Review

MicroRNAs in chronic lymphocytic leukemia

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Abstract

Chronic lymphocytic leukemia (CLL) is the most common leukemia in the western world. Recent research, conducted primarily in basic science laboratories, has indicated a role for microRNAs (miRNAs) in the pathogenesis and prognosis of this disease. MiRNAs are small, non-coding, functional RNAs, that mediate post-transcriptional inhibition of messenger RNAs. Because miRNA expression levels in CLL patients differ from that of normal patients, there may be a role for these novel small molecules as biomarkers in this disease.

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Introduction

The National Cancer Institute’s Surveillance Epidemiology and End Results (SEER) database reported an incidence rate of 4.1 per 100,000 men and women per year (5.6 per 100,000 men, 2.9 per 100,000 women) for 2000–2006 with median age at diagnosis of 72, and a median age at death of 79. In this time period 19.3% of CLL patients were between the ages of 55 and 64, and 11% were under age 55 (Altekruse et al., 2010). CLL is characterized by accumulation of at least 5000 mature B lymphocytes/μL peripheral blood that express CD19, CD20, CD23 and co-express T-cell associated antigen CD5. A defining characteristic of the B-CLL lymphocyte is low expression of the B-Cell Receptor (BCR) (Dighiero and Hamblin, 2008). The BCR is a complex consisting of a surface immunoglobulin homodimer (IgD or IgM) noncovalently bound to the CD79a/CD79b heterodimer, which function together as the transmembrane component of the B lymphocyte’s antigen-actuated signal transduction pathway.

Clinical staging systems for CLL, proposed by Rai et al. (1975) and Binet et al. (1981), remain valid even today. Currently, the National Cancer Institute (NCI) recommends a “watch and wait” strategy for low Rai and Binet stage patients (Hallek et al., 2008). Interestingly, the widespread clinical use of flow cytometers, has enabled the detection of low levels of lymphocytes (<5000 lymphocytes/μL), usually displaying the B-CLL immunophenotype in up to 3–5% of healthy elderly individuals, a condition termed monoclonal B-cell lymphocytosis (MBL). Approximately 2% of MBL cases progress to CLL (Marti et al., 2005). This increasing ability to detect low levels of B-CLL lymphocytes has led to a corresponding rise in the diagnosis of early-stage disease. In the 1970s 15% of CLL diagnoses were Binet stage A, compared to 80% in the 1990s (Rawstron, 2009).

Early-stage CLL patients display a highly variable disease course, with roughly 50% developing a more aggressive, faster-progressing disease than anticipated (Van Bockstaele et al., 2009). While the Rai and Binet staging systems are valuable for helping physicians decide...
when to begin the treatment, they are unable to predict disease progression, especially for early-stage patients (Chiorazzi et al., 2005). Several predictive markers have been proposed over the past few decades including serum markers like lactate dehydrogenase (LDH), beta2-microglobulin, soluble CD23, cytogenetic abnormalities, immunoglobulin heavy chain variable region (IgVH) gene mutation status and zeta-chain-associated protein kinase 70 (ZAP-70) expression levels (Van Boeckelstea et al., 2009). Cytogenetic abnormalities can be seen in more than 80% of CLL patients, with the most common abnormalities being deletion at 13q14 (~50%) associated with a more favorable disease course. In contrast, trisomy 12 (15–30%), deletion at 11q22-23 (15–20%) and deletion at 17p13 (10%) are each associated with a poor prognosis. Del (17p13) in particular confers a very poor prognosis, as the TP53 tumor suppressor gene is contained within that locus (Oscier et al., 2002). The IgVH mutation status is related to the stage of B-cell differentiation. Earlier studies by Schroeder and Dighiero (1994) and Fais et al. (1998) showed that contrary to the classical assumption that B-CLL lymphocytes were derived from naïve, pre-germinal center B cells, the CLL-lymphocytes also represent expansions of previously-triggered, post germinal center (GC) “memory” B cells. Damle et al. (1999) and Hamblin et al. (1999) showed that the presence of unmutated IgVH genes (IgVH homology to germline=0–98%) predicted an inferior clinical course. Oscier et al. (1997) correlated IgVH mutational status with several of the common cytogenetic abnormalities. The determination of IgVH mutational status, now considered the “gold standard” of CLL prognostic markers, relies upon sequencing, which remains prohibitively expensive and time-consuming for routine clinical implementation. Zeta-chain-associated protein kinase 70 (ZAP-70), a 70 kD tyrosine kinase, typically absent from “normal” B cells, is expressed to varying degrees in T cells and CLL B cells. A comparative microarray experiment identified ZAP-70 as part of a typical B-CLL genotype, and identified it as the gene most differentially expressed between CLLs with unmutated and mutated IgVH segments (Rosenwald et al., 2001). Several studies have shown that high expression of this protein is usually correlated with IgVH germline mutational status and could be a possible surrogate marker, though not without difficulties (Crespo et al., 2003; Rassenti et al., 2004; Best et al., 2006). Hence, the search for potential surrogate markers to correlate with IgVH mutational status is an active area of research.

