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Commentary

MicroRNAs in cancer management and their modulation by dietary agents

Tommy Karius, Michael Schnekenburger, Mario Dicato, Marc Diederich *

Laboratoire de Biologie Moléculaire et Cellulaire de Cancer, Hôpital Kirchberg, 9, rue Edward Steichen, L-2540 Luxembourg, Luxembourg

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ABSTRACT

MicroRNAs (miRNAs) represent a class of small (21–23 nucleotides) non-coding RNAs that emerged as key post-transcriptional gene regulators, implicated in numerous physiological and pathological processes. Currently, a main focus of miRNA research is related to the roles of miRNAs in cancer development. The biogenesis and modes of action of miRNAs have not been completely elucidated; however, miRNA-mediated translational repression is involved in the regulation of almost every cellular process. Thus, pathological alterations in miRNA expression signatures are commonly associated with disease development. This review specifically focuses on miRNAs in cancer, with an emphasis on their use as potential biomarkers for cancer diagnosis and prognosis. Then, we discuss the potential use of synthetic antisense or miRNA mimetic oligonucleotides and dietary agents to modulate miRNA expression for chemotherapy and chemoprevention of cancer, respectively.

1. Introduction

The concept of post-transcriptional regulation of gene expression by antisense RNAs was introduced in 1993 when Lee et al. published the first report of a small RNA (lin-4) with antisense complementarity to the 3′UTR of lin-14 m RNA; importantly, lin-4 displayed translational inhibition potential in *Caenorhabditis elegans* [1]. The micro RNA (miRNA) era began with the detection of the small non-coding RNA let-7. Currently, the Sanger database miRbase 17.0 (http://www.mirbase.org) contains 1424 mature human miRNA sequences that may regulate at least one-third of all human protein-coding genes [2].

Abbreviations: ACTR1A, ARP1 actin-related protein 1 homolog A centractin alpha; AGTR1, angiotensin II receptor type 1; AICDA, activation-induced cytidine deaminase; AKT, v-akt murine thymoma viral oncogene homolog; ALL, acute lymphocytic leukemia; AML, acute myeloid leukemia; APAF1, apoptotic peptidase activating factor 1; APL, acute promyelocytic leukemia; ARHI, age-related hearing impairment; ASO, antisense oligonucleotides; ATRA, all-trans retinoic acid; BACH1, BTB and CNC homology basic leucine zipper transcription factor; BAK1, BCL2-antagonist/killer 1; BCL2, B-cell CLL/lymphoma 2; BIM, BCL2-interacting mediator of cell death; CAGR, cancer-associated genomic region; CCN, cyclin; CDC2, Cell division control protein 2 homolog; CDC25A, cell division cycle 25A; CDK, cyclin-dependent kinase; CDKN, CDK inhibitor; CEBPB, CCAAT/enhancer binding protein (C/EBP) beta; CLL, chronic lymphoid leukemia; c-Kit, transcription factor; CREB, cAMP responsive element binding protein; DGCR8, DiGeorge syndrome critical region 8; DIM, 3,3′-diindolylmethane; DNMT, DNA methyltransferase; E2F, E2F transcription factor; EGCG, epigallocatechin gallate; EGFR, epidermal growth factor receptor; ERBB/HER, epidermal growth factor receptor class avian erythroblastosis oncogene B; ERK, extracellular signal-regulated kinase; ESF1, ESF1 nucleolar pre-rRNA processing protein homolog; ESR1, estrogen receptor 1; ETS1, v-ets erythroblastosis virus E26 oncogene homolog 1; Fas, tumor necrosis factor receptor superfamily member 6; FDA, food and drug administration; FOX, forkhead box; HAT, histone acetyltransferase; HDAC, histone deacetylase; HMGA2, high mobility group AT-hook 2; HOX, homeobox; I3C, indole-3-carbinol; IGF1R, insulin-like growth factor 1 receptor; IGF2, insulin-like growth factor 1; IL6R, interleukin 6 receptor; IRS1, insulin receptor substrate 1; JUN, jun proto-oncogene; KRAS, v-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog; LATS2, LATS large tumor suppressor homolog 2; LDOC1, leucine zipper downregulated in cancer; MAFK, v-maf musculoaponeuritic fibrosarcoma oncogene homolog K; MATR3, matrin 3; MCL1, myeloid cell leukemia sequence 1; MCM2, minichromosome maintenance complex component 2; MET, met proto-oncogene tyrosine kinase; miRNA, microRNA; mirtron, pri-miRNA-containing intron; MNT, MAX binding protein; MSH2, mutS homolog 2; mTOR, mammalian target of rapamycin; MYOD, myogenic differentiation; NFIB, nuclear factor I/B; NF-κB, nuclear factor kappa B; NRAS, neuroblastoma RAS viral (v-ras) oncogene homolog; PACT, protein kinase R activating protein; PDCD4, programmed cell death 4; PDCD6IP, programed cell death 6 interacting protein; PML-RARα, promyelocytic-retinoic receptor alpha; PRIM1, primase DNA polypeptide 1; PTEN, phosphatase and tensin homolog; RAS, proto-oncogene; RAB, member of the RAS oncogene family; RAR, retinoic acid receptor; RARE, retinoic acid response elements; Rho, rhodopsin; RISC, RNA-induced silencing complex; RNA Pol, RNA polymerase; RXR, retinoid X receptor; SHIP1, SH2 domain-containing inositol phosphatase 1; SNAI2, snail homolog 2 (Slug); SNP, single nucleotide polymorphism; SOCS, suppressor of cytokine signaling; SP1, specificity protein 1; TCL1, T-cell leukemia/lymphoma 1A; TGFBR, transforming growth factor beta receptor; TIMP3, Tissue inhibitor of metalloproteinases 3; TM6SF1, transmembrane 6 superfamily member 1; TP, tumor protein; TP53INP1, TP53 inducible nuclear protein 1; TPM1, tropomyosin 1; TRBP (TARBP), trans-activator RNA binding protein; TSG, tumor suppressor gene; UTR, untranslated region; VIM, vimentin; WT1, Wilms tumor 1; ZBTB10, zinc finger and BTB domain containing 10; ZEB, zinc finger E-box binding homeobox.

