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Post-transcriptional processing of genetic information and its relation to cancer

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Abstract

During the development, progression and dissemination of neoplastic lesions, cancer cells hijack normal pathways and mechanisms, especially those involved in repair and embryologic development. These pathways include those involved in intercellular communication, control of transcription, post-transcriptional regulation of protein production including translation of mRNAs, post-translational protein modifications, e.g., acetylation of proteins, and protein degradation. Small, non-translatable RNAs, especially microRNAs (miRs), are important components of post-transcriptional control. MiRs are produced from areas of the genome that are not translated into proteins, but may be co-regulated with their associated genes. MiRs bind to the 3' untranslated regions of mRNAs and regulate the expression of genes in most cases by either promoting the degradation of mRNA and/or inhibiting the translation of mRNAs into proteins; thus, miRs usually cause a decrease in protein levels that would be expected if the mRNAs were translated normally. It is early in our understanding of how miRs affect neoplastic processes, but miRs are expressed differentially in most cancers and have been associated with tumor progression, chemoresistance and metastasis. MiRs are present in nanovesicles, such as exosomes, and thus are likely involved in intercellular communication, especially in neoplasia. MiRs are attractive targets for novel therapies of cancer as well as potential biomarkers that might be useful for early detection and diagnosis, and for prediction of therapeutic efficacy. MiRs also could aid in determining prognosis, evaluating novel therapies, and developing preventive strategies by their use as surrogate end points.

Keywords

biomarkers; mRNA; microRNA; post-transcriptional regulation; transcriptional regulation; translation

Transcription is the process by which sequences of the genome are read by the enzyme RNA polymerase II and pre-forms of messenger ribonucleic acid (mRNA) are produced. These pre-forms of mRNA (pre-mRNA) are converted into mRNA and the mRNAs subsequently are translated into proteins by ribosomes that match the sequences of the mRNA with triplet codes on transfer RNAs (tRNAs), each of which carries a unique amino acid. The complex

of ribosomes, mRNA and tRNAs translate mRNA into amino acids that are bound together in a growing polypeptide chain ultimately to become a protein that matches the mRNA. Based on studying the genomics of prokaryotes, the concept arose that “one gene” was translated into “one protein”; however, based on the study of eukaryotic genomics, it is recognized that one gene ultimately can generate many different proteins. Therefore, fewer than 40,000 different genes may produce hundreds of thousands of unique proteins. In general, proteins generate the phenotypes of normal and diseased cells and tissues.

Because each cell type has specific roles and functions at multiple levels, i.e., organism, tissue and cell, the abundance, variety and type of proteins in each cell type may vary and may be cell-specific. Thus, a hepatocyte of the liver must be able to run the metabolic machinery necessary to produce glucose by gluconeogenesis and also produce and secrete many different proteins, e.g., albumin. In addition, the liver converts some waste products into bile. By contrast, skeletal muscle cells use glucose to power contractile proteins so that these cells can change size and shape rapidly. The cells of skeletal muscle do not produce glucose, albumin or bile. Because the DNA code is the same in each cell of an organism, accurate maintenance of the selective phenotypic characteristics in different types of cells is accomplished by genetic and epigenetic control of transcription, post-transcriptional processing including control of translation, and post-translational modifications of proteins.

In general, the mRNA produced from DNA in prokaryotic cells reproduces the base pattern of the complementary strand of the DNA. In eukaryotic cells, the DNA of a gene is separated into transcribed exons and untranscribed introns, i.e., the codes of introns are not incorporated into the final mRNA. Introns and other untranscribed areas of DNA may control the transcription of the gene or produce small RNAs that may regulate mRNA. In eukaryotic cells, a precursor form of mRNA (pre-mRNA), which includes the RNA codes of introns and exons, initially is transcribed from the DNA, then the pre-mRNA is edited to remove the regions of the mRNA that correspond to the introns. During processing of pre-mRNA, specific exons may or may not be included in the final mRNAs, which results in “splice variants” of proteins. Similarly, recent studies have shown that there may be additional editing of mRNAs by unknown mechanisms so that some mRNAs may not mirror the DNAs from which they were originally transcribed (Li et al. 2011); however, these results are controversial.

Post-transcriptional regulation

After transcription, many processes (Table 1) may occur to produce the large number of proteins that make up both the cellular and extracellular components of a tissue, hence its phenotype. These processes produce many changes in the proteins that would not be predicted based on the code and/or structure of the DNA. Of the post-transcriptional processes, we focus here on how small RNAs regulate mRNA, therefore the amount of proteins produced from specific genes.

