MicroRNAs in nasopharyngeal carcinoma

Jeff P. Bruce* and Fei-Fei Liu1,2,3,4

Abstract
MicroRNAs (miRNAs) provide insight into both the biology and clinical behavior of many human cancers, including nasopharyngeal carcinoma (NPC). The dysregulation of miRNAs in NPC results in a variety of tumor-promoting effects. Furthermore, several miRNAs are prognostic markers for NPC. In addition to cellular miRNAs, NPC samples also contain miRNAs encoded by Epstein-Barr virus, and these miRNAs may impact NPC biology by targeting both cellular and viral genes. Given their numerous putative roles in NPC development and progression, a thorough understanding of the impact of miRNA dysregulation in NPC is expected to shed light on useful biomarkers and therapeutic targets for the clinical management of this disease. In this review, we describe the efforts to date to identify and characterize such miRNAs in the context of NPC.

Key words Nasopharyngeal carcinoma, microRNA, gene regulation, small RNAs, Epstein-Barr virus

MicroRNAs (miRNAs) have been shown to provide insight into both the biology and clinical behavior of numerous human cancers, including nasopharyngeal carcinoma (NPC). miRNAs are known to function as both tumor suppressor genes and oncogenes, and their dysregulation has been found to be related to disease prognosis and clinical outcome. Hence, the examination of miRNA dysregulation in NPC can (1) provide useful insight into the biological workings of this disease, aiding in the development of novel targeted therapies and (2) provide clinical prognostic and predictive biomarkers to aid physicians in treatment decision making, and thus improve outcome for future NPC patients.

miRNAs
miRNAs are endogenous, small (18–25 nt), non-protein-coding RNA molecules1. Originally discovered in C. elegans, miRNAs have now been identified in over 200 different species2. In general, miRNAs bind to transcripts of target protein-coding genes in a sequence-specific manner, functioning primarily to decrease the transcript and/or protein levels of their targets. However, miRNA-target interactions resulting in increased protein levels have also been noted3,4. In recent decades, miRNAs have been increasingly recognized as important genetic regulators in the mammalian system1. Moreover, numerous miRNAs have been reported to function as both oncogenes and tumor suppressors, regulating tumor initiation and progression at all levels5,6.

miRNA Biogenesis and Function
The biogenesis of miRNAs is a multistep process that is tightly regulated within the cell. Figure 1 depicts the steps in canonical miRNA processing—from transcription in the nucleus to the interaction with miRNAs in the cytoplasm. Genes that encode miRNAs can be located in intergenic regions or within the exons or introns of other genes. Transcription of these miR-genes is performed predominantly by RNA polymerase II (Pol II), though RNA Pol III performs transcription in some cases6,7. A variety of Pol II–associated transcription factors direct miRNA transcription, thereby regulating miRNA expression at the level of transcription8. The RNA product that is transcribed is called a primary miRNA (pri-miRNA). These pri-miRNAs vary in length from hundreds to thousands of base pairs and exist in diverse stem-loop structures6. Following transcription, the pri-miRNA is cleaved within the nucleus by the dsRNA-specific transporting complex composed of Exportin-5 and GTP-bound ras-related nuclear protein (RAN-GTP)9.

In the cytoplasm, the pre-miRNA is further processed by Dicer and its cofactor trans-activation-responsive RNA-binding protein (TRBP) to release the ~22 nt, mature miRNA duplex10. One strand of this duplex, termed the “guide strand,” is then preferentially

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Authors’ Affiliations:1 Princess Margaret Cancer Centre, University Health Network, Toronto, ON, Canada; 2Department of Radiation Oncology, Princess Margaret Cancer Centre, University Health Network, Toronto, ON, Canada; 3Department of Radiation Oncology, University of Toronto, Toronto, ON, Canada; 4Department of Medical Biophysics, University of Toronto, Toronto, ON, Canada.

Corresponding Author: Fei-Fei Liu, Department of Radiation Oncology, Princess Margaret Cancer Centre, 610 University Avenue, Toronto, Ontario, Canada M5G 2M9. Tel.: +1-416-946-2123; Fax: +1-416-946-4586; Email: Fei-Fei.Liu@rmp.uhn.on.ca.

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FIGURE 1. MicroRNA (miRNA) biogenesis. miRNAs are processed through a complex series of highly regulated steps in the nucleus and the cytoplasm, from transcriptional to functional roles as transcript and protein level regulators. Abbreviations: RNA Pol II, RNA polymerase type II; pri-miRNA, primary microRNA; pre-miRNA, precursor microRNA; DGCR8, DiGeorge syndrome critical region gene 8; XPO5, nuclear export factor exportin 5; RAN, ras-related nuclear protein; GTP, guanosine triphosphate; AGO, Argonaute; TRBP, TAR (HIV-1) RNA-binding protein 2; PACT, protein kinase, interferon-inducible double stranded RNA; Dicer, Dicer 1 ribonuclease Type III; miR*, passenger strand from mature miRNA duplex; miRISC, microRNA RNA-induced silencing complex; P-body, processing body.