* Corresponding author. Tel.: +352 2468 4040; fax: +352 2468 4060.
E-mail address: marc.diederich@lbmcc.lu (M. Diederich).

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miRNAs are a family of 19- to 24-nucleotide non-protein-coding RNAs that post-transcriptionally regulate mRNA function. miRNAs are involved in many fine-tuned biological processes; however, miRNA genes and the mechanisms by which miRNAs are processed are hotspots for pathological aberrations. Analyses of the patterns of these alterations reveal promising cancer biomarkers as well as therapeutic targets, such as synthetic antisense oligonucleotides or miRNA mimetic molecules. Since studies show that dietary agents have an influence on miRNA expression patterns, the cancer-preventing potential of these compounds will be discussed.

2. Biogenesis and *modus operandi* of microRNAs

Genes coding for miRNAs are located either in intergenic regions or in defined transcription units. Approximately 50% of the miRNA genes are found in introns or exons of both protein-coding and long non-coding transcripts and are consequently co-transcribed with their host gene.

Although miRNAs located in Alu repeats are transcribed by RNA polymerase (RNA Pol) III, miRNA genes are usually transcribed by RNA Pol II into polycistronic primary transcripts (pri-miRNAs) with lengths of approximately 1–10 kb (Fig. 1). Pri-miRNAs are characterized by a 5′-methyl cap structure, a poly(A) tail at the 3′ end and at least one hairpin structure of approximately 70 nucleotides. In the canonical miRNA pathway, a complex consisting of the double-stranded RNA-specific endoribonuclease III Drosha, the binding protein Pasha and the DiGeorge syndrome critical region 8 protein (DGCR8) processes pri-miRNAs into 70- to 100-nucleotide pre-miRNAs. In addition to a stem-loop structure, pre-miRNAs bear 3′-dinucleotide overhangs. An alternative mechanism of pri-miRNA processing occurs through the mirtron pathway. In this pathway, pre-miRNA structures are generated from pri-miRNA-containing introns (mirtrons) by the nuclear splicing machinery. The exportin-5/Ran-GTPase heterocomplex transports pre-miRNA from the nucleus to the cytoplasm, where it undergoes further maturation. The pre-miRNA is subsequently processed by Dicer III into a 19- to 24-nucleotide double-stranded

