MicroRNAs and their antagonists as novel therapeutics

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A central gene regulatory mechanism, recently identified, is regulation by short non-coding RNAs termed microRNAs (miRNAs; Fig. 1). miRNAs are ~22 nucleotide long molecules that control gene expression by binding to the 3' untranslated regions (UTR) of mRNA transcripts [1]. After base pairing between the miRNA and its target gene within a minimal six nucleotide region, the target mRNA is destined for facilitated degradation or translation inhibition [2] (Fig. 1). In humans, there are around 700 reported unique miRNAs [3,4] very often expressed at thousands of copies per cell, and these are expected to regulate about half of our genes [5]. miRNAs are important for a diverse range of biological processes such as cell growth, proliferation and differentiation.

Several miRNAs were shown to act as oncogenes and tumour suppressors indicating their direct involvement in cancer [6]. In addition, miRNA expression profiles were shown to classify human cancers with accuracy better than mRNA/gene profiles. However, cancer classification is not the only virtue of miRNAs as their expression patterns can also predict and determine the clinical behaviour of certain cancers. Expression of the let-7 miRNA, for example, has been shown to correlate with reduced survival in several cancers [7].

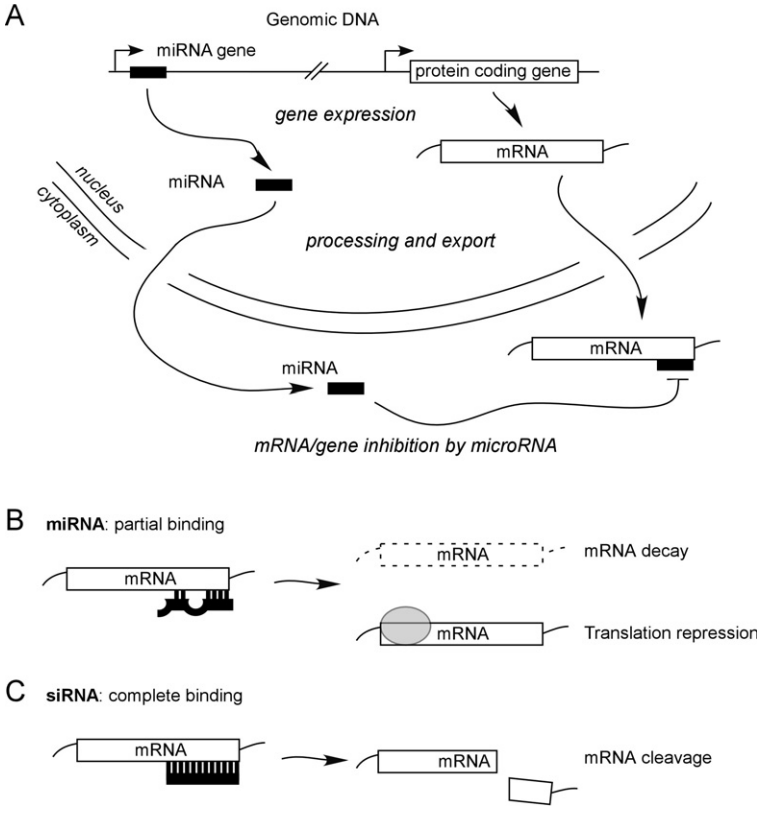

Fig. 1. The gene expression pathway is tightly regulated by miRNAs (A). Gene repression by miRNAs is associated with mRNA decay, translation inhibition (B) or target cleavage (C). The latter is mostly evoked by full complementary binding often seen with siRNAs.

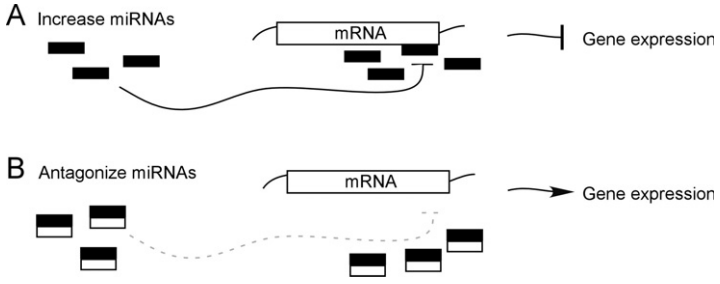

Fig. 2. Approaches for controlling mRNA target levels through (A) increasing or (B) blocking miRNA levels using antisense oligonucleotides.

