MicroRNA regulation of tumorigenesis, cancer progression and interpatient heterogeneity: towards clinical use

S Patrick Nana-Sinkam1,2* and Carlo M Croce2,3*

Abstract
In the past two decades, microRNAs have emerged as crucial mediators of organ development and human disease. Here, we discuss their role as drivers or suppressors of the hallmarks of cancer during tumorigenesis and progression, in defining interpatient heterogeneity and the promise of therapeutic application.

Introduction
Cancer continues to generate a significant global medical and socioeconomic burden, despite molecular-based screening, targeted therapeutics, and our increased understanding of the molecular pathogenesis of tumor initiation and progression. As we move into an era of personalized cancer management, an increased understanding of cancer risk and tumor heterogeneity will be essential to the success of early detection and new targeted therapies. High-throughput platforms designed to interrogate the human genome and proteome are successfully being used to improve our understanding of the heterogeneity that exists within both solid and hematological malignancies, and to develop clinical biomarkers and discover new therapeutic targets.

In the past two decades, investigators have identified non-coding components of the human genome, such as microRNAs (miRNAs), as critical mediators of organ development and human disease [1]. miRNAs are non-coding RNAs 18–25 nucleotides in length that are endogenously processed in the cell and then target RNA for silencing either by RNA degradation or inhibition of transcription (Figure 1) [2]. Given the fact that miRNAs have the capacity to regulate tens to hundreds of mRNAs, this can result in the simultaneous regulation of multiple biological pathways [3,4]. miRNAs tend to be localized to fragile chromosomal regions that are susceptible to deletions, translocations and amplifications [5]. These same chromosomal regions are often altered in cancers. Additionally, miRNAs may exist within introns or exons (harboring an independent promoter) or within a host gene [6]. Furthermore, the mechanisms by which epigenetic, genetic and environmental factors converge to regulate miRNAs in cancer are also complex and continue to be uncovered.

The applications of miRNAs in the clinical management of cancers are starting to be realized, as evidenced by an increasing number of miRNA-based clinical trials. Specifically, miRNAs are being applied as both prognostic and therapeutic biomarkers in the setting of clinical trials. The goal is to use miRNAs as another means for delineating the molecular and clinical heterogeneity that exist within cancers (Table 1). As we increasingly apply high-throughput strategies, such as genome sequencing, and identify additional oncogenic mutations that drive tumorigenesis and define heterogeneity, it is likely that a larger role for miRNAs in cancer biology will be uncovered.

The early observations that miRNAs are globally dysregulated in cancer suggested that miRNAs may contribute to both the initiation and progression of cancers [16–18]. Since these initial observations, miRNAs have been implicated as either effectors or targets of almost all of the hallmarks of cancer, including proliferation, resisting cell death, avoiding growth suppression, angiogenesis, replicative immortality and invasion/metastasis [19–23]. The roles of miRNAs as key regulators of each of these hallmarks of cancer continue to be extensively investigated and have been previously reviewed [24]. As investigators continue to identify new mechanisms for cancer initiation and progression, and to elucidate the relative contributions of the primary tumor and components of
its environment to carcinogenesis, the eventual application of miRNAs in human cancer will come to fruition. For example, the recent observation that miRNAs may be integral to reprogramming of energy metabolism in cancer has provided an additional layer of complexity to miRNAs in cancer and led to the identification of new targets. Here, rather than attempt to review the broad field of miRNAs in cancer biology, we provide an overview of some of the most promising and emerging areas in miRNA investigation. In particular, we focus on miRNAs as regulators of metabolic programming, their role in metastasis, the new concept of extracellular vesicular miRNAs as drivers of tumorigenesis and, lastly, the biological links between miRNAs and established oncogenic mutations. Each of these new and exciting areas has the potential for translating to clinical application.

**MicroRNAs and metabolic reprogramming in cancer**

The contribution of metabolic reprogramming of cancer cells to a largely glycolytic pathway to tumor initiation and progression remains poorly understood. However, there is increasing evidence that tumor dependence on anaerobic glycolysis regardless of oxygen stores (known as the Warburg effect) is driven by both tumor suppressors and oncogenes [25,26]. This metabolic shift confers a biological advantage to cancer cells, thus supporting both initiation and progression of tumors. Several miRNAs have been shown to regulate cancer cell metabolism, either through direct regulation of components of glycolysis or by targeting key oncogenic pathways.

The discovery that the miR-15a/16/1 cluster is downregulated or deleted in chronic lymphocytic leukemia was one of the first observations of miRNA deregulation
in cancer [22]. This initial observation further supported the concept of miRNAs being localized to fragile chromosomal regions. We identified both aldolase A (ALDOA) and triosephosphate isomerase 1 (TPI1), which have been both implicated in glycolysis, as potential targets for miR-15a/16-1. ALDOA is central to the glycolytic process and its overexpression in lung cancer has been associated with poor survival [27]. Since these initial observations, several other miRNAs have been identified as regulators of components of metabolic pathways in cancer. For example, monocarboxylate transporters (MCTs) contribute to lactate homeostasis through both influx and efflux across cell membranes. As a result, targeting MCTs is a viable therapeutic approach in cancer. Several tumor suppressor miRNAs, including miR-29b, have been shown to target components of lactate generation, including MCTs [28]. A third example of miRNA-mediated regulation of cellular metabolism involves one of the earliest described miRNAs. First described in Caenorhabditis elegans as crucial to larval development [29], Lin-28 is a highly conserved RNA-binding protein that has been shown to regulate glycolytic enzymes, components of mitochondrial oxidative phosphorylation and the miRNA Let-7 [29]. In addition, Lin-28 has emerged as an oncogene [30]. A recent study showed that Lin-28a is essential to programming bioenergetics during embryonal development and that Lin-28a-driven reprogramming of metabolism contributes to tissue repair [31]. The potential links between Lin-28 and cancer metabolism are still being investigated. Lastly, Singh and colleagues [32] recently identified a new link between miRNA deregulation, cancer metabolism and tumor progression. The authors [32] observed that the redox-sensitive basic leucine zipper family transcription factor nuclear factor erythroid-2-related factor 2 promotes tumorigenesis both in vitro and in a murine model through epigenetic regulation of miR-1 and miR-206. This leads to reprogramming of glucose metabolism through activation of components of the pentose phosphate pathway. The relationships between miR-1, miR-206 and components of the pentose phosphate pathway were also observed in human tissues [32].

