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MicroRNAs in cancer therapeutics: “*from the bench to the bedside*”

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Abstract

MicroRNAs (miRNAs) are non-coding RNA transcripts that regulate physiological processes by targeting proteins directly. Their involvement in research has been robust, and evidence of their regulative functions has granted them the title: master regulators of the human genome. In cancer, they have been considered important therapeutic agents, due to the fact that their aberrant expression contributes to disease development, progression, metastasis, therapeutic response and patient overall survival. This has endeavored fields of biomedical sciences to invest in developing and exploiting miRNA-based therapeutics thoroughly. Herein we highlight relevant ongoing/open clinical trials involving miRNAs and cancer.

Introduction

MicroRNAs are small RNA transcripts (18–20 nucleotides in length), which are transcribed from non-coding genes. Their main mechanism of action is binding to the 3′-untranslated region (UTR) of messenger RNAs (mRNAs), thereby blocking translation. Alternatively, they can increase mRNA instability facilitating their degradation (¹). There are 2 important facts that support their relevance as therapeutic agents. Firstly, they can target hundreds/thousands of proteins, and thus have the ability to control the entire human genome. Secondly, in almost every type of disease (including cancer), there are significant differences in the levels of expression of miRNAs when compared with normal tissues (^{2, 3}).

MiRNAs are crucial for cancer initiation, progression, and dissemination. They have been demonstrated to have important roles in the development of tumors due to their association with every single one of the cancer hallmarks (⁴). Consequently, over the past years an important question has arisen regarding miRNAs in cancer therapies: which are the translational approaches that are currently being taken “from the bench to the bedside”? In view of this, we briefly introduce the ongoing directions of the open clinical trials involving miRNAs and cancer, with emphasis in studies being developed in the United States (Table 1).

Clinical trials involving miRNAs and cancer

a. Premalignant diseases and increased cancer risk

There are several risk factors that can increase the risk of individuals suffering cancer. A handful of pathologies have been associated with a higher probability of developing cancer, and some examples of these are: Barrett's esophagus, metabolic syndrome, Lynch syndrome and solid pulmonary nodules (^{5–8}). When studying premalignant diseases that predispose cancer development, recent focus has been centered on the role of miRNA expression in increasing the risk. Thus, several clinical trials are currently exploring this field. For example, a recent study is evaluating the sensitivity/specificity of tissue and serum microRNA expression to accurately diagnose gastro-esophageal reflux disease (GERD) or Barrett's esophagus, both premalignant lesions that could develop into esophageal adenocarcinoma (ClinicalTrials.gov Identifier: NCT02464930). More so, changes in the miRNA profile of these patients after treatment with zinc is being explored, to examine possible chemo-preventive effects (ClinicalTrials.gov Identifier: 01984580). Furthermore, the potential of miRNAs as biomarkers of patient response to exercise treatment is currently being assessed in African-American women with metabolic syndrome, a condition considered to be premalignant in these patients, and one that increases their risk of breast cancer (ClinicalTrials.gov Identifier: NCT02103140).

In a similar manner, 2 additional studies have focused on chemo-preventive strategies in patients diagnosed with Lynch syndrome or sub-solid lung nodules, conditions which predispose to colorectal cancer (CRC) or lung cancer (respectively). In patients with Lynch syndrome, a randomized phase 1b trial is identifying the side effects of Naproxen in preventing CRC, and alongside they are exploring changes in the miRNA profile of the colonic mucosa to determine their contribution in enhancing/delaying tumorigenesis (ClinicalTrials.gov Identifier: NCT02052908). Similarly, a randomized phase 2 trial is evaluating the sensitivity of miRNAs in identifying patients with ground glass opacities or partially solid nodules and determining the effect of aspirin (a suggested chemo-preventive agent for lung cancer), in reducing the probability of lung cancer development (ClinicalTrials.gov Identifier: NCT02169271).