MicroRNAs (miRs)

MiRs are short (hence the name), approximately 22 nucleotide forms of RNA that are single-stranded; they are not translated into proteins. By affecting the degradation and translation of mRNA, however, miRs can modulate levels of proteins.

For convenience, microRNA usually is abbreviated miR. We will use miR for this class of molecules and mir as a prefix to denote specific human precursor forms of miRs (pre-miRs), which ultimately may be processed into the same mature miRs; thus an example of a mature miR is miR-let7 while an immature form would be mir-let7. The second half of this sentence does not follow the first half. You introduce “mir,” then give an example that does not contain this designation. To date, miRs have been described in most cells except some types of plants, e.g., certain marine plants and some fungi (Lee et al. 2010). The functions of miRs may vary in plants and lower organisms; however, we will focus primarily on the importance of miRs in mammals.

MiRs were discovered in the worm, *C. elegans*. In this worm, the extent of the expression of the heterochronic gene, lin-14, that regulates developmental timing critical for larval transition (Chalfie et al. 1981) occurs by the complementary binding of a small RNA, lin-4, to the 3' untranslated region (3'-UTR) of the lin-14 mRNA (Lee et al. 1993, Wightman et al. 1993). Subsequently, a small non-coding RNA, let-7, in *C. elegans*, was identified as a critical regulator of cellular development, which suggests that these miRs may act as fundamental developmental regulators (Reinhart et al. 2000). Ultimately, RNA molecules of the let-7 type were found to be conserved in many species including humans. With this observation, it became apparent that regulatory small RNAs were a general biological mechanism for post-transcriptional control of genetic information. MiRs function in the normal development and growth of cells from plants to man. Most miRs target developmental processes that involve cellular control, proliferation, and cell death. By contrast, processes that characteristically involve routine maintenance functions common to all cells typically are not controlled by miRs. At present, it is believed that about 1/3 of the human genome may be under transcriptional regulation by miRs (Chen 2005, Phillips 2008, McDanel 2009).

Production of miRs

Typically, the genes that produce miRs can be located in an anti-sense orientation to exons or introns or in areas of DNA that were thought to be non-coding. Nevertheless, the genes that produce miRs are regulated by promoters and other regulatory mechanisms. Also, some genes for miRs may be in a sense orientation within introns or other non-coding areas of the DNA. This orientation within genes permits a miR to be co-regulated with its “related gene.” For example, a genetic sequence that codes for a specific miR, e.g., microRNA-xyy, which regulates the mRNA transcribed from gene y is located within the intron between exons 4 and 5 of the gene for y. Thus, as gene y is transcribed, the miR that binds to the mRNA of gene y would be transcribed with y and would be regulated, in part, by factors that control the transcription of y.

MiRs usually are produced from specific genes by RNA polymerase II (less commonly by RNA polymerase III) as a “primary miR” (pri-miR) that contains hundreds of nucleotides and a poly A tail at the 3′ end. When pri-miR is from a transcribed gene, pri-miR may be separated in the course of splicing, e.g., removing the intron areas of the mRNA. RNase III enzymes, Drosha and Pasha, enzymatically generate from the pri-miR approximately a 70 base form of RNA designated pre-miR, which leaves the nucleus as a complex with Exportin-5 (Chen 2005, Phillips 2008, McDanel 2009). The structure of the pri- and pre-forms of miR, though short, includes a hairpin loop. Once processed to miR, the hairpin loop is removed. The pre-miR then is cleaved by an RNA III enzyme, dicer, and the cleaved form of RNA is incorporated into an Argonaute-protein-containing complex called an RNA induced silencing complex or RISC. When bound as part of the RISC, the RNA is composed of two complementary strands. One strand then is cleaved, released by the RISC and degraded. The RISC orients the remaining strand (now designated a mature miR) so that it can bind optimally to target areas of mRNAs (Chen 2005, Phillips 2008, McDanel 2009).

Functions of miRs

The target areas of miRs in most cases are specific sequences of the 3′-UTR of the mRNA. The same RISC-miR complex can bind and regulate many different mRNAs if they have the same or similar sequences in their 3′-UTRs so that the same miR can modulate concomitantly many different mRNAs (e.g., 100) (Chen 2005, Phillips 2008, McDanel 2009).

