

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***Address for Correspondence:** Divyashree MS, Manipal Academy of Higher Education, Manipal, Karnataka, India – 576104, India, E-mail: divyashree.ms@manipal.edu*

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