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RNA-Directed Therapy: The Next Step in the miRNA Revolution

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RNA, once regarded as merely a messenger molecule in the process of gene expression, has recently emerged as a promising target for cancer therapy (reviewed in [1]). A major role for RNA in eukaryotes is carrying a DNA message from the cell nucleus to the cytoplasm, where it provides a template for protein synthesis. However, the recent discovery of small RNAs or microRNAs (miRNAs) that regulate the function and stability of messenger RNAs (mRNAs) has provided new roles for RNA regulating cell processes. Additionally, small RNAs are being exploited as a tool in systems biology to understand gene regulatory networks. We have just returned from a Forbeck Foundation Forum (http://www.wgfrf.org), held annually in Hilton Head Island, South Carolina, at which 16 leaders in the miRNA field talked about their latest work. Theirs is a message that deserves the widest circulation, for it portends a major change in our concepts of the origins, diagnosis, and treatment of cancer. These small RNAs may prove “imperial” like the diminutive Napoleon Bonaparte who was also short . . . but mighty.

Instructions for about 20,000 protein-coding genes are contained in the DNA sequence of the human genome. mRNAs are strands of hundreds to thousands of nucleotides that serve as templates for synthesis of proteins by ribosomes found in the cytoplasm. Translation into proteins may be affected by several factors, including amino acid availability, the levels of specific proteins involved in translation, and feedback effects of the coded proteins. Regulation of translation has mainly been ascribed to interactions between proteins and the noncoding portions of the mRNA itself. It has generally been thought that these proteins were solely responsible for control of translation. Now, evidence is mounting that miRNAs bind to these noncoding regions of mRNA and exert profound effects on protein synthesis and consequently cell functions. The implications for cancer are astonishing.

First discovered 14 years ago in Caenorhabditis elegans [2, 3], a primitive worm, miRNAs may target at least one third of all mRNAs. On average, each of the approximately 600 miRNAs found in mammalian cells contains partial sequence homology to 100–200 mRNAs. miRNAs have been implicated in the regulation of a diversity of processes, such as B- and T-cell development, antigen response, immune surveillance and tolerance, and other basic functions such as cell proliferation and death. In distinction to artificially synthesized small interfering RNAs, which target a single mRNA and cause its digestion by endonucleases, miRNAs target multiple mRNAs through partial sequence complementarity and function primarily by inhibiting protein translation (Fig. 1). However, new work by a Yale team has added a new dimension, suggesting that, in synchronously replicating cells, miRNAs may reverse course and become stimulatory to RNA translation [4].

Recent work from several laboratories has revealed that, in the development of lymphoid cells from undifferentiated precursors to mature antigen responders, specific miRNAs...
appear at specific stages in development (reviewed in [5]). The Rajewsky laboratory knocked out one of these miRNA genes (miR150), which stops B cells along their developmental pathway, and another miRNA gene (miR155) that demonstrates defects in plasma cells, the terminal stage of B-cell development. The Jacks laboratory knocked out another group of miRNA genes (miR-17–92 clusters). These mice demonstrated lung hypoplasia and heart developmental defects and died shortly after birth. Interestingly, the fetal livers of these mice demonstrated greater apoptosis of pro-B cells. Conversely, the overexpression of the miR-17–92 cluster in normal B-cell precursors can produce B-cell malignancies. The Croce laboratory and others have found that specific miRNAs appear to be causally related to chronic lymphocytic leukemia (miRNAs 15a and 16-1 and miR29a). Other miRNAs, such as let-7, exert a strong anti-proliferative and tumor suppressive effect on various oncogenes, including myc, myb, and ras expression, and are downregulated or deleted in most cancers (reviewed in [6]). Restoration of their activity reverses the malignant behavior of lymphoid, lung, and neuroblastoma tumor cells.

Because miRNA misregulation affects gene expression, and thus development and disease progression, miRNAs are considered candidate targets for therapeutic intervention. Overexpressed miRNAs can be inhibited by anti-miRs, which are complementary oligonucleotides that can bind to miRNAs and block their function. These 21- to 22-nucleotide RNAs are easily synthesized, but are susceptible to nuclease digestion in the plasma and do not readily cross the cell membrane. Fortunately, only small amounts of inhibitory nucleotide are required inside the cell. Efforts to deliver and stabilize anti-miRs are focusing on the use of liposomes or nanoparticles, coupling to peptides, or stabilizing oligonucleotides by chemical modification (such as 2′-0-methylation or 2′-4′ linkage) of its sugar phosphate backbone. The 2′-4′ linked (Locked Nucleic Acid) modification by Santaris Pharma of Denmark has particular promise in that it markedly increases the affinity of the molecule for binding to mRNA or miRNA. Each of these various species of inhibitory nucleotides may be targeted to tumor cells with monoclonal antibodies or affinity peptides. Thus, a workable technology for targeting miRNAs is currently evolving, and at last count 10 clinical trials of such molecules had begun in cancer and in other diseases. The replacement of deleted or underexpressed miRNAs is also possible but represents an even bigger challenge, and may
require the use of viral vectors to bring new DNA into the cell, coding for the missing miRNA.

The further implications of this rapidly evolving story for cancer diagnosis and for understanding cancer inheritance are profound. miRNAs may explain the inheritance of cases of familial cancers, such as breast or colon cancer, currently not ascribable to known full-length genes. Dissecting the biology of key miRNAs will undoubtedly point to new mechanisms that contribute to a host of important cell processes, including malignant transformation and progression. Profiling of miRNA is certain to distinguish subsets of human tumors not previously appreciated, and could well become a most important diagnostic, predictive, and prognostic tool, in that each miRNA influences the translation of multiple messages and complex pathways. Indeed, the miRNAs represent a new level of inherited biology, not previously appreciated, but certain to gain importance for cancer doctors and researchers. There is nothing micro about these Napoleons of cell biology (Fig. 2).

REFERENCES


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