MicroRNAs

More recently, several microRNAs (miRNAs) have been proposed as prognostic markers for CLL and other human cancers (Bartels and Tsongalis, 2009). MicroRNAs are short (~22 nt in humans), endogenous non-coding ssRNA molecules that regulate gene expression via translational repression or transcript degradation. The first identified miRNA was lin-4, which Lee et al. (1993) associated with the timing of C. elegans development. Since then, a myriad of miRNAs have been identified in both plants and animals. In contrast to their plant counterparts, animal miRNAs typically bind to mRNA targets rather imprecisely. A single metazoan miRNA may inhibit the translation of 100 or more mRNAs. In addition, multiple miRNAs may bind to the 3′-UTR of a single mRNA, forming a highly complex and precise mechanism for translational repression (Bartel and Chen, 2004). Bioinformatic and reverse genetics approaches to identifying miRNAs were initially hampered by this typically low degree of complementarity between animal miRNAs and the 3′ UTR of their target mRNAs. However, more recent algorithms have both improved upon target detection and limited false-positive associations by taking into account sequence conservation between orthologous sites and by placing emphasis upon “seed” regions — 6 nt regions (nucleotides 2–7) at the 5′ end of a miRNA typically displaying contiguous base-pairing with a region within the 3′ UTR of its target mRNA. (Bartel, 2009). These and other increasingly sophisticated bioinformatics approaches have raised estimates of the total number of human miRNAs to over 800 (Bentwich et al., 2005; Berezikov et al., 2005).

Most miRNA genes are isolated, relying on their own independent promoters for transcription. However, some miRNAs are found in clusters, indicating that they may be processed and regulated as units (Ambros, 2004). MicroRNAs are typically transcribed from genes which may be far removed from their respective mRNA targets, indicating that they are likely transcribed independently (Lee and Ambros, 2001). However, several miRNAs in animals are found within the introns of coding genes. These miRNAs, referred to as “mirtrons,” are most often found in a sense orientation relative to their host genes, suggesting that genes and their associated mirtrons can form transcription units (Berezikov et al., 2007; Okamura et al., 2007; Ruby et al., 2007).

MicroRNAs are typically transcribed by Pol II or possibly (and infrequently) Pol III to form longer primary miRNAs (pri-miRNAs) (Borchert et al., 2006; Lee et al., 2004). Pri-miRNAs typically demonstrate a highly-folded secondary structure, with many hairpin and stem-loop features. Inside the nucleus, pri-miRNA transcripts are processed by the “microprocessor complex,” which consists of the Class 2 RNAse III endonuclease Drosha bound to accessory protein DGCR8 (often referred to as “Pasha”) (Lee et al., 2006; Gregory et al., 2004). The microprocessor complex converts pri-miRNAs into “precursor miRNAs” (pre-miRNAs) — dsRNA structures with characteristic hairpin structures and imperfect base pairing. An exception to this processing pathway occurs with the aforementioned mirtrons. They bypass the microprocessor complex, and are instead transcribed directly into pre-miRNA, and are effectively processed via the splicing of their parent introns (Okamura et al., 2007; Ruby et al., 2007). After formation, pre-miRNAs are exported from the nucleus into the cytoplasm by Exportin 5 (Lund et al., 2004). In the cytoplasm, pre-miRNAs are further processed by Dicer, another RNAse III enzyme. Dicer removes the hairpin loop from pre-miRNA, yielding a ~22 nt dsRNA molecule consisting of the mature miRNA base-paired to a roughly complementary fragment (miRNA*) which is derived from the opposite strand of the pre-miRNA. The miRNA strand from the miRNA:miRNA* duplex then binds to the RNA-induced silencing complex (RISC), while the miRNA* is released and rapidly degraded in the cytoplasm (Lee et al., 2002). The newly-formed RISC is a ribonucleoprotein complex consisting of yet another RNAse endonuclease – one of the various members of the Argonaute family – bound to the mature miRNA, which acts as a guide template. RISCs may incorporate other proteins, though an Argonaute protein is always required (Pratt and MacRae, 2009). Once a miRNA is incorporated into a RISC, it can act upon potential mRNA targets in one of two ways, both of which act to down-regulate gene expression (Pratt and MacRae, 2009).