The biological relationships between miRNAs and components of cellular metabolism continue to be established particularly in the setting of tumorigenesis. These findings will further serve to drive our understanding of the biology of cancer metabolism in tumor progression miRNAs as potential therapeutic targets in altering these important pathways.

MicroRNAs and metastasis

Metastatic disease is a major cause of mortality in solid malignancies. For instance, in lung cancer, less than 20% of patients present with localized disease. Thus, the identification of actionable targets that can be used clinically both as biomarkers and as potential therapeutic targets in the metastatic setting is essential. The process by which tumors progress to metastatic disease is a complex one. This process relies on a sequence of events that integrate both cues from the primary tumor and the surrounding microenvironment. Epithelial-mesenchymal transition (EMT) is a central mechanism that drives the eventual detachment, invasion, circulation and extravasation of cancer cells that define the metastatic process [33]. miRNAs have been shown to regulate the metastatic process by either targeting components of EMT, targeting signaling pathways that drive EMT or by selective targeting of other miRNAs. Given that miRNAs are increasingly being used as both directed therapies and as diagnostic/prognostic biomarkers, one could envision select miRNAs being targeted in cases of metastatic disease or being used as biomarkers to monitor tumor response or recurrence.

### Table 1 Selected microRNA-based clinical trials

| Cancer type                        | Type of trial | Intervention or tissue type | Clinical application                                      | Reference |
|------------------------------------|---------------|----------------------------|----------------------------------------------------------|-----------|
| Hepatocellular or liver metastasis | Therapeutic   | miR-34 delivery (MRK-34)    | Phase 1 toxicity trial                                   | [7]       |
| Thyroid                            | Biomarker     | Tissue (fine needle aspiration) | Diagnosis, chemoresponse                               | [8]       |
| Breast                             | Biomarker     | Blood                      | Prognosis, surveillance, cardiotoxicity                  | [9]       |
| Breast                             | Biomarker     | Tissue                     | Chemoresponse, diagnosis                                 | [9]       |
| Glioma                             | Biomarker     | Tissue                     | miR-10b levels in diagnosis and prognosis                | [10]      |
| Leukemia                           | Biomarker     | Blood                      | miR-155 as predictor of graft versus host disease        | [11]      |
| Lung                               | Biomarker     | Tissue                     | Chemoresponse                                            |           |
| Neuroblastoma                      | Biomarker     | Tissue                     | Prognosis, tumor classification                          | [12]      |
| Colon                              | Biomarker     | Tissue                     | Disease stratification, chemoresponse                    | [13]      |
| Renal                              | Biomarker     | Cell                       | Tissue chemoresponse                                     | [14]      |
| Esophageal                         | Biomarker     | Tissue                     | Predictor of response to zinc                            | [15]      |
| Melanoma                           | Biomarker     | Blood                      | Predictor of response to propranolol                     |           |

miR, microRNA.
The miR-200 family is perhaps the best-studied group of miRNAs that are known to target key transcriptional drivers of EMT, such as ZEB-1 and ZEB-2 [34–37]. For example, Davalos et al. [38] showed that miR-200 is susceptible to dynamic methylation silencing in cancer cells with mesenchymal properties but is unmethylated in tumors maintaining epithelial characteristics. In addition, tumor-suppressive miRNAs are also susceptible to regulation by mediators of EMT during metastasis. For example, Yang and colleagues [39] determined in a murine model of Kras-induced lung adenocarcinoma that a subpopulation of metastasis-prone cancer cells were dependent on Jagged2 for their metastatic potential both in vitro and in vivo. Furthermore, they determined that Jagged2 drives metastasis through the downregulation of miR-200 [39]. A separate study [40] showed that members of the miR-200 family are not the only miRNAs implicated in the metastatic process. ZEB1 promotes metastasis through the downregulation of the tumor suppressor miR-34a [40]. The observation that miRNAs may either drive or suppress hallmarks of cancer through direct or indirect regulation of other miRNAs is a relatively new one that has emerged in the past few years. For example, this concept has been observed in promoting the metastatic process. A recent study by Song et al. [41] demonstrated that miR-22 could contribute to and promote metastases in breast cancer through miRNA regulation. The investigators showed both in vitro and in vivo that miR-22 can suppress miR-200 through direct targeting of members of the Ten eleven translocation family, thus leading to hypermethylation of members of the miR-200 family [38].

The process of metastasis is a complex one that currently lacks any therapeutic target. As a result, metastatic cancers can be extremely challenging to treat. The increasing number of studies linking miRNAs, particularly members of the miR-200 family, to components of EMT has increased our understanding of the biology of EMT and the potential for miRNAs as regulators of EMT. Although these studies have yet to translate to clinical application, they do provide the opportunity for using miRNAs as biomarkers of therapeutic response in cases of advanced disease or in the setting of surveillance.