If there is a strong complementary Watson-Crick match with the bases of the target region of a mRNA, the mRNA is cleaved by an energy requiring (ATP) process so that the poly A end of the 3′ mRNA and the capped 5′ end of the RNA are removed, which enables rapid mRNA degradation of each fragment of the mRNA by exonucleases (Chen 2005, Phillips 2008, McDanel 2009). The RISC and its miR are stable and continue to be biologically active so it can bind other mRNA molecules (Chen 2005, Phillips 2008, McDanel 2009). Unlike mRNAs, mature miRs are thought to be very stable in vitro as well as in vivo; in addition, miRs can be identified in fixed and paraffin embedded tissues so archival paraffin blocks are used for their analysis (Bovell et al. 2012).

If the miR does not have a strong base pairing with a sequence of the 3′-UTR, it still may bind, but less avidly, to the target mRNA. In such cases, the binding may not result in cleavage of the mRNA, but the bound miR inhibits the translation of the mRNA and sets up the mRNA for eventual degradation by the transfer of the mRNA to processing bodies or “P-bodies,” the sites where most mRNAs, whether regulated by miRs or not, are destroyed or are stored prior to degradation (Chen 2005, Phillips 2008, McDanel 2009). MiRs also may act in other ways to affect genetic information. For example, they may bind to regulatory introns to modulate transcription and/or miRs may inhibit translation of mRNAs (Chen 2005, Phillips 2008, McDanel 2009).

It is important to understand how miRs are identified to interpret the literature. As indicated, “mir” precedes the name of a pre-miR while “miR” precedes the designation of a mature miR. Over the years, specific miRs have been numbered to distinguish and identify them.

Usually, the numbers range from 1 to 9999; the small numbers designate miRs that were identified earlier. An initial three letter prefix may refer to species associated with the miR. Some species designations are listed in Table 2. You should add a sentence here that explains designation of species also, since you add this element to the first sentence that suggests that the paragraph concerns numbering. Thus the designation for miR 130 in humans could be “hsa-miR-130,” while the miR 130 in mice would be designated “mmu-miR-130.” A pre-miR may produce miRs from different ends of the molecule; if one of two miRs comes from the 3' end, it is designated, -3p, and if from the 5' end, -5p.

When mRs differ by only one or two nucleotides from the form of miR identified originally, the related miRs are designated by a letter, e.g., “a,” “b,” “c,” and in some cases where there are three very similar miRs as “b#.” Also, if two miRs come from the same pre-miR, but one is the minor component, it may have been labeled previously as “*.” Thus, miR-130* is the minor component and miR-130 is the major form of miR-130 in a cell; however, designations recently have been changed to -3p or -5p to describe such forms. Examples of various designations of miRs are shown in Fig. 1.

Frequently the species designation, hsa, is omitted for miRs for studies of human specimens and species prefixes often are deleted if a publication is limited to one species. Of great use to investigators studying miR is the web site, “mirbase.org,” currently 2011 version 18, that can be used to search for specific miRs or information about miRs. This web site contains more than 18,000 entries concerning more than 150 species and is organized to be accessed using several approaches. One approach is based on “species: chromosome: sequences.” If one enters *Equus caballus* (horse), for example, and chromosome 2, 18 “mirs” are listed, and each represents the pre-form of the miR. Specifically, one finds eca-mir-30e on chromosome 2. The mirbase.org site was less useful, however, for searching for miRs involved in cancer. By contrast, the “Human MicroRNA Disease Database” and the “miR2 disease database” are much more useful concerning the literature related to the involvement of miRs in diseases in general and neoplasia specifically (Jiang et al. 2008, Lu et al. 2008). These databases can be searched by organ, cancer or type of cancer, e.g., carcinoma, but sometimes must be searched under “neoplasia.”

Frequently, miRs provide a mechanism by which the amounts of proteins can be down-regulated. This function of miRs may occur by facilitating the degradation of mRNAs, which inhibits the translation of mRNAs or the transcription of mRNAs. Sometimes the mRNAs and their associated proteins that are down-regulated are involved primarily in the metabolism or degradation of important driver genes. For example, some proteins are controlled primarily by the degradation of the protein product (e.g., p27^{kip-1} metabolized by Skp-2); thus, if miRs inhibit the metabolic enzyme targeting a phenotypically important protein, the phenotypically important molecule would be expected to increase. Similarly, miRs can be inhibited by methylation of their promoters as well as by proteins from other genes, and less commonly, may stimulate translation directly and thus increase specific proteins (Vasudevan et al. 2007).

Because miRs function in the normal development and growth of cells, they would be expected to be dysregulated in disease processes and are likely to be important for at least

some aspects of all human diseases. We are just beginning to understand their importance in human diseases (Jiang et al. 2008, Lu et al. 2008). As expected, because miRs frequently are involved in developmental processes, congenital malformations of many organ systems, including the heart and brain, may occur if miRs are dysregulated.