mRNA cleavage occurs more frequently in plants and also occasionally in animals when a RISC miRNA guide template closely complements an mRNA target sequence. The miRNA guide template will then bind to the mRNA transcript and activate the RNAse activity of its associated Argonaute protein, which will cleave the mRNA transcript. Translational Repression occurs more frequently in animals, and arises from the miRNA guide molecule in a RISC binding imperfectly with a sequence in the 3′-UTR of a target mRNA. The ~6 nt “seed” region at the 5′ end of the miRNA is most critical for target recognition and binding of the RISC to the target mRNA. In this case, instead of cleaving the mRNA target, the RISC will simply remain bound to the transcript, inhibiting ribosome activity.

Clinical researchers quickly became interested in miRNAs when evidence began to suggest that miRNAs could be used to accurately classify and assess the progression of a variety of cancers (Lu et al., 2005). Further research indicated that some miRNAs could function as either tumor-suppressors or oncogenes (referred to as oncomirs), suggesting a possible future role for miRNA therapy in cancer management and treatment (Esquela-Kerscher and Slack, 2006).
**Micro RNAs in CLL pathogenesis**

miR-15a and miR-16

Calin et al. (2002) published the first compelling evidence of the involvement of a miRNA in CLL pathogenesis, when they observed the 13q14 deletion present in roughly 50% of CLL cases. Hemizygous and/or homozygous loss at 13q14 is the most frequent chromosomal abnormality in CLL and this abnormality is also seen in mantle cell lymphoma, multiple myeloma, DLBCL, mature T-cell lymphoma, and solid tumors, suggesting the presence of tumor suppressor genes at 13q14 (Bullrich et al., 2001). This region has been extensively studied and a minimally-deleted region (MDR) which contains the deleted in leukemia (DLEU) 2 gene as well as the miR-15a/miR-16-1 cluster has been identified (Calin et al., 2002; Liu et al., 1997; Lagos-Quintana et al., 2001; Migliazza et al., 2001). In SNP array studies, Pfeiffer et al. (2007) further validated that del (13q14) targeted miR-15a and miR-16-1. Calin et al. (2005) identified germline mutations in the primary precursors of miR-15a and miR-16-1 in 2% of CLL cases. Point mutation in the 3′ flanking region of miR-16-1 mutations in the New Zealand Black Mouse strain has been associated with reduced miR-16-1 expression, and mice harboring this mutation developed a B-cell lymphoproliferative disorder that is a model for human CLL (Raveche et al., 2007). These studies emphasize that these two miRNAs are critical in CLL pathogenesis, functioning as micro-managers that fine tune gene expression (Bartel and Chen, 2004).

Cimmino et al. (2005) proposed that miR-15a and miR-16-1 function as tumor suppressor genes by modulating BCL2 (B-cell CLL/lymphoma 2), an anti-apoptotic protein that is highly expressed in CLL. Specifically, by analyzing homology between these two miRNAs and the BCL2 mRNA sequence, Cimmino et al. found that the first nine nucleotides from the 5′ ends of both miRNAs are complementary to the BCL2 cDNA. Whereas in normal CD5+ tonsils, the levels of both miRNAs were high and the BCL2 protein was expressed in low levels, the opposite was true in leukemic cells. Hence miR-15a and miR-16-1 produce their anti-tumorigenic effect by targeting the BCL2 gene (Cimmino et al., 2005). Cimmino et al. validated their work by transfecting a human megakaryocytic cell line with vectors containing both miRNAs and found that BCL2 levels were highly reduced and in further TUNEL assays showed that BCL2 down-regulation by miR-15 and miR-16-1 triggers apoptosis. While some studies support the BCL2 mechanism of tumorigenesis (Hanlon et al., 2009), others are not in agreement (Fulci et al., 2007; Linsley et al., 2007; Klein et al., 2010). Fulci et al. (2007) found that only patients who were hemizygous for del(13q14) (roughly 11% of their cohort) exhibited a significant down-regulation of miR-15a and miR-16, while those patients bearing a hemizygous deletion at 13q14 were indistinguishable from controls. In addition, Fulci et al. found no correlation between miR-15a/miR-16-1 down-regulation and BCL2 up-regulation, even in patients who were homozygous for the 13q14 deletion, albeit this finding was based on 6 cases. In a microarray profiling analysis, Linsley et al. (2007) showed that miR-16 down-regulated transcripts were enriched with genes (CDK6, CDC2, CARD10, and C10orf46) whose expression was silenced by interfering miRNAs. Other genes targeted by down-regulation of miR-15a and miR-16-1 include BAD (BCL2-associated death agonist) and RF41 (up-regulated) and RASSF5, MKK3 and LRIG1 (down-regulated) (Hanlon et al., 2009).