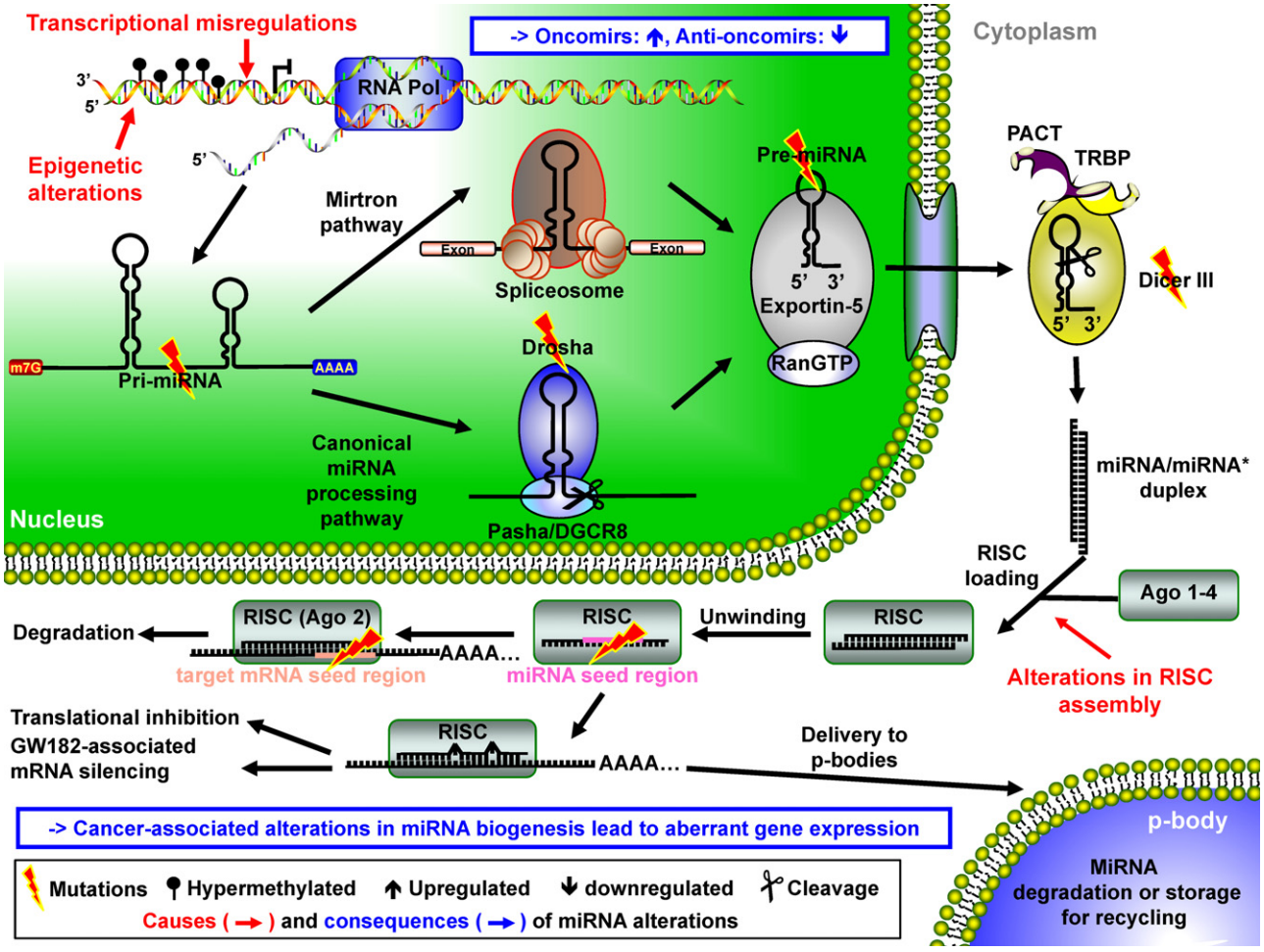

Fig. 1. miRNA biogenesis and cancer-associated alterations in microRNA pathways. First, a microRNA gene is transcribed into a primary miRNA (pri-miRNA) by an RNA polymerase (RNA Pol). miRNA genes are usually transcribed by RNA Pol II; however, miRNAs located in Alu repeats are transcribed by RNA Pol III. The pri-miRNA is further modified through either canonical processing or the alternative mirtron pathways into a pre-miRNA. In the next step, the pre-miRNA is exported from the nucleus by exportin-5 in a RanGTP-dependent mechanism into the cytoplasm, where it is cleaved by Dicer III. The resulting miRNA/miRNA* duplex is then loaded into the RISC complex, where it is unwound. The remaining single-stranded miRNA interacts with the target mRNA. In general, perfect complementarity between miRNA and mRNA sequences and the presence of the Ago2 endonuclease leads to mRNA degradation. Remarkably, incomplete complementarity can either induce deadenylation and degradation or lead to GW182-associated translational inhibition (*e.g.*, by preventing circularization or inhibiting the initiation of translation). Moreover, RISC complexes with captured target mRNAs can be delivered to parking bodies, where mRNA is degraded or stored for recycling. In cancer cells, mutations can occur in intermediate stages of miRNA (*i.e.*, pri- and pre-miRNAs), in the mature miRNA seed region, in the target mRNA sequence or in miRNA-processing proteins. Moreover, alterations in the expression pattern of miRNA-regulating transcription factors, abrogation of RISC assembly and aberrations in epigenetic mechanisms involved in the regulation of the expression of miRNA genes can enhance oncomir expression and repress tumor suppressor miRNA expression. Consequently, alterations in the miRNA biogenesis process lead to aberrant gene expression. DGCR8, DiGeorge syndrome critical region 8; PACT, protein kinase R activating protein; RISC, RNA-induced silencing complex; RNA Pol, RNA polymerase; TRBP, trans-activator RNA binding protein.