**Extracellular microRNAs as drivers of tumorigenesis**

One particular area that has evaded investigators has been the process by which miRNAs may drive local and distant tumor-environment interactions. Recently, studies have shown that miRNAs may circulate either freely packaged within extracellular vesicles (EVs) or bound to specific proteins (such as the miRNA processing molecule Ago2) [42–44]. EVs are a family of small membrane-encapsulated fluid particles, comprising shedding microvesicles and exosomes, that are released from either multivesicular bodies or directly from plasma membranes [45]. EVs are released from a wide variety of cell types by independent cellular mechanisms and have become the focus of intense investigation [45,46]. Studies have shown that, in cancers, both tumor- and stromal-derived EVs (and their contents, including miRNAs) may function as conduits for the transport and release of mediators that drive or suppress the immune response, angiogenesis, inflammation, extracellular matrix remodeling and invasion/metastasis [47–50]. EVs ‘communicate’ with cells by fusing to the plasma membrane and delivering their functional cargo of proteins, lipids, mRNAs or miRNAs.

We recently identified an additional biological function for exosomal miRNAs [51]. We demonstrated [51] that exosomes may serve as ligands for Toll-like receptor-8 (TLR-8) in humans and its homolog Tlr7 in mice. We determined that certain miRNAs, including miR-21 and miR-29, compartmentalized within exosomes could activate the TLR-8 in a recipient cell to activate an inflammatory pro-metastatic response involving nuclear factor κB and the secretion of tumor necrosis factor alpha and interleukin-6 [51]. These observations suggested an additional paracrine function for miRNA in driving the metastatic process that could be targeted.

Exosomes and microvesicles, which range in size from 30 to 1,000 nm, are detectable in several body fluids ranging from plasma to urine to sputum and are the likely explanation for the observed stability of miRNAs in body fluids [52]. As a result, they are being investigated as potential non-invasive biomarkers in several cancers. Early studies [53–56] demonstrated that circulating exosomes could be used as potential diagnostic tools in ovarian, lung and prostate cancers.

Our understanding of EVs in tumorigenesis remains in its infancy; however, several studies now suggest that they may be central to intercellular communication in cancer. Additionally, their discovery supports a new area of investigation of EVs as non-invasive biomarkers in several cancers. Early studies [53–56] demonstrated that circulating exosomes could be used as potential diagnostic tools in ovarian, lung and prostate cancers.

**MicroRNAs in cancer heterogeneity**

High-throughput analyses of the human genome have led to the discovery of several previously unrecognized somatic mutations that contribute to the development of both solid and hematological malignancies. In several cancers, including lung cancer, assessment of patients for specific, more common mutations has become standard of care to guide the use of therapies that target those mutations; however, several relatively common mutations in cancer remain without effective therapies. For patients with these mutations in particular, miRNAs that function as effectors, targets and predictive biomarkers in mutation-driven cancers can provide us with additional insight into...
the underlying mechanisms involved and help guide drug
development and therapeutic decisions. Below, we provide
some examples of more common mutations that are being
applied in the clinical setting.

**Kras**
Approximately 20-25% of tumors harbor mutations in
genes encoding Ras family proteins, with Kras being the
most common. Through activation of downstream mole-
cules, including the Raf-MEK-ERK and PI3K-Akt path-
ways, Kras signaling confers both a growth and survival
advantage to tumors. Although many Kras-targeted thera-
peutics are in clinical trials, none have yet been approved
for use in the clinic. The primary reason for the lack of
therapeutic targets in Kras-driven cancers is the recog-
nized complexity of Kras signaling. Thus, it is imperative
that investigators continue to identify new actionable
pathways that may be eventually applied in the large
percentage of cancers that harbor these mutations.

Several miRNAs have been found to regulate Kras, in-
cluding Let-7, one of the earliest described tumor suppres-
sor miRNAs that has been shown to be downregulated in
cancers [57]. This initial observation has led several re-
searchers to identify polymorphisms within the Let-
7-complementary Kras 3′ untranslated regions [58–61]
and Let-7 expression as prognostic biomarkers in cancer.
Furthermore, given the establishment of Let-7 as a tumor
suppressor, Let-7 has been systemically delivered in vivo
as a directed therapeutic in lung cancer [62,63]. Two addi-
tional miRNAs, miR-30b and miR-27, have been also vali-
dated as direct regulators of Kras and function as tumor
suppressors in solid cancers [64,65]. A separate study
demonstrated that use of a miR-34 mimic could function
as a tumor suppressor and be applied as a directed thera-
peutic in a murine model of Kras-induced lung tumori-
genesis [66]. Conversely, the inhibition of miRNAs such as
miR-143 and miR-145 by oncogenic Ras signaling has been
identified as a mechanism for driving tumor progres-
sion [67]. The miRNA miR-21 is consistently deregulated
in cancers, including lung, glioblastoma and B-cell lymph-
oma [68–70], and Hatley et al. [71] demonstrated that
miR-21 is a potent driver of lung tumorigenesis in a mur-
ine model of Kras-induced lung adenocarcinoma. They
showed that miR-21 directly antagonizes inhibitors of Ras,
including sprouty1, sprouty2, B-cell translocation gene 2
and programmed cell death 4 [71].

**Epidermal growth factor receptor**
The discovery of epidermal growth factor receptor (EGFR)
mutations in lung cancer was a major step forward, as was
the successful targeting of EGFR-mutated tumors using
EGFR tyrosine kinase inhibitors (TKIs such as gefitinib
or erlotinib), which enables individualized therapy in
approximately 10% of patients with lung cancer [72].