These studies are susceptible to imperfections in current algorithms for predicting targets via sequence similarities (Lichter, 2010) and in-vitro cell systems. The causality of miR-15a/miR-16 deletion in CLL pathogenesis was recently experimentally verified by Klein et al. (2010), who developed an elegant mouse model with del(14q3), the murine conserved region corresponding to the human 13q14 region. Klein et al. generated transgenic mice with a deleted MDR (containing both miR-15a/miR-16-1 and DLEU2) and those with deletion of the two miRNA genes only. At 15–18 months, 5% of these mice developed monoclonal B cell lymphocytosis (MBL), a possible precursor of CLL (Rawstron et al., 2008). A quarter of these mice developed clinical signs of CLL/small lymphocytic lymphoma (SLL) with splenic white pulp disease and smudge cells visible in peripheral blood smears. A smaller fraction (9% with MDR deleted and 2% with miR-15a/miR-16-1 deleted) further developed a more aggressive diffuse large B cell lymphoma (DLBCL) phenotype. Mice with the miR-15a/miR-16-1 deletion developed a more indolent disorder compared to mice with the MDR deletion who eventually succumbed to their tumors. To understand the mechanism by which the miRNA gene deletions lead to clonal B-lymphoproliferations, Klein et al. performed bromodeoxyuridine (BrdU) incorporation assays, which measure active DNA synthesis. They demonstrated that miR-15a/miR-16-1 deleted B cells began to synthesize DNA earlier than wild-type mice, apparently by up-regulating the expression of several proliferation-associated proteins (CCND2, CCND3, CDK4, and CDK6) that have important roles in the G0/G1-S phase transition. These findings corroborate earlier observations that the miR-15a/miR-16-1 locus controls B cell expansion by modulating proliferation, rather than influencing survival via regulation of BCL2 (Raveche et al., 2007; Linsley et al., 2007; Liu et al., 2008; Bandi et al., 2009). This disease progression model simulates human CLL disease (Klein et al., 2010).

miR-29, miR-181

miR-29 has been described as a tumor-suppressing miRNA which targets several oncoproteins including TCL1, MCh1, CDK2 (Pekarsky et al., 2006; Mott et al., 2007; Zhao et al., 2010), or conversely, as an onco-miRNA in AML (Han et al., 2010). The T cell leukemia gene 1 (TCL1) oncogene was first discovered in T-cell prolymphocytic leukemia (T-PLL) (Virgilio et al., 1994). TCL1 is highly expressed in CLL and correlates with an aggressive phenotype often displaying unmutated IgVH, high ZAP-70 expression and del(11q22-23) (Herling et al., 2006), To further investigate TCL1’s role in B-cell malignancies, Bichi et al. (2002) created Eμ-TCL1 transgenic mice with TCL1 expression up-regulated by a Vh promoter and an Igμ-Eμ enhancer. The Eμ-TCL1 mice developed disease closely resembling human CLL with hepatosplenomegaly, lymphadenopathy and clonal CD5+ B lymphocytes. In a subsequent microarray analysis, Pekarsky et al. (2006) showed that TCL1 protein expression in CLL was inversely correlated with miR-29 and miR-181 expression. Since TCL1 was associated with a more aggressive CLL, Pekarsky et al. postulated that a down-regulation of miR-29 miRNA in CLL could contribute to the development of a more aggressive phenotype. To show a more direct pathogenetic mechanism of miR-29 in CLL, Santanam et al. (2010) created a Eμ-miR-29 mouse model with miR-29 expression controlled by the Vh promoter/IgH-Eμ enhancer combination. The transgenic mice went on to develop CLL at a higher rate than wild-type controls. They showed that 85% of transgenic mice developed an expanded CD5 + lymphocyte population starting at 2 months and by 2 years greater than 65% of B cells were CD5+. Only a minor subset (4/20) of these developed frank leukemia and died of disease; a model simulating definitive human disease (Gladkikh et al., 2010).

