HHS Public Access

Author manuscript

*Clin Chem*. Author manuscript; available in PMC 2019 January 15.

Published in final edited form as:

*Clin Chem*. 2013 December ; 59(12): 1811–1812. doi:10.1373/clinchem.2012.198176.

# MicroRNA Involvement in Human Cancers

**Nozomu Yanaihara**[1,2] and **Curtis C. Harris**[1,*]

[1]Laboratory of Human Carcinogenesis, Center for Cancer Research, National Cancer Institute, National Institutes of Health, Bethesda, MD

[2]Department of Obstetrics and Gynecology, Jikei University School of Medicine, Tokyo, Japan.

Yanaihara N, Caplen N, Bowman E, Seike M, Kumamoto K, Yi M, et al. Unique microRNA molecular profiles in lung cancer diagnosis and prognosis. Cancer Cell 2006;9:189–98.[3]

Recent evidence has revealed that microRNAs (miRNAs) function as tumor suppressors and oncogenes, and therefore miRNAs might prove useful in the diagnosis and treatment of cancer. In 2002, Croce's group reported the first connection between miRNAs and cancer, showing that the *MIR15A*[4](microRNA 15a) and *MIR16–1* (microRNA 16–1) genes were deleted and/or downregulated in the majority of B-cell lymphomas *(1).* The findings that miRNAs were frequently located at cancer-associated genomic regions, including fragile sites, prompted these investigators to propose that miRNA genes were a new dass of genes involved in human tumorigenesis *(2).* The development of miRNA gene expression profiling allowed the identification of miRNA gene expression signatures unique to specific solid tumors (e.g., lung, breast, stomach, prostate, and colon) and their cellular origins *(3).* These reports indicated the extensive involvement of miRNAs in the pathogenesis of solid cancer and highlighted their potential as biomarkers for cancer. Additional studies have shown a strong correlation between impaired expression of miRNA genes and oncogenesis *(4).* For example, the *RAS* oncogenes are regulated by the let-7 family of miRNAs, and *MIR155* and *MIR* gene clusters *17—92* are associated with the *MYC* [v-myc myelocytomatosis viral oncogene homolog (avian)] oncogene. These findings suggest that miRNAs play a substantial role in the pathogenesis of human cancers.

In 2006, when our *Cancer Cell* report was published, the field was primarily focusing on known coding genes and proteins to define the molecular network of lung carcinogenesis. Both our group and another *(5)* investigated whether miRNAs might lead to a better understanding of the biology of lung cancer. The results published in our report showed that lung cancer had extensive alterations in miRNA gene expression. Furthermore, miRNA gene expression profiles correlated with survival of lung adenocarcinomas, including those

*Address correspondence to this author at: Laboratory of Human Cardnogenesis, National Cancer Institute, National Institutes of Health, 37 Convent Dr., Bldg. 37, Rm. 3068, Bethesda, MD 20892-4255. Fax 301-496 0497; Curtis_Harris@nih.gov.

**Author Contibutions:**All autors confirmed they have contributed to the intellectual content of this paper and have met the following 3 requirements: (a) significant contributions to the conception and desingn, acquisition of data, or analysis and interpretation of data; (b) drafiting or revising the article for intellectual content; and (c) final approval of the published article.

**Authors' Disclosures or Potential Conflicts of Interest:** No authors declared any potential conflicts of interest.

[3]This article has been cited more than 1000 times since publication.

