RNAi-MEDIATED THERAPEUTICS

Núria Morral and Scott R. Witting

Department of Medical and Molecular Genetics and Center for Diabetes Research, Indiana University School of Medicine, Indianapolis, Indiana

1 INTRODUCTION

Ribonucleic acid interference (RNAi) is the phenomenon by which small noncoding RNAs suppress the expression of a gene. In the early 1990s, experiments to block protein expression using antisense technology [i.e., RNA complementary to the target messenger RNA (mRNA)] indicated that introduction of the sense strand could also promote silencing [45, 55], suggesting that the silencing effect was the result of an independent mechanism. Later on, Fire and collaborators observed that in *Caenorhabditis elegans*, administration of double-stranded RNA (dsRNA) was at least two orders of magnitude more potent than the antisense or sense strands alone [46]. Furthermore, the interference effect spread from the tissue in which the dsRNA was injected to other tissues, and it was passed from the parental animal to the next generation through the germ line [46].

This seminal work triggered interest in determining whether RNA interference would be observed in other organisms. Present in most eukaryotes, including plants, *Neurospora*, *Drosophila*, and mammals [42, 57, 122, 140, 167], it is now clear this is a universal mechanism used to modulate gene expression. RNAi is triggered by dsRNA of variable lengths, which are processed to short RNA duplexes, approximately 21–28 nucleotides (nt) long. The first RNA silencing mechanisms were discovered as part of an antiviral response believed to protect organisms from viral infection. It was later discovered that cells have the capacity to synthesize small RNAs known as microRNA (miRNA), which regulate hundreds of genes, coordinating complex developmental as well as physiological responses. Based on the fact that miRNA molecules modulate gene expression in all mammalian tissues, RNAi is being exploited as a system for the treatment of human diseases as well as to study gene function.

2 MECHANISMS OF GENE SILENCING

2.1 MicroRNA

MicroRNAs (miRNAs) are small RNA molecules that regulate expression of genes involved in cellular metabolic pathways, development, cell differentiation, proliferation, and death [14, 22, 78, 138, 185]. It has been estimated that in eukaryotes, approximately 0.5–1% of predicted genes encode a microRNA, which in humans, regulates 30% of genes at an average of 200 genes per miRNA [86, 160]. MicroRNAs are tissue specific and differentially expressed during development [5, 80]. Although the gene targets of the majority of miRNA are still unknown, some have been determined. One such example is miR-122, which is abundantly expressed in liver, where it regulates a large number of cholesterol synthesis genes [78]. Another example is brain-specific miR-134, which negatively modulates the size of dendritic spines [148]. MicroRNAs have become targets for the treatment of cancer, as many are dysregulated in

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