**Signature and prognostic miRNAs in CLL**

Several microarray studies have analyzed hundreds of miRNAs to determine which may help identify the leukemic cells involved in CLL. Using miRNA-specific microarrays, Calin et al. (2004) found at least 25
miRNAs that were differentially expressed in CLL cells versus CD5+ ‘normal’ cells and validated their findings for four miRNAs including miR-16-1, miR-26a, miR-206, and miR-223 by northern blot analysis. In 2007, Fulci et al. also identified a set of miRNAs including miR-155, miR-21, miR-150, miR-92 and miR-222 that were differentially expressed between CLL lymphocytes and their “normal” counterparts via qRT-PCR and molecular cloning techniques. Marton et al. (2008) used qRT-PCR and northern blot analysis to identify several miRNAs that are differentially expressed between CLL lymphocytes and CD19+ control cells, including miR-181, miR-30d and let-7a.

Several studies also attempted to identify miRNAs that could act as prognostic indicators in CLL, typically by correlating expression levels of these miRNAs with previously established prognostic indicators such as IgVH mutation status or ZAP-70 expression. Based on microarray studies, Calin et al. (2005) published a signature of 13 miRNAs that were differentially expressed between unmutated IgVH§/ZAP-70+ and mutated IgVH§/ZAP70-CLL patients and could predict the time from diagnosis to initial treatment. This signature included miR-15a, miR-195, miR-221, miR-23b, miR-155, miR-223, miR29a-2, miR-24-1, miR-29b-2, miR-146, miR-16-1, miR-16-2, and miR-29c. A study using quantitative RT-PCR of mature RNAs correlated the expression of these three miRNAs – miR-150, miR-223 and miR-29b/c – with IgVH§ mutation status (Fulci et al., 2007). However, they also noted that while these miRNAs were on average over-expressed in patients with CLL with IgVH§ mutations, they were not perfect surrogate markers for IgVH§ mutation status — i.e., not all patients with mutated IgVH§ demonstrated over-expression of these three miRNAs. Marton et al. (2008) correlated expression levels of several miRNAs, including miR-15a, miR-16 and miR-29a, with IgVH§ mutation status. Stamatopoulos et al. (2009) found decreased expression of miR-29c and miR-223 correlated with progression of disease from Binet stage A to C, poor prognostic sub-groups defined by IgVH§ unmutated status, positive ZAP-70 expression and LPL expression and with treatment-free survival (TFS) and overall survival (OS). They also developed a quantitative RT-PCR score combining miR-29c, miR-223, ZAP70 and lipoprotein lipase (each given a score of 1), based on the finding that with a progressive score from zero to 4 the median TFS progressively decreased from 312 months to 12 months. Over-expression of miR-21 and low miR-181b expression have been reported as unfavorable prognostic factors independent of other clinical-pathologic factors (Rossi et al., 2010). Based on high miR-21 expression and del(17p) analysis by either karyotype or FISH, Rossi et al. (2010) developed a “21FK” score [1 point each for high miR-21 and 17p deletion; 0 points each for low miR-21 and normal karyotype/normal FISH] and found that the survival of patients with a score of 0/2 was significantly higher than those with 0/1 and 2/2, even in low Rai stage patients. In multivariate analysis including beta-2-microglobulin, ZAP-70, IgVH§, CD19+ and CD38+, the “21FK” score was associated with the lowest P value.

Chemo-resistant CLL: 17p deletion, p53 and miR-34a

TP53, located at the 17p13.1 locus, is the gene that encodes the tumor-suppressor protein p53, which is a stress—response protein activated by genetic instabilities or cytotoxic signals. p53 plays a central role in regulating the cell cycle and apoptosis by up-regulating a number of genes which generally arrest the cell cycle, including p21 (which causes G1-arrest) and PUMA (which induces apoptosis), or down-regulating cyclin dependent kinases (CDK4) and cyclins (Cyclin E2) (Vosden and Lane, 2007). CLL patients with loss of TP53 via 17p deletions are resistant to treatment with fludarabine and have poor clinical outcomes (Grever et al., 2007). Zenz et al. (2009) showed that monolellic p53 inactivation is associated with poor prognosis, and survival was equally poor for patients with 17p deletion only, 17p deletion plus TP53 mutation, and TP53 mutation only. In 2007 several groups demonstrated that members of the miR-34 family are direct p53 targets. miR-34 genes are up-regulated by p53, and their over-expression in turn causes senescence, apoptosis, or cell cycle arrest by regulating proteins such as BCL2, Cyclin D1, Cyclin E2, CDK4, and c-MYC Sirt-1, depending on the cell type (Bommer et al., 2007; Chang et al., 2007; Corney et al., 2007; He et al., 2007; Raver-Shapira et al., 2007; Tarasov et al., 2007; Tazawa et al., 2007). Two independent studies suggested that p53 mutations are equivalent to p53 deletions in that both lead to low miR-34a expression and hence are associated with impaired DNA damage response, apoptosis, and fludarabine refractory CLL disease (Rossi et al., 2010; Zenz et al., 2009).

