EDITORIAL

miRNAs and cancer

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MicroRNAs (miRNAs) are small 21-25 nucleotide RNA molecules that comprise an evolutionarily conserved class of ribo-regulators which modulate gene expression via the RNA interference pathway. Initially considered a peculiarity of nematodes it is now known that these small non protein coding RNAs also occur in a wide variety of other organisms like plants, arthropods and vertebrates such as amphibians, birds, fish and mammals. Often their sequences and spatial/temporal expression patterns are conserved. Currently 4039 entries have been made in the miRNA registry, version 8.2 (http://microrna.sanger.ac.uk) including 462 human miRNAs that can be classified into several families of related miRNAs. It is estimated that there are as many as a thousand miRNA genes in the mammalian genome that regulate one-third of the protein coding genes. Hence, there will be very few cellular processes that are not affected by miRNAs.

miRNA genes are transcribed by RNA polymerase II forming long (up to several kb) primary miRNAs that are capped and polyadenylated. The pri-miRNAs fold into a stem-loop structure and are converted to their mature forms in two sequential processing steps by a nuclear (Drosha) and a cytoplasmic (Dicer) RNase III endonuclease. The miRNAs function within large protein complexes (RNA induced silencing complex/RISC) to negatively regulate specific target mRNAs. They do so by base-pairing with their target sequence - often in the 3' UTR of mRNAs – which results in translational repression or mRNA degradation. Contrary to plants, in animals most miRNAs have an imprecise complementarity to their target sequences. Computational algorithms aimed at identifying mRNA targets indicate that most miRNAs have multiple targets ranging from dozens to hundreds and that each target mRNAs may bind multiple miRNAs.

miRNAs have been implicated in the control of many fundamental cellular and physiological processes such as developmental timing, cell differentiation, cell proliferation, apoptosis and stem cell division. However the precise function of most miRNAs is still unknown as is their involvement in diseases like cancer. Enhanced proliferation and dysregulated cell death are important cancer cell characteristics. Notably several of the first miRNAs described in *Caenorhabditis elegans* (*lin-4*) and *Drosophila* (*bantam*, *miR-14*, *miR-2/6/11/13/308*) were shown to affect just these cancer relevant pathways. Moreover, a study in which 90 different human miRNAs were down-regulated by antisense oligonucleotides demonstrated that multiple miRNAs affect cell proliferation and apoptosis in cervical (Hela) and lung (A549) carcinoma cells. In addition, it was found that miRNA genes are frequently found in genomic regions and fragile sites associated with cancer and that the expression of many miRNAs is dysregulated in clinical cancer samples (Zhang et al, 2006). Calin et al were the first to report that miRNAs may function as tumor suppressors. It was shown that the cluster of *miR-15a* and *16-1* genes, localized on chromosome 13q14, was found to be deleted or down-regulated in more than 65% of B-cell chronic lymphatic leukemia (B-CLL) patients, in 50% of mantle cell lymphomas, 16-40% of multiple myeloma and 60% of prostate cancer (Calin et al, 2002). Also, *miR-143* and *miR-145* whose expression is reduced in colorectal cancers, and *let-7* family members that were found to be down-regulated in lung cancer, may have a tumor suppressing role. A reduced *let-7* expression in lung cancer was found to be associated with shorter post-operative survival. Alternatively, an up-regulation of *miR-155/BIC* was detected in breast cancer, diffuse large B-cell lymphoma and several other hematological malignancies. A significant over-expression of *miR-197* and *miR-346* was observed in follicular thyroid carcinoma, *miR-221*, *miR-222* and *miR-146* were found up-regulated in papillary thyroid carcinoma and a polycistronic miRNA cluster *miR-17-92* is over-expressed in lung cancers and B-cell lymphomas. Further studies provided experimental proof

implicating the *miR-17-92* cluster as potential oncogene because over-expression of the cluster accelerated c-MYC induced tumor development in a mouse B-cell lymphoma model (He et al, 2005).

Up till now very limited information is available about the physiological mRNA targets recognized by the miRNAs that are aberrantly expressed in cancers. *miR-15a* and *miR-16-1* may induce apoptosis by targeting the anti-apoptotic BCL2, *let-7* targets the critical oncogene RAS and *miR-17-5p* and *miR-20a*, that belong to the *miR-17-92* cluster, negatively regulate the translation of the MYC target gene *E2F1*. Interestingly, the expression of the *miR-17-92* cluster itself is induced by the MYC oncogene, suggesting the existence of complex genetic connections controlling cellular proliferation (O'Donnell et al, 2005).

Clearly, we are only just beginning to understand the role of miRNAs and the extent to which they contribute to carcinogenesis and other disorders. Of direct clinical value are the findings that miRNA expression profiles can be used to classify cancers, even better so than regular mRNA expression profiling involving thousands of genes. From these profiling studies one may identify prognostic miRNA signatures that may be used for diagnostic purposes (Yanaihara et al, 2006). Equally intriguing is the possibility to therapeutically intervene through the over-expression or silencing of specific miRNAs. It was shown that endogenous miRNAs in mice were efficiently and specifically silenced by intravenous injection of chemically modified, cholesterol-conjugated, single stranded RNA analogs complementary to the mature miRNAs (antagomirs) (Krützfeldt et al, 2005). A silencing effect could be observed in all tissues except the brain for prolonged periods of time. As miRNA research gains speed we will soon learn more about this new regulatory layer of gene expression.

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