Interestingly, miRNAs may both drive EGFR signaling
and serve as targets for EGFR signaling.

A recent elegant study by Shen and colleagues [73] de-
termined that Ago2 could function as a binding partner
for EGFR. In particular, in response to hypoxia, EGFR
directly phosphorylates Ago2 at Tyr393, thus interfering
with precursor miRNA loading and processing. Other
studies have attempted to correlate EGFR mutational sta-
tus with patterns of miRNA expression. Investigators have
also attempted to use miRNAs as EGFR-specific diagnost-
ic biomarkers. For example, Bjaanaes et al. [74] identified
17 miRNAs, including miR-184 and miR-30d, that distin-
guished EGFR-mutated lung adenocarcinomas from wild-
type tumors. Additionally, they identified three miRNAs
that distinguished Kras-mutated lung cancers from wild-
type tumors; however, the biological significance of most
of these miRNAs and their validation as Kras-specific
biomarkers remains relatively unexplored [74]. In an
independent investigation, miR-21 levels were identified
as a predictor of response to EGFR TKI therapy [75].

For clinicians, managing the development of EGFR inhi-
bitor resistance in patients continues to be a major ob-
stacle. Although several mechanisms for intrinsic resistance
to EGFR inhibitors have been identified, a substantial per-
centage of resistance develops with no known mechanism.
Investigators have demonstrated that particular miRNAs
may function as actionable targets in managing resistance.
Park et al. [76] discovered that CRIPTO-mediated (an
EGF-CFC protein family member involved in trans-
forming growth factor β signaling) downregulation of
miR-205, which leads to EMT and activation of the Src
oncogene pathway, is a mechanism for EGFR inhibitor
resistance in non-small-cell lung cancer. Re-expression
of miR-205 led to downregulation of EMT and Src activa-
tion, and restored EGFR-inhibitor sensitivity, suggesting
that miR-205 may serve as a predictive biomarker of re-
sponse to EGFR inhibition [76]. Another example in which
it would be useful to predict which patients would benefit
from EGFR antibody therapy is metastatic colorectal
cancer. Although targeting EGFR using monoclonal
antibodies, such as cetuximab and panitumumab, has
proven successful in metastatic colorectal carcinoma,
less than half of patients with Kras wild-type tumors
are responsive to EGFR targeting. miR-31-3p expression
was identified as a predictive biomarker in colorectal can-
cer patients receiving EGFR antibody therapy [77].

**Liver kinase B1**
In the late 1990s, investigators discovered that a germline
inactivating mutation in the serine threonine kinase
liver kinase B1 (LKB1) gene increased susceptibility to
Peutz-Jeghers syndrome, which manifests as sporadic
benign and malignant tumors in several organs [78].
LKB1 activates several downstream kinases, including
ALK harboring molecular rearrangements in sub-populations of lung cancer patients (between 2-7%) best examples is the identification and selection of decision-making in cancer [83,84]. Perhaps one of the has emerged as a biomarker that can inform therapeutic fusion protein in anaplastic large-cell lymphoma (ALCL), tyrosine kinase first described as part of an oncogenic deregulation of anaplastic lymphoid kinase (ALK), a

Anaplastic lymphoid kinase

Deregulation of anaplastic lymphoid kinase (ALK), a tyrosine kinase first described as part of an oncogenic fusion protein in anaplastic large-cell lymphoma (ALCL), has emerged as a biomarker that can inform therapeutic decision-making in cancer [83,84]. Perhaps one of the best examples is the identification and selection of sub-populations of lung cancer patients (between 2-7%) harboring molecular rearrangements in ALK who have demonstrated survival benefit with the use of ALK-targeting agents such as crizotinib [85].

Knowledge of the links between ALK biology and miRNA is growing, with several studies identifying distinct patterns of miRNA expression in ALK+ versus ALK− malignancies, including ALCL [86]. Most of these studies have focused on ALCL. Liu et al. [87] recently identified a panel of seven miRNAs that distinguished ALK+ from ALK− ALCLs (miR-512-3p, miR-886-5p, miR-886-3p, miR-708, miR-135b, miR-146a and miR-155), although the biological consequences of these patterns remain largely unknown. However, two recent studies in ALCL identified downregulated miR-29 as an inducer of cell survival through targeting of induced myeloid leukemia cell differentiation protein (MCL-1) [88] and downregulated

miR-16 as a driver of vascular endothelial growth factor expression in ALK+ disease [89]. Additionally, the c-Myc-driven cluster miR-17-92 has been shown to serve as a mediator of signal transducer and activator of transcription signaling in ALK+ ALCL [90], thus supporting a role for miRNAs in the biology of ALK signaling.

Conclusions

In the past two decades, miRNAs have emerged as molecules central to cancer biology. miRNAs represent an additional layer of complexity to cancer biology and have been further validated as regulators of processes fundamental to cancer. The rapid expansion in knowledge regarding the molecular underpinnings of cancer initiation and progression and identification of new somatic mutations has only served to expand the landscape of cancer biology. miRNAs clearly have an integral role in driving cancer. This is a field that is rapidly changing, with metabolic reprogramming and extracellular vesicular biology representing two of the most recent potential actionable targets.

Here, we have reviewed emerging concepts in miRNAs as drivers of cancer heterogeneity and progression with a focus on metabolic reprogramming, metastasis and extracellular vesicular biology. Over the past 10 years, we have moved from a phase of recognition of the global deregulation of miRNAs in cancer to one of validation of miRNAs as tumor suppressors or oncogenes, and we are moving to a future that includes clinical trials with miRNAs as therapeutic biomarkers and as directed therapies. For example, miRNAs including miR-122 and miR-34 are currently in clinical trials as directed therapies in hepatitis C and hepatocellular carcinoma, respectively. There remain several obstacles to miRNAs reaching their full clinical application. These include improving our understanding of their fundamental biology in regulating biological pathways, developing improved methods for their reliable detection and the development of new and safe methods for in vivo delivery. Although miRNAs have yet to reach clinical practice, they are poised to do so in the near future.