incorporated into the miRNA-inducible silencing complex (miRISC).[8] Although this process is not completely understood, the guide strand is almost always the strand with the 5' terminus that is least thermodynamically stable.[10] The miRISC is a multipart entity with several potential members. The key functional element of miRISC is the Argonaute protein (in mammals, one of AGO1-4).[6]

In addition to Argonaute, several other proteins may be involved in miRISC, including the P-body marker fragile X mental retardation 1 protein (FMRP)[11] and the de-capping activator RCK/p54.[12,13]

Once a mature miRNA is incorporated, miRISC can then bind to a target mRNA at a sequence-specific binding site. A particular miRNA may bind to hundreds of different genes, sometimes even onto multiple sites for a given target mRNA. Binding occurs with either perfect complementarity or, more often, imperfect complementarity.[5] In these instances of imperfect complementarity, there is often a short, ~6-8 nt “seed” region, located near the 5' end of the miRNA, which appears to be of paramount importance in terms of dictating binding to specific target mRNAs.[1] These seed regions are often conserved among species and form the basis for many of the current in silico target prediction algorithms.[6,14-16].
miRNAs can regulate expression of their targets through either mRNA degradation or translational inhibition. In instances of perfect or near-perfect miRNA-mRNA complementarity, degradation of target mRNAs can be mediated by AGO2, the only Argonaute protein with “slicer” activity. In cases of imperfect complementarity, all 4 Argonaute proteins are capable of inhibiting protein translation as part of miRISC. In addition, miRNA-target relationships with imperfect binding can also result in mRNA degradation through a non-sequence-specific mechanism within cytoplasmic processing bodies (P-bodies). In most cases, the net effect of miRISC binding to a target mRNA is a decrease in its protein levels. However, recent reports have demonstrated a few instances wherein protein levels is actually increased. For example, miR-10A can bind the 5’ untranslated region (UTR) of the mRNA transcript for several ribosomal genes, increasing the expression of these genes.

miRNAs in Cancer

As the list of miRNAs has grown, so has our knowledge regarding their biological functions. Indeed, miRNAs have been found to play a role in most, if not all, cellular processes, including many pathways related to cancer development and progression. miRNAs function as tumor suppressor genes or oncogenes, with some miRNAs mediating contradictory roles in different diseases. Aberrant miRNA expression and function have been described in a wide variety of human malignancies, with chromosomal amplifications/deletions, point mutations, or epigenetic alterations as potential causes.

Comprehensive miRNA expression profiling has been performed in a variety of human cancers, yielding a number of interesting observations. These include expression signatures that are capable of distinguishing cancer cells from normal cells or one cancer from another; predicting response to a particular drug; or predicting patient outcome. Indeed, miRNA signatures capable of predicting patient outcome have been developed for a number of human cancers including lung cancer, breast cancer, brain cancer, and chronic lymphocytic leukemia. Prognostic, predictive, and biological roles have also been described for miRNAs in NPC, as discussed below.

Human miRNA expression in NPC

The first study on the global profiling of miRNAs in NPC was published in 2008 by Paul Ahliquist’s group at the National Cancer Institute (NCI). Using a microarray-based approach to profile 31 laser-capture microdissected NPC samples and 10 normal nasopharyngeal epithelial samples, they discovered several miRNAs to be dysregulated in NPC. In particular, miR-29c was significantly down-regulated in NPC, and several miR-29c targets involved in extracellular matrix synthesis and function were identified and validated. Subsequently, other groups have identified a number of dysregulated miRNAs in both nasopharyngeal tumor and blood samples from patients with NPC. (Table 1).

In addition to alterations in miRNA expression in NPC, we and others have demonstrated phenotypic roles for miRNAs in nasopharyngeal tumorigenesis using in vitro and in vivo models. The first miRNA characterized in the context of NPC was miR-29c, which was the main focus of the first miRNA profiling reported by Sengupta et al. In this initial study, the authors demonstrated that miR-29c plays a potential tumor suppressive role, targeting mRNAs that encode extracellular matrix proteins (collagens 3A1, 4A1, and 15A1, and laminin γ1). They postulated that suppression of miR-29c will subsequently increase the migration and invasion of NPC cells through up-regulation of these components of the extracellular matrix. However, they stopped short of testing this hypothesis in the initial study, and further reports supporting these claims have not been published to date. Subsequent studies by two other groups corroborated the role of miR-29c as a tumor suppressor in NPC, but these reports differed in their causal mechanisms and putative targets. While Liu et al. demonstrated that down-regulation of miR-29c resulted in the promotion of NPC cell migration and invasion through increased expression of T-cell lymphoma invasion and metastasis 1 (TMP1), Zhang et al. showed that miR-29c knockdown resulted in increased resistance to radiotherapy and cisplatin through up-regulation of the anti-apoptotic regulators Mcl-1 and Bcl-2. Thus, much like other miRNAs, miR-29c can act through a number of pathways to suppress the proliferation, survival, and motility of NPC cells.

