MicroRNAs hit the big time

Excitement growing about small RNA's role in several diseases

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2005 was the year when microRNAs (miRNAs) truly joined the small RNA revolution.

There has been great excitement in using the gene-silencing ability of small interfering RNAs (siRNAs) and RNA interference (RNAi) to treat disease. With several recent studies showing the involvement of miRNAs in several diseases, and as miRNAs and siRNAs use the same RNAi machinery to silence genes, the hope is that there might be more than one point of therapeutic intervention in the RNAi pathway.

Both miRNA and siRNA are short segments of double-stranded RNA, around 21 nucleotides in length. Whereas siRNAs silence genes by targeting specific messenger RNAs for cleavage, miRNAs are produced endogenously and are thought to regulate the expression of many genes in developing cells. Estimates set the number of miRNAs in humans at about 230 — almost 1% of the total human gene number, and on a par with important gene regulatory elements such as transcription factors.

A recent study by researchers at Rockefeller University and Alnylam Pharmaceuticals showed for the first time that specific miRNAs can be silenced (Krutzfeldt, J. *et al. Nature* 438, 685–689; 2005). The long-lasting, non-toxic silencing generated by injecting chemically engineered single-stranded RNA analogues called 'antagomirs' in mice was unexpected, as antagomirs didn't merely inhibit the miRNA — they degraded it.

"We believe this study points directly towards therapeutic opportunities based on the targeting of miRNA," says Nagesh Mahanthappa, Senior Director of Business Development and Strategy at Alnylam Pharmaceuticals.

A co-exclusive license relating to therapeutic uses of miRNA from the Max Planck Society, recently granted to Alnylam and Isis Pharmaceuticals, looks set to keep them at the forefront of work in the area. But others are also looking at miRNAs in normal and pathological settings, most notably a collaboration between Ambion and Rosetta Genomics.

As with other nucleic-acid-based therapies, delivery of an miRNA-targeting agent to the right place at the right time will be a key challenge. But before that another major challenge lies in "identifying the right disease hypotheses — knowing what miRNA should be inhibited for what disease," says Mahanthappa. Antagomirs will undoubtedly help establish miRNA function; the *Nature* study showed that one miRNA, called *miR-122*, is involved in cholesterol biosynthesis.

Oncology is the main focus for investigating miRNA-based therapeutic opportunities. Several papers published last year provided evidence for over- or misexpression of miRNAs in tumours. One study reported that 13 miRNAs form a signature associated with prognosis and disease progression in chronic lymphocytic leukaemia (Calin, G. A. *et al. NEJM* 353, 1793–1801; 2005).

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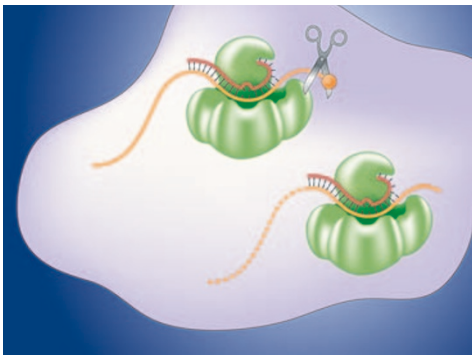

Targeting microRNAs could help tackle diseases like cancer.

Another identified miRNA expression patterns in hepatocellular carcinoma (Murakami, Y. *et al. Oncogene* 5 Dec 2005; doi:10.1038/sj.onc.1209283.).

Antivirals are also being looked at with a keen eye. Viral miRNAs have been found in virally infected cells, notably those containing Epstein–Barr virus and Kaposi's sarcoma-associated herpesvirus. Human miRNAs have also been identified that can target crucial HIV-1 genes. (Hariharan, M. *et al. Biochem. Biophys. Res. Comm.* 337, 1214–1218; 2005). How such miRNAs act within, or interact with, virus and host, is still unclear.

The number of diseases for which there is known to be a clear aberration in the activity of a particular protein is far larger than the number of diseases that can be attributed to faulty miRNA activity, so efforts in the short-term will still mainly focus on siRNA-mediated silencing of genes. But increased understanding of miRNAs role in disease will be good for RNAi-based therapeutics, says Mahanthappa. "We should endeavour to identify the best points of intervention in the RNAi pathway in relation to our understanding of a particular disease process."