b. Genetic cancer predisposition

The exponential increase in genomics-based research orchestrated over the past decade has emphasized the significance of focusing on patients as individuals, due to the fact that their genetic profile is unique (⁹). Mutations (even of only 1 nucleotide), have proven to predispose to cancer development, and those involving miRNA deregulation are not the exception (¹⁰). Evidence of this are several clinical trials that are currently ongoing, one of them focused on investigating the role of germline miRNA-binding site mutations. By isolating saliva from patients with breast/ovarian cancer, researchers aim to investigate if these mutations increase the risk of cancer development (ClinicalTrials.gov Identifier: NCT02253251). On the same line, another trial is focusing on a mutation in patients with Pleuropulmonary blastoma (PPB), which represented the first reported cancer predisposition syndrome. PPB is a rare fast-growing lung tumor, and a particular germline mutation of the DICER1 gene has been demonstrated to predispose to its development (ClinicalTrials.gov

Identifier: NCT01247597). Similarly, a more recent trial has also been focusing on DICER1 mutations and deregulated miRNA biogenesis in two other rare types of tumors: ovarian and testicular stromal tumors (ClinicalTrials.gov Identifier: NCT01970696).

c. Profiling and biomarker identification

Microarray-based gene expression profiling as well as next-generation sequencing have been very useful techniques to determine differences in genetic expression of non-coding genes⁽²⁾. They have been particularly popular over the past years, and are being applied in many clinical settings as a tool to investigate potential biomarkers for the characterization of diseases, progression, and therapeutic response⁽⁴⁾. Many studies investigating anti-cancer therapeutics are focused on assessing levels of miRNA expression in patient samples to determine patterns of significance. Some of these involve young patients with neuroblastoma, pediatric brain tumors, acute lymphoblastic leukemia, hepatocellular carcinoma, central nervous system tumors, and other solid tumors (ClinicalTrials.gov Identifier: NCT00958659, NCT01556178, NCT00896766, NCT02412579, NCT01595126 and NCT01050296 respectively).

MiRNA profiling techniques are currently employed in clinical trials to study different cancer types⁽¹¹⁾. For example, a trial centered on breast cancer is currently using miRNA profiling to deter the nature/extent of molecular genetic alterations in lobular carcinoma in situ, to better understand the biology that drives tumor progression (ClinicalTrials.gov Identifier: NCT00581750). In another study, the primary aim is to determine whether miRNA profile characterization is feasible with tissue collection from serum and nipple aspirate fluid in patients with in situ and invasive breast cancer, after intranasal oxytocin is given (ClinicalTrials.gov Identifier: NCT02127073). Altogether these clinical trials are representatives of an even bigger group of studies that focus on miRNA profiling and biomarker identification in cancer.

d. Prognostic/diagnostic implications

Due to their tumor/tissue-specific expression, miRNAs have emerged as attractive candidates for diagnostic/prognostic applications. Evidence of this is the number of clinical studies currently ongoing. To date, there has been an increase in trials evaluating the effect of miRNAs in predicting response to therapeutic treatments, or patient prognosis. For example, in a study to determine the safety and tolerability of belinostat in combination with cisplatin and etoposide in adults with small cell lung carcinoma, miRNA profiling is being evaluated to examine the effect that changes in their levels of expression can have on treatment efficacy (ClinicalTrials.gov Identifier: NCT00926640). Similarly, miRNA profiling of treatment naïve and treatment-exposed breast tumors and sequential samples of blood/serum are being assessed, to identify miRNA markers of prognosis or indicators of potential targets for personalized therapies (ClinicalTrials.gov Identifier: NCT01231386). On a separate note, the potential of miRNAs in dictating patient overall survival (OS) is also being currently explored. The prognostic value of plasma miRNAs in OS of patients with non-small cell lung cancer is being evaluated after treatment with chemo-/radiation therapy with or without panitumumab (ClinicalTrials.gov Identifier: NCT00979212). Finally, in a recent clinical trial, primary glioma samples are being collected to determine miR-10b expression patterns,

and determine its value as a prognostic/diagnostic marker. More so, investigators will test in vitro the sensitivity of individual primary tumors to anti-miR-10b treatment (ClinicalTrials.gov Identifier: NCT01849952).