Abbreviations

ALCL: anaplastic large-cell lymphoma; ALK: anaplastic lymphoid kinase; EGFR: epidermal growth factor receptor; EMT: epithelial-mesenchymal transition; EV: extracellular vesicle; LKB1: liver kinase B1; MCT: monocarboxylate transporter; miRNA: microRNA; TKI: tyrosine kinase inhibitor; TLR: Toll-like receptor.

Competing interests

The authors declare that they have no competing interests.

Author details

1Division of Pulmonary, Allergy, Critical Care and Sleep Medicine, The Ohio State University, 473 West 12th Avenue, Columbus, Ohio 43210, USA. 2James Comprehensive Cancer Center, The Ohio State University, 300 West 10th Avenue, Columbus, Ohio 43210, USA. 3Department of Molecular Virology, Immunology & Medical Genetics, The Ohio State University, 410 West 10th Avenue, Columbus, Ohio 43210, USA.
Published online: 31 August 2014

References

1. Olsen PH, Ambros V: The lin-4 regulatory RNA controls developmental timing in Caenorhabditis elegans by blocking LIN-14 protein synthesis after the initiation of translation. Dev Biol 1999, 216:671–680.

2. Robbins H, Li Y, Padgett RW: Incorporating structure to predict microRNA targets. Proc Natl Acad Sci USA 2005, 102:4006–4009.

3. Volinia S, Galasso M, Costinien S, Tagliavini L, Gamberoni G, Drusco A, Marchesi J, Mascellani N, Sana ME, Abu Jarour R, Desponts C, Teitell M, Baffa R, Aqelian R, Iorio M, Taccioni C, Garzon R, Di Leva G, Fabbi M, Catozzi M, Previati M, Ambros S, Palummo T, Garofalo M, Veronese A, Bottoni A, Gasparini P, Harris CC, Visone R, Pekarsky Y, et al: Reprogramming of miRNA networks in cancer and leukemia. Genome Res 2010, 20:589–599.

4. Esteller M: Non-coding RNAs in human disease. Nat Rev Cancer 2011, 11:861–874.

5. Croce CM: Causes and consequences of microRNA dysregulation in cancer. Nat Rev Cancer 2009, 10:704–714.

6. Calin GA, Croce CM: MicroRNA signatures in human cancers. Nat Rev Cancer 2006, 6(5):57–66.

7. Bader AG: MicroRNA: A microRNA signature associated with prognosis and therapeutic outcome in colon adenocarcinoma. Cancer Res 2007, 67:1503–1510.

8. Xiao B, Wang Y, Li W, Baker M, Guo J, Corbet K, Tsalik EL, Li QJ, Palmer SM, Visani M, de Biase D, Marucci G, Cerasoli S, Nigrisoli E, Bacchi Reggiani ML, Texas JC, Liu CG, Spizzo R, Calin GA, Croce CM, Harris CC, Visone R, Pekarsky Y, A, Gasparini P, Harris CC, Visone R, Pekarsky Y, et al: Reprogramming of miRNA networks in cancer and leukemia. Genome Res 2010, 20:589–599.

9. Esteller M: Non-coding RNAs in human disease. Nat Rev Cancer 2011, 11:861–874.

10. Croce CM: Causes and consequences of microRNA dysregulation in cancer. Nat Rev Cancer 2009, 10:704–714.

11. Calin GA, Croce CM: MicroRNA signatures in human cancers. Nat Rev Cancer 2006, 6(5):57–66.

12. Al-Saleem T, Schetter AJ, Leung SY, Sohn JJ, Zanetti KA, Bowman ED, Yanaihara N, Yuen ST, Liu CG, Spizzo R, Calin GA, Croce CM, Harris CC, Visone R, Pekarsky Y, A, Gasparini P, Harris CC, Visone R, Pekarsky Y, et al: Reprogramming of miRNA networks in cancer and leukemia. Genome Res 2010, 20:589–599.

13. Esteller M: Non-coding RNAs in human disease. Nat Rev Cancer 2011, 11:861–874.

14. Croce CM: Causes and consequences of microRNA dysregulation in cancer. Nat Rev Cancer 2009, 10:704–714.

15. Calin GA, Croce CM: MicroRNA signatures in human cancers. Nat Rev Cancer 2006, 6(5):57–66.

16. Bader AG: MicroRNA: A microRNA signature associated with prognosis and therapeutic outcome in colon adenocarcinoma. Cancer Res 2007, 67:1503–1510.

17. Xiao B, Wang Y, Li W, Baker M, Guo J, Corbet K, Tsalik EL, Li QJ, Palmer SM, Visani M, de Biase D, Marucci G, Cerasoli S, Nigrisoli E, Bacchi Reggiani ML, Texas JC, Liu CG, Spizzo R, Calin GA, Croce CM, Harris CC, Visone R, Pekarsky Y, et al: Reprogramming of miRNA networks in cancer and leukemia. Genome Res 2010, 20:589–599.