Abnormalities related to miRs may occur at several levels including deregulation of the pri-miR, pre-miR, or mature miR. Other types of dysregulation may occur by modifications of the target 3'-UTR of mRNAs that affect the binding of miRs. Specific changes in the mRNA may cause the 3'-UTR no longer to bind a specific miR or it may cause binding to the 3'-UTR of a previously unbound miR. All the possibilities above may occur as somatic mutations or gene dysregulation during the development and progression of specific cancers or as germ line mutations by which such abnormalities are transmitted to offspring and result in familial diseases.

MiRs and exosomes

MiRs represent one of several newly described categories of molecules and pathways that “fine tune” cellular functions. MiRs can be transcribed and function not only within cells, but they also can be transferred to cells as a form of intercellular communication. This can be accomplished by packaging of miRs in membrane bound vesicles that are released from cells into the interstitial space. The vesicles within interstitial spaces may act locally through autocrine, paracrine or other-crine activities, or they may be picked up by blood or other bodily fluids to provide endocrine-like signals to distant cells (Kosaka and Ochiya 2012). The exosome is one type of vesicle that has been reported to contain molecules of miR. Exosomes are bilayered-membrane-bound nanovesicles that are released from the vesicular bodies of normal and diseased cells. Exosomes are present in most body fluid including blood. In blood, exosomes typically are 30–100 nm in diameter, have been described as “cup-shaped” and they express specific molecules such as the tetraspanins, CD9, CD63 and CD81. Although the details are uncertain, the molecular features of the external surfaces of exosomes control their uptake by cells, hence the effects of their contents on cellular functions (Zhang and Grizzle 2011).

Exosomes have been reported to contain functional proteins, mRNAs and lipids as well as miRs. Again, the details about how these molecules are sorted selectively into exosomes remains elusive. Nevertheless, typical exosomes contain hundreds of miRs and the packaging of miRs in exosomes may protect them from RNases (Kosaka and Ochiya 2012). How specific miRs in exosomes function and provide signals to cells is uncertain.

The molecules contained in exosomes, especially the proteins, peptides and mRNA, have been reported to be characteristic of the cells from which they arise. Because tumors secrete exosomes, i.e., tumor-derived (TD) exosomes, their contents, especially proteins, peptides, mRNA and miRs, have been found to be characteristic of the tumors from which they arise. Because TD exosomes contain miRs, it has been proposed that these miRs can be used as biomarkers that are useful for translational research focused on diagnosis, risk assessment, prediction, measurement of therapeutic responses and determination of prognosis (Lu et al. 2005, Grizzle et al. 2012, Zhang and Grizzle, in press). Circulating TD-exosomes of patients

with ovarian cancer have been reported to contain eight miRs whose expressions were significantly distinct from those observed in benign diseases (Taylor and Gercel-Taylor 2008). In many cases, the miRs were expressed differentially in exosomes compared to the matching fluids; thus, miRs contained within exosomes may provide greater sensitivity and specificity for translational studies (Kosaka and Ochiya 2012, Nair et al. 2012).

Other small RNAs

siRNAs are double-stranded small RNAs that are present in prokaryotes, plants and animals evolutionarily below worms where they protect against certain viruses and intracellular parasites. In some cases, this double-stranded RNA attracts a protein complex containing dicer, which cleaves the double-stranded RNA. Like miRs, they are bound by Argonaute and other molecules into an RNA-induced silencing complex (RISC), which then is processed as described previously for miR and whose action may be similar to miRs. Alternatively, siRNAs may be bound with Argonaute into a different complex, the RNA induced transcriptional silencing complex (RITS), which can inhibit transcription of genes.

There are other endogenous forms of small RNAs that also act post-transcriptionally on mRNA and are related to, but currently are considered distinct from, miRs (Lee et al. 2010, Naqvi et al. 2009). Small RNAs that mimic siRNA may be synthesized exogenously and used experimentally to decrease specific mRNAs, hence, proteins; these also typically are called siRNAs (Devi 2006).

MicroRNAs in cancer

Pre-invasive and invasive neoplastic cells typically hijack embryological and repair processes and pathways to facilitate neoplastic development and progression. Pathways controlling proliferation, apoptosis, cellular motility, cellular invasiveness and cellular orientation (polarity) are typical pathways that are dysregulated in neoplastic cells to facilitate their growth and survival. While pathways controlling proliferation and apoptosis, for example, are regulated carefully in normal tissues, these pathways frequently are dysregulated in neoplasia. Also, with increased proliferation and dysregulated apoptosis, mutations in genes, overexpression of genes, and changes in the epigenetic control of transcription may develop in neoplasia.