In a recent study, Asslaber et al. (2010) found that miR-34a expression in transgenic Equ-TCL1 mice in the preleukemic phase was comparable to that of wild-type littermate controls. However, miR-34a expression increased more than 20-fold in the leukemic phase, suggesting that p53 expression was highly up-regulated during this transition. This was further confirmed by increased p21 and PUMA mRNA levels, the downstream effectors of p53. In the same study human B-CLL blood samples showed a 4.6-fold increase in miR-34a expression compared to controls. These increases in miR-34a expression were mostly in patients with wild-type TP53 while those patients with either TP53 mutations or 17p deletions consistently showed low miR-34a levels. Asslaber et al. also showed that low miR-34a levels predicted shorter time to treatment. In further transfection experiments with synthetic oligonucleotides that mimic mature miR-34 transcripts in B-CLL cell lines, they found that miR-34a could induce apoptosis only in patients without ‘p53 attenuation’ indicating that the apoptosis-inducing effects of miR-34a require p53 activation and suggests a positive feedback loop between miR-34a and p53. In some patients decreased miR-34a is seen without p53 aberrations. These patients were homozygous for the single nucleotide polymorphism 309 (SNP309) in the intronic promoter of MDM2, a negative regulator of p53. These findings led Asslaber et al. to recommend miR-34a as an easily detected surrogate marker for any deregulation in the p53 pathway, including mutations or deletions of TP53 or its upstream regulators.

The above studies indicate that the p53 tumor-suppressor pathways and associated miR-34a expression may be a promising avenue of research into the pathogenesis and prognostic assessment of CLL and may prove more useful in aiding early-stage identification of patients with fludarabine-refractory CLL.

Conclusions

The rapid advancement of miRNA research in just the past few years suggests that the roles of many more miRNAs in CLL have yet to be discovered. For instance, the miR-17-92 cluster is a group of miRNAs that have been studied in a wide variety of cancers. This miR-17-92 cluster consists of the seven miRNAs: miR-17-5p, miR-17-3p, miR-18, miR-19a, miR-20, miR-19b-1 and miR-19b-2 transcribed from the MIR17 Host Gene (MIR17HG) at locus 13q31.3, and members of this cluster are thought to coexpress with the proto-oncogenic transcription factor MYC (He et al., 2005). In addition, one study suggests that miR-17-5p and miR-92 are up-regulated by TP53 activation, albeit to much less of an extent than miR-34a (Tarasov et al., 2007). Several profiling studies show that expression of members of the miR-17-92 cluster is altered to some degree in CLL (Fulci et al., 2007; Calin et al., 2004).

miRNA research will likely have an increasing influence in the diagnosis, prognosis and treatment of human cancers, including CLL. In CLL, miRNAs such as miR-21c, miR-223, miR-21 and miR-34a, may prove to be novel surrogate markers for common cytogenetic lesions and prognostic indicators such as IgVH§ mutation status (Calin et al., 2005; Fulci et al., 2007; Rossi et al., 2010). In addition, the discovery of the oncogenic and tumor-suppressive properties of various miRNAs raises the possibility of miRNA therapy in the future. Experiments in RNA-interference therapy are already underway (Bumrcot et al.,...
2006), and it is not hard to imagine scenarios in which oligonucleo-
tides that mimic the activities of natural miRNAs might be employed in
antitumorigenic applications. Conversely, Krutzfeldt et al. (2005)
developed “antagonims” — synthetically-manufactured oligonucleo-
tides that are designed to silence oncogenic miRNAs via complementa-
tory base pairing. The oncogenic pathways involving miRNAs are
highly complex, subtle, and multifaceted, raising questions as to the
practical limitations and unintended consequences of miRNA-based
therapies. Though caution is warranted, miRNAs remain one of the
most exciting new avenues for cancer research.

References

SEER data submission, posted to the SEER website.