18. Esteller M: Non-coding RNAs in human disease. Nat Rev Cancer 2011, 11:861–874.

19. Croce CM: Causes and consequences of microRNA dysregulation in cancer. Nat Rev Cancer 2009, 10:704–714.

20. Calin GA, Croce CM: MicroRNA signatures in human cancers. Nat Rev Cancer 2006, 6(5):57–66.

21. Al-Saleem T, Schetter AJ, Leung SY, Sohn JJ, Zanetti KA, Bowman ED, Yanaihara N, Yuen ST, Liu CG, Spizzo R, Calin GA, Croce CM, Harris CC, Visone R, Pekarsky Y, A, Gasparini P, Harris CC, Visone R, Pekarsky Y, et al: Reprogramming of miRNA networks in cancer and leukemia. Genome Res 2010, 20:589–599.

22. Esteller M: Non-coding RNAs in human disease. Nat Rev Cancer 2011, 11:861–874.

23. Croce CM: Causes and consequences of microRNA dysregulation in cancer. Nat Rev Cancer 2009, 10:704–714.

24. Calin GA, Croce CM: MicroRNA signatures in human cancers. Nat Rev Cancer 2006, 6(5):57–66.

25. Bader AG: MicroRNA: A microRNA signature associated with prognosis and therapeutic outcome in colon adenocarcinoma. Cancer Res 2007, 67:1503–1510.

26. Xiao B, Wang Y, Li W, Baker M, Guo J, Corbet K, Tsalik EL, Li QJ, Palmer SM, Visani M, de Biase D, Marucci G, Cerasoli S, Nigrisoli E, Bacchi Reggiani ML, Texas JC, Liu CG, Spizzo R, Calin GA, Croce CM, Harris CC, Visone R, Pekarsky Y, et al: Reprogramming of miRNA networks in cancer and leukemia. Genome Res 2010, 20:589–599.

27. Esteller M: Non-coding RNAs in human disease. Nat Rev Cancer 2011, 11:861–874.

28. Croce CM: Causes and consequences of microRNA dysregulation in cancer. Nat Rev Cancer 2009, 10:704–714.

29. Calin GA, Croce CM: MicroRNA signatures in human cancers. Nat Rev Cancer 2006, 6(5):57–66.

30. Bader AG: MicroRNA: A microRNA signature associated with prognosis and therapeutic outcome in colon adenocarcinoma. Cancer Res 2007, 67:1503–1510.

31. Xiao B, Wang Y, Li W, Baker M, Guo J, Corbet K, Tsalik EL, Li QJ, Palmer SM, Visani M, de Biase D, Marucci G, Cerasoli S, Nigrisoli E, Bacchi Reggiani ML, Texas JC, Liu CG, Spizzo R, Calin GA, Croce CM, Harris CC, Visone R, Pekarsky Y, et al: Reprogramming of miRNA networks in cancer and leukemia. Genome Res 2010, 20:589–599.

32. Esteller M: Non-coding RNAs in human disease. Nat Rev Cancer 2011, 11:861–874.

33. Croce CM: Causes and consequences of microRNA dysregulation in cancer. Nat Rev Cancer 2009, 10:704–714.

34. Calin GA, Croce CM: MicroRNA signatures in human cancers. Nat Rev Cancer 2006, 6(5):57–66.

35. Bader AG: MicroRNA: A microRNA signature associated with prognosis and therapeutic outcome in colon adenocarcinoma. Cancer Res 2007, 67:1503–1510.

36. Xiao B, Wang Y, Li W, Baker M, Guo J, Corbet K, Tsalik EL, Li QJ, Palmer SM, Visani M, de Biase D, Marucci G, Cerasoli S, Nigrisoli E, Bacchi Reggiani ML, Texas JC, Liu CG, Spizzo R, Calin GA, Croce CM, Harris CC, Visone R, Pekarsky Y, et al: Reprogramming of miRNA networks in cancer and leukemia. Genome Res 2010, 20:589–599.

37. Esteller M: Non-coding RNAs in human disease. Nat Rev Cancer 2011, 11:861–874.

38. Croce CM: Causes and consequences of microRNA dysregulation in cancer. Nat Rev Cancer 2009, 10:704–714.

39. Calin GA, Croce CM: MicroRNA signatures in human cancers. Nat Rev Cancer 2006, 6(5):57–66.

40. Bader AG: MicroRNA: A microRNA signature associated with prognosis and therapeutic outcome in colon adenocarcinoma. Cancer Res 2007, 67:1503–1510.

41. Xiao B, Wang Y, Li W, Baker M, Guo J, Corbet K, Tsalik EL, Li QJ, Palmer SM, Visani M, de Biase D, Marucci G, Cerasoli S, Nigrisoli E, Bacchi Reggiani ML, Texas JC, Liu CG, Spizzo R, Calin GA, Croce CM, Harris CC, Visone R, Pekarsky Y, et al: Reprogramming of miRNA networks in cancer and leukemia. Genome Res 2010, 20:589–599.

42. Esteller M: Non-coding RNAs in human disease. Nat Rev Cancer 2011, 11:861–874.

43. Croce CM: Causes and consequences of microRNA dysregulation in cancer. Nat Rev Cancer 2009, 10:704–714.

44. Calin GA, Croce CM: MicroRNA signatures in human cancers. Nat Rev Cancer 2006, 6(5):57–66.

45. Bader AG: MicroRNA: A microRNA signature associated with prognosis and therapeutic outcome in colon adenocarcinoma. Cancer Res 2007, 67:1503–1510.