MiRs are involved in most aspects of neoplasia from the development of neoplastic lesions to the spread of cancer by metastasis. MiRs involved in cancer have been designated as “oncomiRs” (Cho et al. 2007, Esquela-Kerscher and Slack 2007, Lujambio 2009). OncomiRs can modulate the development, progression and dissemination of neoplastic processes by acting as either tumor suppressors (e.g., miR-34a) or oncogenes (e.g., mir-17-92 cluster). It is of interest that the tumor suppressors, miR-18a, miR-34b/c and miR-9, can be silenced by hypermethylation and this silencing facilitates nodal metastasis (Cho et al. 2007, Lujambio 2009).

MetastamiRs are miRs that are involved specifically in the metastatic process (Hurst et al. 2009, White et al. 2011, Lopez-Camarillo et al. 2012). They frequently function as an intermediate signal in pathways that inhibit or facilitate cancer, e.g., miR146a/b acts

downstream of the BRMS1 gene, which suppresses metastasis in breast cancer, but miR146a/b acts prior to genes that are identified as regulated by BRMS1 (Hurst et al. 2009). Other miRs involved in metastasis of breast cancers include miR-335, miR-126, miR-10b, miR-9 and miR-155 (Tavazoie et al. 2007, Ma et al. 2007, 2010, Negrin and Calin 2008, Xiang et al. 2011). Similarly, miR-31 usually acts as a general tumor suppressor as well as a suppressor of metastasis by its action on integrin- α 5, radixin and RhoA, while the miR-200 family (miR-200a, b, and c, miR-141 and miR-429) may inhibit or facilitate metastasis depending on whether effects of epithelial to mesenchymal transition or mesenchymal to epithelial transition dominate (Dykxhoo 2010).

MiRs have been claimed to be useful for early detection, diagnosis and prognosis of various cancers and for management of patients by prediction of therapeutic efficacy, monitoring responses to therapy or as targets for therapy (Mak et al. 2005, Waldman and Terzic 2007, Martello et al. 2010, Manne et al. 2010, Shah et al. 2009). It has been suggested that MiRs potentially are important clinically for most cancers and specifically for cancers of the ovary (Shah et al. 2009, Taylor and Gercel-Taylor 2008), lung (Rabinowitz et al. 2009, Mallick et al. 2010), breast (Pigati et al. 2010, Xiang X et al. 2011), pancreas (Wang et al. 2009, Srivastava et al. 2011), prostate (Coppola et al. 2010) and brain (Delfino et al. 2011).

Small non-translatable RNAs such as miRs now are recognized as an important group of regulatory molecules that are involved primarily in post-transcriptional regulation of genetic information. There are thousands of different miRs that bind to the untranslated 3' ends of mRNAs and thereby modulate the degradation of these mRNAs and inhibit their translation. MiRs can be carried within exosomes to provide autocrine, paracrine, and endocrine type intercellular signals among normal and diseased cells, and especially neoplastic cells. MiRs also are involved in disease by their dysregulation. MiRs likely represent one of the biological pathways that neoplastic lesions use to promote their development, progression and dissemination; therefore, these molecules may be attractive targets for novel approaches to therapy, diagnosis and prevention of cancer.

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Fig. 1.

Table 1

Post-transcriptional regulation in eukaryotes

Editing of the pre-mRNA
Alternate splicing of the pre-mRNA to include or exclude specific exons
Editing of the mRNA by enzymes, e.g., adenosine, to inosine
Editing of the mRNA by undefined mechanisms, changing the code of the mRNA and ultimately the structure of the proteins expected based on the DNA
Modulation of movement of mRNA out of the nucleus
Modification of the mRNA by small forms of RNA, including miRs
Degradation of the mRNA including control of degradation by miRs
Incorporation of atypical coded bases in tRNA, e.g., inosine, and their exit from the nucleus
Control of translation of mRNA to protein by miRs and by ribosomes, e.g., protein interactions with the internal ribosomal entry site (IRES)
Primary post-translational modifications of the initial proteins
Control of proteins by degradation

Table 2

Species and designation for miR

Species	Designation
human	hsa
mouse	mmu
rat	rno
sheep	oar
dog	cfa
chicken	gga
viral	__v
<i>Drosophila</i>	d__