Given that miRNA deregulation is associated with many cancer types and cancer development, it is of interest to exploit them for therapeutic manipulations and novel treatments. Along these lines, tumour-suppressive miRNAs may be directly up-regulated for an anti-cancer effect and oncogenic miRNAs can be targeted for down-regulation using antisense oligonucleotides (Fig. 2). Numerous studies have shown the effectiveness of customized antisense oligonucleotides to target specific pathologic miRNAs. In breast cancer, for example, reduced migration and invasion can be induced by miR-125 [8] while miR-21 can inhibit proliferation [9]. In order to aid in their cellular delivery, antisense oligonucleotides were linked with lipid molecules. These exhibited stable, nuclease resistant, potent anti-tumour effects when administered into mouse tumour models [10]. Intravenous administration of these to mice was shown to result in a powerful and specific silencing of endogenous miRNAs in a variety of organ systems for several weeks following a single injection [11]. A combination of miRNA associated therapy and conventional cancer treatments was also proven effective [12].

Small interfering RNAs (siRNAs) are double stranded RNAs introduced exogenously into mammalian cells for the purpose of gene knockdown. siRNAs are involved in the RNA interference (RNAi) pathway coined for their potent interference of the target gene expression [13]. The miRNA and siRNA pathways share critical RNAi components of regulation in spite of their difference in structural complementarity with their target genes (partial versus full; Fig. 1). In the past few years RNAi was exploited as a valuable tool in various systems to knockdown specific gene expression levels. Given their power and flexibility of target specific regulation (designed by the researcher), siRNAs are often also explored for cancer treatments. In pre-clinical studies, siRNAs demonstrated the ability to silence two oncogenes and consequently ceased proliferation of cancer cells.

Altogether, the features of miRNAs described here underscore them as potential targets for therapeutic intervention. In addition, miRNAs, siRNAs, or antagonists thereof, are powerful regulators that will surely become a valuable and novel class of drugs in the foreseeable future.

Conflict of interest statement

None declared.

References

1 Bushati N, Cohen SM. MicroRNA functions. *Annu Rev Cell Dev Biol* 2007;**23**:175–205.
2 Filipowicz W, Bhattacharyya SN, Sonenberg N. Mechanisms of post-transcriptional regulation by microRNAs: are the answers in sight? *Nat Rev Genet* 2008;**9**:102–14.
3 Griffiths-Jones S, Saini HK, van Dongen S, Enright AJ. miRBase: tools for microRNA genomics. *Nucleic Acids Res* 2008;**36**:D154–8.
4 Artzi S, Kiezun A, Shomron N. miRNAminer: a tool for homologous microRNA gene search. *BMC Bioinformatics* 2008;**9**:39–46.
5 Lewis BP, Shih IH, Jones-Rhoades MW, Bartel DP, Burge CB. Prediction of mammalian microRNA targets. *Cell* 2003;**115**: 787–98.
6 Boyerinas B, Park SM, Shomron N, et al. Identification of let-7-regulated oncofetal genes. *Cancer Res* 2008;**15**:2587–91.
7 Takamizawa J, Konishi H, Yanagisawa K, et al. Reduced expression of the let-7 microRNAs in human lung cancers in association with shortened postoperative survival. *Cancer Res* 2004;**64**:3753–6.
8 Scott GK, Goga A, Bhaumik D, et al. Coordinate suppression of ERBB2 and ERBB3 by enforced expression of micro-RNA miR-125a or miR-125b. *J Biol Chem* 2007;**282**:1479–86.
9 Frankel LB, Christoffersen NR, Jacobsen A, et al. Programmed cell death 4 (PDCD4) is an important functional target of the microRNA miR-21 in breast cancer cells. *J Biol Chem* 2007; **283**:1026–33.
10 Fluiter K, ten Asbroek AL, de Wissel MB, et al. In vivo tumor growth inhibition and biodistribution studies of locked nucleic acid (LNA) *Nucleic Acids Res* 2003;**31**:953–62.
11 Krutzfeldt J, Rajewsky N, Braich R, et al. Silencing of microRNAs in vivo with 'antagomirs'. *Nature* 2005;**438**:685–9.

12 Weidhaas JB, Babar I, Nallur SM, et al. MicroRNAs as potential agents to alter resistance to cytotoxics anticancer therapy. *Cancer Res* 2007;**67**:11111–6.

13 Fire A, Xu S, Montgomery MK, Kostas SA, Driver SE, Mello CC. Potent and specific genetic interference by double-stranded RNA in Caenorhabditis elegans. *Nature* 1998;**391**:806–11.