e. Predictors of treatment efficacy

Regarding miRNA therapeutics, a handful of clinical trials are focusing on miRNA levels as predictors of treatment response in malignancies such as prostate cancer, Hodgkin lymphoma, CRC and other solid tumors. For example, a study began in March 2015 aiming to identify exosomal miRNAs from peripheral blood of prostate cancer patients (with systemic disease), which could potentially predict response to Androgen deprivation therapy (ADT). Its purpose is to identify and validate exosomal RNA signatures markers that predict response to ADT by collecting samples at time of enrollment, after 3 months of treatment and upon disease progression, to compare them all and determine patterns of significance (ClinicalTrials.gov Identifier: NCT02366494). Similarly, in a study of patients with relapsed or refractory Hodgkin lymphoma, the association between response to treatment and levels of miRNAs is currently being explored. In brief, miRNA profiles are being determined, alongside treatment with brentuximab vedotin and gemcitabine hydrochloride, to compare specific levels of expression or changes over time between patients with complete response or patients without it (ClinicalTrials.gov Identifier: NCT01780662). Moreover, miRNA-array analysis is also being used in CRC patients receiving treatment with regorafenib in order to identify biomarkers of treatment response (ClinicalTrials.gov Identifier: NCT02402036). Finally, in a phase I clinical trial of patients with different solid tumors, the serum concentration of circulating miRNAs is being assessed before the treatment dose and at the end of it, in order to verify changes induced upon treatment, and potential effects of miRNAs in predicting therapeutic response (ClinicalTrials.gov Identifier: NCT01999972).

Interestingly, miRNA levels have been validated to determine disease progression. In a phase 2 trial, researchers are investigating mechanisms of counteraction in hormone-resistant prostate cancer by analyzing the molecular changes of miRNA levels (acquired from peripheral blood at the time of disease progression), in tumor metastasis (ClinicalTrials.gov Identifier: NCT01503229). On the other hand, miRNA profiling is being used as an accessory tool along with other types of tests to predict tumor growth. For example, in order to determine the efficacy of the combinatorial treatment of crolibulin and cisplatin in patients with anaplastic thyroid cancer, clinicians are comparing miRNA array analysis with positron emission tomography scans. They believe that by using a combination of tests, more accurate predictions of treatment efficacy can be achieved (ClinicalTrials.gov Identifier: NCT01240590). Alongside, as part of a recent clinical trial, relative expression differences (in individual miRNAs and miRNA profiles) between patients with stage IB-III esophageal cancer responding and not responding to combination chemotherapy are currently being compared. The main purpose is assessing significant signature changes between complete responders vs. patients not achieving a pathological complete response. The purpose is to better understand which patients benefit from the standard treatments (ClinicalTrials.gov Identifier: NCT02392377).

f. MiRNA mimics/direct interventional approach

The lead candidate in the miRNA drug discovery process has most certainly been MRX34 from *Mirna Therapeutics*, which has represented a new class of anti-cancer agent (¹²). Since 2013, the initiation and development of MRX34- the liposome-encapsulated miR-34 mimic for patients with unresectable primary liver cancer (or solid cancers with liver involvement) has evolved into a (currently open) clinical trial. The study involves patients with liver cancer, but also a separate cohort of patients with other cancer types or with hematological malignancies for which the treatment is being evaluated to determine its efficacy. It is currently completing phase I, open-label, multicenter, dose-escalation study to investigate the safety, pharmacokinetics and pharmacodynamics of the MRX34 (ClinicalTrials.gov Identifier: NCT01829971).

Concluding Remarks

There are many advantages of using miRNAs as anti-cancer therapeutic agents. Aside from the fact that they are small in size, their isolation is relatively feasible, and has allowed the development of numerous clinical trials that are identifying patterns and understanding the significance of miRNA deregulation in cancer. More so, emphasis on targeting miRNAs is being thoroughly explored, given the fact that targeting one single miRNA results in a dramatic effect due to the combinatorial effect of gene expression changes in all these related downstream targets. However, there are still several areas to be fully explored in order to achieve *in vivo* delivery of these miRNA-therapies. Probably the most important one is developing adequate delivery mechanisms. More efficacy data in human subjects over the next few years promises to provide more insight into miRNA mimics and antagomiR biology and will further strengthen the enthusiasm for this new class of anti-cancer agents.