46. Xiao B, Wang Y, Li W, Baker M, Guo J, Corbet K, Tsalik EL, Li QJ, Palmer SM, Visani M, de Biase D, Marucci G, Cerasoli S, Nigrisoli E, Bacchi Reggiani ML, Texas JC, Liu CG, Spizzo R, Calin GA, Croce CM, Harris CC, Visone R, Pekarsky Y, et al: Reprogramming of miRNA networks in cancer and leukemia. Genome Res 2010, 20:589–599.
38. Davalos V, Moutinho C, Villanueva A, Bogue R, Silva P, Carneiro F, Esteller M: Dynamic epicrine regulation of the microRNA-200 family mediates epithelial and mesenchymal transitions in human tumorigenesis. Oncogene 2012, 31:2062–2074.

39. Yang Y, Ahn YH, Gibbons DL, Zang Y, Lin W, Thilagathan N, Alvarez CA, Moreira DC, Creighton CJ, Gregory PA, Goodall GJ, Kurie JM: The Notch ligand Jagged2 promotes lung adenocarcinoma metastasis through a miR-200-dependent pathway in mice. J Clin Invest 2011, 121:1373–1385.

40. Ahn YH, Gibbons DL, Chakravartty D, Creighton CJ, Riizi ZH, Adams HP, Pertsemidis A, Gregory PA, Wright JA, Goodall GJ, Flores ER, Kurie JM: ZEB1 drives prometastatic actin cytoskeletal remodeling by downregulating miR-34a expression. J Clin Invest 2012, 122:3170–3183.

41. Song SJ, Poliseno L, Song MS, Alu A, Webster K, Ng C, Biering G, Brikbak NJ, Yuan X, Cantley LC, Richardson AL, Pandolfi PP: MicroRNA-antagonism regulates breast cancer stemness and metastasis via TET-family-dependent chromatin remodeling. Cell 2013, 154:311–324.

42. Valadi H, Ekstrom K, Bossios A, Sjostrand M, Lee JJ, Lofwall JO: Exosome-mediated transfer of mRNAs and microRNAs is a novel mechanism of genetic exchange between cells. Nat Cell Biol 2007, 9:654–659.

43. Hunter MP, Ismail N, Zhang X, Aguda BD, Lee EJ, Yu L, Xiao T, Schafer J, Lee ML, Christensen BC, Moyer BJ, Avissar M, Ouellet LG, Plaza SL, McClean MD, Nana-Sinkam and Croce CM, Nana-Sinkam P, Perrotti D, Croce CM: MicroRNA signatures of tumor-derived extracellular circulating microRNA. Nucleic Acids Res 2011, 39:2723–2733.

44. Theoy C: Exosomes: secreted vesicles and intercellular communications. F1000 Biol Rep 2011, 3:85.

45. Gastpar R, Gehrmann M, Bausero MA, Asea A, Gross C, Schroeder JA, Ahn YH, Gibbons DL, Chakravarti D, Creighton CJ, Rizvi ZH, Adams HP, Arroyo JD, Chevillet JR, Kroh EM, Ruf IK, Pritchard CC, Gibson DF, Mitchell PS, Hunter MP, Ismail N, Zhang X, Aguda BD, Lee EJ, Yu L, Xiao T, Schafer J, Lee ML, Christensen BC, Moyer BJ, Avissar M, Ouellet LG, Plaza SL, McClean MD, Nana-Sinkam and Croce CM, Nana-Sinkam P, Perrotti D, Croce CM: MicroRNA signatures of tumor-derived extracellular circulating microRNA. Nucleic Acids Res 2011, 39:2723–2733.

46. Liu C, Yu S, Zinn K, Wang J, Zhang L, Jia Y, Kappes JC, Barnes S, Kimberly RP, Schmittgen TD, Nana-Sinkam SP, Jarjoura D, Marsh CB: miR-34a expression in human peripheral blood microvesicles. Nucleic Acids Res 2011, 39:5003–5008.

47. Turchinovich A, Weiz L, Langheim A, Burwinkel B: Characterization of extracellular circulating microRNA. Cancer Res 2013, 73:1024–1034.

48. Kasinski AL, Slack FJ: miRNA-21 is an antiapoptotic factor in tumour cells. EMBO J 2005, 24:5932–5941.

49. Keates S, Ekmann M, Ward EM, Claesson-Welsh L, Strudwick PJ, Findlay IC, Bridges SJ, Gribble FM, DiMarzo V: Dynamic epigenetic regulation of the microRNA-200 family in cancer. EMBO J 2006, 25:2175–2185.

50. Liao WT, Ye YP, Zhang N, Li T, Wang Y, Sun Y, Wu H, Gao J, Bai S, Huang Y, Ji L, Wang C, Zhang X, Wang J, Ding YQ: MicroRNA-30b functions as a tumour suppressor in human colorectal cancer. Nat Cell Biol 2006, 8:113–122.

51. Yanaihara N, Caplen N, Bowman E, Seike M, Kumamoto K, Yi M, Stephens RM, Lee JH, Sato M, Eckhardt S, Noble M, Hasegawa N, Zhang L, Atreya C, Sausville E, Croce CM, Porter T, Crook T, Croce CM: Characterization of microRNAs derived from circulating exosomes as noninvasive biomarkers for cancer detection. Cancer Res 2006, 66:10785–10794.

52. Keates S, Ekmann M, Ward EM, Claesson-Welsh L, Strudwick PJ, Findlay IC, Bridges SJ, Gribble FM, DiMarzo V: Dynamic epigenetic regulation of the microRNA-200 family in cancer. EMBO J 2006, 25:2175–2185.

53. Keates S, Ekmann M, Ward EM, Claesson-Welsh L, Strudwick PJ, Findlay IC, Bridges SJ, Gribble FM, DiMarzo V: Dynamic epigenetic regulation of the microRNA-200 family in cancer. EMBO J 2006, 25:2175–2185.
Wang Y, Giacccone G. CRIPTO1 expression in EGFR-mutant NSCLC elicits intrinsic EGFR-inhibitor resistance. J Clin Invest 2014, 124:3003–3015.