[4]Human genes: *MIR15A,* microRNA 15a; *MIR16–1,* microRNA 16–1; *MIR155,* microRNA 155; *MYC,* v-myc myelocytomatosis viral oncogene homolog (avian); *MIR21,* miC10RNA 21; *MIRLET7A2,* mir-100-let-7a-2 duster host gene (non-protein coding).

classified as stage I, indicating that the miRNAs might help predict the prognosis for a patient. Ours was one of the first studies to link miRNAs to a patient's prognosis. In our study, 104 pairs of primary lung cancers and corresponding noncancerous lung tissues were analyzed by miRNA microarray. First, we identified miRNA genes that were expressed differently in phenotypic and histologic classifications. When we compared miRNA gene expression in lung cancer tissues and noncancerous lung tissues, the 2 tissue groups showed statistically significant differences in expression for 43 miRNA genes. Interestingly, several of the miRNAs were located inside fragile sites and/or in the cancer-associated genomic regions. Our next question was, "Do the miRNA molecular profiles of lung cancer correlate with patient survival?" A univariate Cox proportional hazards regression model for lung cancer gene expression profiles indicated that 8 miRNAs were related to the survival of patients with adenocarcinoma. Furthermore, the survival analysis of only stage I cases showed that 3 miRNAs were associated with outcome. One was the miRNA encoded by the *MIR21* (microRNA 21) gene, frequently highly expressed in major types of human cancer *(3 ),* has been found to be a robust prognostic classifier of stage I lung adenocarcinoma in 3 different cohorts *(6).* High *MIR155* and low *MIRLET7A2* [mir-100-let-7a-2 cluster host gene (non-protein coding)] expression has also been correlated with poor survival in both univariate and multivariate analyses for *MIR155.* The relationship between miRNA gene expression signature and outcome was confirmed by real-time reverse-transcription PCR analysis of precursor miRNAs and was cross-validated with an independent set of adenocarcinomas. To investigate the biological consequence of altered *MIR155* expression, we collaborated with Dr. Stephens's group in the Advanced Biomedical Computing Center at the National Cancer Institute, Frederick National Laboratory (SAIC-Frederick, Inc.). This group conducted a bioinformatics analysis grouping of the predicted targets of *MIR155* by Gene Ontology terms. We found a significant enrichment of putative transcripts associated with transcription.

It is clear that miRNAs have a promising future in the clinical application of cancer diagnosis and treatment. The administration of antisense oligonucleotides for oncogenic miRNAs or modified miRNA molecules of suppressor miRNAs could regulate their target genes, which in turn could affect tumor phenotypes. Further studies will help elucidate the roles of miRNAs in cancer, which could provide a better understanding of the disease, as well as novel strategies for diagnosis and therapy.

## References

1. Calin GA, Dumitru CD, Shimizu M, Bichi R, Zupo S, Noch E, et al. Frequent deletions and down-regulation of micro- RNA genes miR15 and miR16 at 13q14 in chronic lymphocytic leukemia. Proc Natl Acad Sci U S A 2002,99: 15524–9. [PubMed: 12434020]
2. Calin GA, Sevlgnanl C, Dumitru CD, Hyslop T, Noch E, Yendamuri S, et al. Human mlcroRNA genes are frequently located at fragile sites and genomic regions Involved in cancers. Proc Natl Acad Sci U S A 2004;101: 2999–3004. [PubMed: 14973191]
3. Volinla S, Calin GA, Liu CG, Ambs S, Cimmino A, Petrocca F, et al. A microRNA expression signature of human solid tumors defines cancer gene targets. Proc Natl Acad Sci U S A 2006;103:2257–61. [PubMed: 16461460]
4. Schetter AJ, Leung SY, Sohn JJ, Zanettl KA, Bowman ED, Yanaihara N, et al. MicroRNA expression profiles associated with prognosis and therapeutic outcome in colon adenocarcinoma. JAMA 2008;299:425–36. [PubMed: 18230780]

5. Takamizawa J, Konishi H, Yanaglsawa K, Tomida S, Osada H, Endoh H, et al. Reduced expression of the let-7 microRNAs in human lung cancers in association with shortened postoperative survival. Cancer Res 2004;64: 3753–6. [PubMed: 15172979]

6. Saito M, Schetter AJ, Mollerup S, Kohno T, Skaug V, Bowman ED, et al. The association of microRNA expression with prognosis and progression In early-stage, non-small cell lung adenocarcinoma: a retrospective analysis of three cohorts. Clin Cancer Res 2011;17:1875–82. [PubMed: 21350005]