In 2011, we reported that miR-375 is a potential tumor suppressor in head and neck cancers, including NPC. We discovered that the metastader (MTDH), a newly emerging oncogene, was an important target for down-regulation by miR-375 and that MTDH overexpression was particularly detrimental to NPC patients, resulting in an increased risk of distant relapse.

Another moderately well studied miRNA in the context of NPC is miR-9. Not only has miR-9 been identified as a potential circulating biomarker of advanced NPC, several potential targets and functions of miR-9 have also been reported. Recently, two studies describing putative tumor suppressive mechanisms for miR-9 in NPC have been published. Lu et al. reported that hypermethylation and subsequent underexpression of miR-9 led to up-regulation of its putative target C-X-C chemokine receptor type 4 (CXCR4), resulting in increased cell growth, migration, and invasion through activation of the Mitogen-activated protein kinase (MAPK) pathway. In contrast, Gao et al. postulated a role for miR-9 in modulating the immune response to NPC by targeting several interferon (IFN)-induced genes, multiple members of the major histocompatibility complex (MHC) class I molecule, and a number of interleukins and related genes.

Other potential, functionally active miRNAs in NPC include miR-26a, miR-98, miR-155, miR-200a/b, miR-205, and miR-218. Proposed targets of these miRNAs represent regulators of important processes such as the epithelial-to-mesenchymal transition (EMT), as well as signaling pathways including Notch, phosphatidylinositol-4,5-bisphosphate 3-kinase (PI3K)-Akt, and MAPK. Intriguingly, the function, pathways, and targets affected by many of the miRNAs involved in nasopharyngeal tumorigenesis overlap. Two such miRNAs are miR-26a and miR-218, which both target enhancer of zeste homolog 2 (EZH2), resulting in decreased oncogenic properties of migration, invasion, and cell survival. This overlapping functional impact of multiple miRNAs adds an increased layer of complexity when attempting to elucidate their biological role;
MicroRNAs in NPC

Table 1. Summary of microRNA (miRNA) expression in studies using primary nasopharyngeal carcinoma (NPC) samples

| miR-Encoded | Patients with NPC vs. healthy controls | Prognostic association |
|-------------|----------------------------------------|------------------------|
|             | Up-regulated | Down-regulated | Positive | Negative |
| *miR-16     | let-7a        | miR-18a          | *miR-9    |
| miR-17      | *miR-9        | miR-22           | miR-28a   |
| miR-18a     | miR-26a       | miR-93           | miR-29c   |
| miR-20a     | miR-26b       | *miR-572          | miR-30e   |
| *miR-21     | miR-29c       | *miR-638          | miR-451   |
| *miR-24     | *miR-29c      | *miR-99           | miR-142-3p |
| miR-93      | miR-30c       | *miR-1234         |           |
| miR-141     | miR-34b       |                   |           |
| miR-144     | miR-101       |                   |           |
| miR-146a    | miR-138       |                   |           |
| miR-155     | miR-142-3p    |                   |           |
| *miR-155    | miR-200b      |                   |           |
| *miR-214-3p | miR-216b      |                   |           |
| miR-214-3p  | miR-218       |                   |           |
| miR-663     | *miR-223      |                   |           |
| *miR-3135a  | miR-375       |                   |           |
| *miR-378    | *miR-451      |                   |           |
|             |              |                   |           |

The miRNAs included in this table satisfy each of the following criteria: (1) a statistically significant alteration in their expression was identified in specimens from patients with NPC, and (2) some degree of validation (either in additional samples, using an alternate analytical method, or functional validation) was reported. Patients with NPC vs. healthy controls: for these miRNAs, levels were significantly increased in specimens from patients with NPC, and (2) some degree of validation (either in additional samples, using an alternate analytical method, or functional validation) was reported. Patients with NPC vs. healthy controls: for these miRNAs, levels were significantly increased.

Conclusions

In summary, the interrogation of miRNAs in the context of NPC has provided both clinical and biological insight into the behavior of these viral proteins by BART-encoded miRNA can influence multiple cellular properties including cell proliferation, survival, and evasion of host immune response. Host targets of BART-encoded miRNAs include the pro-apoptotic effectors p53 up-regulated modulator of apoptosis (PUMA) and Bcl-2 interacting mediator of cell death (Bim), and translocase of outer mitochondrial membrane 22 homolog (TOMM22), as well as several genes thought to influence host immune response, including MHC class I-related chain B (MICB), importin 7 ( IPO7), and Dicer. Overall, EBV-encoded miRNAs play a complementary role to the viral proteins expressed in NPC, contributing to evasion of the host immune response and promoting the survival and proliferation of NPC cells.
of this disease. Further development of strategies to measure and manipulate miRNAs and their targets in a clinical setting would be required before such findings can be translated into improvements in the management of this disease.

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