77. Manceau G, Imbeaud S, Thiebaut S, Liebaert C, Fontaine K, Rousseau F, Genin B, Corne DL, Didelot A, Vincent M, Bacht JF, Chibaude B, Bouché O, Landi B, Biseau F, Leroy K, Poulet-Liocra F, Van Laethem JL, Demeter P, Tespier S, Rossi S, Mosakhani N, Osterlund P, Ristamäki R, Sarhadi V, Knoufia S, Boige V, André T, Laurent-Puig P. Hsa-miR-31-3p expression is linked to progression-free survival in patients with KRAS wild-type metastatic colorectal cancer treated with anti-EGFR therapy. Clin Cancer Res 2014, 20:3338–3347.

78. Hemminoki A, Markie D, Tomlinson I, Avizienyte E, Roth S, Loukola A, Manceau G, Imbeaud S, Thiebaut R, Liebaert F, Fontaine K, Rousseau F, Liu C, Iqbal J, Teruya-Feldstein J, Shen Y, Dabrowska MJ, Dybkaer K, Lim MS, Merkel O, Hamacher F, Laimer D, Sifft E, Trajanoski Z, Scheideler M, Godlewski J, Nowicki MO, Bronson RT, Lindeman NI, Christiani DC, Lin X, Shapiro GI, Jänne PA, Contreras CM, Li D, Chen L, Krishnamurthy J, Koivunen J, Chirieac LR, Padera RF, Bronson RT, Lindernal NI, Christani DC, Lin X, Shapiro GI, Jänne PA, Johnson BE, Meyerson M, Christianson D, Seto T, Crino L, Ahn MJ, De Pas T, Besse B, Desjobert C, Renalier MH, Foisseau E, Ferrari C, Cucuruz G, Liu C, Iqbal J, Cantarella D, Taulli R, Barroso P, Di Cunto F, Medico E, Negrini M, Chan WC, Inghirami G, Piva R. STAT3-mediated activation of microRNA cluster 17–92 promotes proliferation and survival of ALK-positive anaplastic large cell lymphoma. Haematologica 2014, 99:116–124.

79. Dejean E, Renalier MH, Foisseau E, Agirre X, Joseph N, de Paiva GR, Al Saa T, Soulier J, Desjobert C, Lamant L, Prósper F, Felsher DW, Cavaillé J, Prats H, Delso G, Giuriato S, Meggetto F. Hypoxia-microRNA-16 downregulation induces VEGF expression in anaplastic lymphoma kinase (ALK)-positive anaplastic large-cell lymphomas. Leukemia 2011, 25:1882–1890.

80. Spaccarotella E, Pellegrino E, Ferracin M, Ferreri C, Cuccuru G, Liu C, Iqbal J, Cantarella D, Taulli R, Provero P, Di Cunto F, Medico E, Negrini M, Chan WC, Inghirami G, Piva R. STAT3-mediated activation of microRNA cluster 17–92 promotes proliferation and survival of ALK-positive anaplastic large cell lymphoma. Haematologica 2014, 99:116–124.

81. Lino E, Li L, Guan Y, Soriani R, Rivers CS, Mohan S, Pandita A, Tang J, Mudrusan Z. Exon array profiling detects EML4-ALK fusion in breast, colorectal, and non-small cell lung cancers. Mol Cancer Res 2009, 7:1466–1476.

82. Shaw AT, Kim DW, Nakagawa K, Seto T, Crino L, Ahn MJ, De Pas T, Besse B, Solomon BJ, Blackhall F, Wu YL, Thomas M, O’Byrne KJ, Moro-Sibilot D, Camdige DR, Mok T, Hirsh V, Rely GI, Iyer S, Tassell V, Polli A, Wilner KD, Jänne PA. Crizotinib versus chemotherapy in advanced ALK-positive lung cancer. N Engl J Med 2013, 368:2385–2394.

83. Merkel O, Hanamcher F, Laimer D, Dist D, Tranjanzus Z, Scheiderer M, Egger G, Hassler MR, Thallinger C, Schmatz A, Turner SD, Greil R, Kenner L. Identification of differential and functionally active miRNAs in both anaplastic lymphoma kinase (ALK) + and ALK- anaplastic large-cell lymphoma. Proc Natl Acad Sci USA 2010, 107:16228–16233.

84. Liu C, Iqbal J, Tetuya-Feldstein I, Shen Y, Dobrowks MD, Dybkaer K, Lim MS, Piva R, Barreca A, Pellegrino E, Spaccarotella E, Lachel CM, Kucuk C, Jiang CS, Hu X, Bhagavathi S, Greiner TC, Weisenburger DD, Aoun P, Perkins SL, McKeithan TW, Inghirami G, Chan WC. MicroRNA expression profiling identifies molecular signatures associated with anaplastic large cell lymphoma. Blood 2013, 122:2083–2092.

85. Desjobert C, Renalier MH, Bergalet J, Dejean E, Joseph N, Kruczyński A, Soulier J, Espino E, Meggetto F, Cavaillé J, Delso G, Lamant L. MiR-29a down-regulation in ALK-positive anaplastic large cell lymphomas contributes to apoptosis blockade through MCL-1 overexpression. Blood 2011, 117:6667–6667.

doi:10.1186/s13059-014-0445-8

Cite this article as: Nana-Sinkam and Croce. MicroRNA regulation of tumorigenesis, cancer progression and interpatient heterogeneity: towards clinical use. Genome Biology 2014 15:445.