References

1. Monroig PD, Calin GA. MicroRNA and Epigenetics: Diagnostic and Therapeutic Opportunities. *Curr Pathobiol Rep*. 2013 Mar; 1(1):43–52. [PubMed: 23515489]
2. Lu J, Getz G, Miska EA, Alvarez-Saavedra E, Lamb J, Peck D, et al. MicroRNA expression profiles classify human cancers. *Nature*. 2005 Jun 9; 435(7043):834–8. [PubMed: 15944708]
3. Volinia 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. *Proceedings of the National Academy of Sciences of the United States of America*. 2006 Feb 14; 103(7):2257–61. [PubMed: 16461460]
4. Berindan-Neagoe I, del Monroig PC, Pasculli B, Calin GA. MicroRNAome genome: a treasure for cancer diagnosis and therapy. *CA: a cancer journal for clinicians*. 2014 Sep-Oct;64(5):311–36. [PubMed: 25104502]
5. Spechler SJ. Barrett esophagus and risk of esophageal cancer: a clinical review. *Jama*. 2013 Aug 14; 310(6):627–36. [PubMed: 23942681]
6. Ait Ouakrim D, Dashti SG, Chau R, Buchanan DD, Clendenning M, Rosty C, et al. Aspirin, Ibuprofen, and the Risk of Colorectal Cancer in Lynch Syndrome. *Journal of the National Cancer Institute*. 2015 Sep.107(9)
7. Dash C, Makambi K, Wallington SF, Sheppard V, Taylor TR, Hicks JS, et al. An exercise trial targeting African-American women with metabolic syndrome and at high risk for breast cancer: Rationale, design, and methods. *Contemporary clinical trials*. 2015 May 8.43:33–8. [PubMed: 25962889]

8. Krochmal R, Arias S, Yarmus L, Feller-Kopman D, Lee H. Diagnosis and management of pulmonary nodules. Expert review of respiratory medicine. 2014 Dec; 8(6):677–91. [PubMed: 25152306]
9. Aggarwal S. Targeted cancer therapies. Nature reviews Drug discovery. 2010 Jun; 9(6):427–8.
10. Nicoloso MS, Sun H, Spizzo R, Kim H, Wickramasinghe P, Shimizu M, et al. Single-nucleotide polymorphisms inside microRNA target sites influence tumor susceptibility. Cancer research. 2010 Apr 1; 70(7):2789–98. [PubMed: 20332227]
11. Paranjape T, Slack FJ, Weidhaas JB. MicroRNAs: tools for cancer diagnostics. Gut. 2009 Nov; 58(11):1546–54. [PubMed: 19834118]
12. Bouchie A. First microRNA mimic enters clinic. Nature biotechnology. 2013 Jul.31(7):577.

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Table 1

Ongoing/open clinical trials involving *miRNAs* and *cancer* in Unites States

Identifier	Study type	Start Date	Condition (s)	Title
NCT00581750	O	October, 2001	Breast Cancer	Molecular Genetic Basis of Invasive Breast Cancer Risk Associated With Lobular Carcinoma in Situ
NCT00896766	O	July, 2006	Leukemia	Childhood Cancer Therapeutically Applicable Research to Generate Effective Treatments (TARGET) Initiative High-Risk ALL Pilot Project: Application of Array-Based Methods and Gene Re-Sequencing to Identify Candidate Molecular Targets for High-Risk Pediatric Acute Lymphoblastic Leukemia
NCT00958659	O	December, 2008	Neuroblastoma	Prognostic Multigene Expression Classification of Neuroblastoma Patients
NCT00926640	I	June, 2009	Carcinoma Neuroendocrine, Small Cell Lung Carcinoma, Malignant Epithelial Neoplasms	A Phase I Study of Belinostat in Combination With Cisplatin and Etoposide in Adults With a Focus on Small Cell Lung Cancer and Other Cancers of Neuroendocrine Origin
NCT01050296	O	January, 2010	Pediatric Solid Tumors	Molecular Analysis Of Solid Tumors
NCT01231386	O	April, 2010	Breast Cancer	MIRNA Profiling of Breast Cancer in Patients Undergoing Neoadjuvant or Adjuvant Treatment for Locally Advanced & Inflammatory Breast Cancer
NCT01240590	I	November, 2010	Thyroid Cancer	A Phase I/II Trial of Crotellin (EPC2407) Plus Cisplatin in Adults With Solid Tumors With a Focus on Anaplastic Thyroid Cancer (ATC)
NCT01247597	O	November, 2010	Pleuropulmonary Blastoma	Dicer1-Related Pleuropulmonary Blastoma Cancer Predisposition Syndrome: A Natural History Study
NCT00979212	I	February, 2011	Lung Cancer	Randomized Phase II Study of Pre-operative Chemoradiotherapy +/- Panitumumab (IND #110152) Followed by Consolidation Chemotherapy +/- Cetuximab in Potentially Operable Locally Advanced (Stage IIIA, N2+) Non-Small Cell Lung Cancer (Cetuximab Closed as of 05/14/10)
NCT01595126	O	December, 2011	Central Nervous System Tumor	A Longitudinal Study of Biomarkers in Pediatric Patients With Central Nervous System Tumors
NCT01503229	I	December, 2012	Prostate Cancer	Open Label Pharmacodynamic Study of Abiraterone Acetate in the Treatment of Metastatic, Castration Resistant Prostate Cancer.
NCT01970696	O	December, 2012	Ovarian Stromal Tumor, Testicular Stromal Tumors	International Ovarian & Testicular Stromal Tumor Registry
NCT01780662	I	January, 2013	Hodgkin Lymphoma	A Phase 1/2 Study of Brentuximab Vedotin (SGN35) in Combination With Gemcitabine for Pediatric and Young Adult Patients With Relapsed or Refractory Hodgkin Lymphoma
NCT01829971	I	April, 2013	Liver Cancer	A Multicenter Phase I Study of MRX34, MicroRNA miR-RX34 Liposomal Injection
NCT01849952	O	May, 2013	Brain Tumors	Evaluating the Expression Levels of microRNA-10b in Patients With Gliomas
NCT01999972	I	February, 2014	Advanced Solid Tumors	A Phase Ib, Open Label, Dose Escalation Study To Evaluate Safety, Pharmacokinetics And Pharmacodynamics Of Axitinib (Ag-013736) In Combination With Crizotinib (PF-02341066) In Patients With Advanced Solid Tumors
NCT02127073	I	March, 2014	Breast Cancer	Identifying the miR Fingerprint in NAF, Serum, and Tissue in Patients With Ductal Carcinoma in Situ (DCIS) or Invasive Breast Cancer
NCT02253251	O	September, 2014	Cancer, KRAS-variant	Clinical Validation of the Role of microRNA Binding Site Mutations in Cancer Risk, Prevention and Treatment

Identifier	Study type	Start Date	Condition (s)	Title
NCT02169271	I	November, 2014	Solitary Pulmonary Nodule	A Randomized Phase II Trial of Low Dose Aspirin Versus Placebo in High-Risk Individuals With CT Screen Detected Subsolid Lung Nodules
NCT02392377	I	February, 2015	Esophageal Adenocarcinoma	Pilot Study of Correlation Between Molecular Phenotype and Response to Two Independent Treatment Regimens, Carboplatin and Paclitaxel vs. 5-Fluorouracil and Oxaliplatin Chemotherapy in Patients With Localized Esophageal Adenocarcinoma
NCT02402036	I	February, 2015	Colon Cancer	Regorafenib in Metastatic Colorectal Cancer: An Exploratory Biomarker Study
NCT02366494	O	March, 2015	Prostate Cancer	Utility of Exosomal microRNAs to Predict Response to Androgen Deprivation Therapy in Prostate Cancer Patients
NCT02412579	O	March, 2015	Hepatocellular Carcinoma	Circulating MicroRNA Isoforms as Biomarkers in Hepatocellular Carcinoma and Associated Liver Transplantation

O – Observational, I – Interventional