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REVIEW

Understanding the role for miRNA in human leukemia

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The biological function of short non-coding RNAs known as micro RNAs (miRNAs) is unravelling to uncover a complex arrangement within every cell whereby they modulate most cellular responses. There has been much investigation as to the influence of miRNA on cell signalling processes and their cellular effects. Moreover, recently miRNA have been implicated in both physiological responses, as well as having critical roles in a variety of diseased states. The effects of these unique biochemical regulators are often subtle, but decisive with regards to a cell's pathophysiology and disease. Researchers have investigated both the regulation of signalling pathways by miRNA, but also the regulation of miRNA generation processes by signalling steps themselves. There exists an interesting interrelationship whereby miRNA can reinforce a cell's signalling effects. Thus miRNA have a role in normal cell physiological functioning. Aberrant miRNA generation would therefore lead to unruly signalling activity through which disease often results from such dysregulation. We will review the roles for miRNA here with emphasis on their function in human leukemia. Better understanding of these mechanisms that underlie pathologically-relevant signalling alterations that create cancer or are involved in cancer chemotherapy-resistance, will lead to better targeting and treatments for not only leukemia, but all relevant cancers.

Keywords: MicroRNA; miRNA; leukemia; acute myeloid leukemia; AML; CLL; NRF2; miR-125b; mir-29b

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Introduction

MicroRNA (miRNA) are 20-24 short non-coding RNA molecules that bind and repress their target mRNA. The pri-miRNA is transcribed in the nucleus by RNA polymerase II. The pri-miRNA contains a hairpin structure which is cleaved off by the enzyme Drosha leaving a 60-70 nucleotide precursor miRNA (pre-miRNA). The hairpin contain the mature miRNA sequence. The pre-miRNA undergoes cytoplasmic translocation by Exportin 5, and is processed by the Dicer/TRBP complex leaving the mature miRNA. Traditionally, one strand will incorporate with the RNA-induced silencing complex (RISC), thus allowing the miRNA to target the 3'UTR of its target mRNA (through complementary base paring). High levels of complementary base pairing result in double stranded mRNA, causing mRNA degradation, while lower levels result in the inhibition of the mRNA translation machinery (the primary method in humans) [1].

Studies have shown miRNA can play an important role in most cellular processes including migration, differentiation,

apoptosis and proliferation [2]. It is therefore not inconceivable that when dysregulated they will be crucial in the pathogenesis and disease generation mechanisms. miRNAs have already shown to play an important role in haematopoiesis (and in physiological processes in general) which is highlighted by mice embryos containing Dicer knockouts being embryonically lethal, which shows their importance and role within organisms[3]. In this review we will be looking at the use of miRNA as prognostic tools and biomarkers in leukemia. We shall also be discussing their importance and function in various leukemia subtypes, plus how their understanding and regulation may prove useful in combatting diseases such as cancer or its treatment resistance.

Acute Myeloid Leukemia

Acute Myeloid Leukemia (AML) is a cancerous disease of blood cells which is characterised to the excess proliferation of myeloid progenitor cells, leading to the accumulation of blasts in the bone marrow. AML is a heterogenous disease comprising of a variety of genetic disorders (which include molecular abnormalities such as FLT3-ITD or WT1 mutations, and chromosomal abnormalities such as t(11q23) or t(8;21). While the majority of AML cases are due to chromosomal translocation, a large number are cytogenetically normal and are therefore characterised by their genetic abnormalities. Common mutations include nucleophosmin 1 (NPM1), CCAAT/enhancer binding protein alpha (CEBPA), runt- related transcription factor 1 (RUNX1), and fms-related tyrosine kinase 3 (FLT3)[4].

MiRNA expression patterns have been shown to successfully discriminate between different subtypes of leukemia. One study used a genome-wide miRNA expression profile between acute lymphocytic leukemia (ALL) and AML, and identified 27 different miRNAs that displayed significant differential expression between these two disease subtypes. The most significant being miR-28a/b which had low expression, along with the miRNAs let7-b and miR-223 which were overexpressed in AML compared to ALL. Furthermore, these four miRNAs alone were adequate to accurately distinguish between AML and ALL, allowing them to be considered almost as biomarkers between these human leukemic disease subtypes [5].

Studies have identified miRNA alterations in AML (compared to control cells) and between a range of AML subtypes. One study investigated miRNA expression in 29 primary AML samples containing a range of common abnormalities [6]. They found each AML subtype had its own individual miRNA profile. AML/ETO (a fusion protein produced as a result of t(8:21)) for example, caused upregulation in 4 miRNA (miR449b, miR-320, miR-126 and miR-328) and a concurrent downregulation in 13 miRNAs (miR-9, miR-196a, miR-10a, miR-135a, miR-125b, miR-148a, miR-133a, and miR-221) compared to the other AML subtypes. Another study identified downregulation of 26 different miRNAs across 122 primary AML patient samples (compared to CD34+ control cells) using a miRNA microarray-based approach to study the disease. miRNA expression was also compared between different AML subtypes and compared to the prognosis. As with the previous study there was variation in miRNA expression dependent on the associated molecular abnormality signature. AML with 11q23 translocation was observed to have a lower expression of the miRNA, miR-196 [7]. miR-196 has previously been implicated in regulating HOXB8. The HOXB8 gene can be considered an oncogene in AML, whereby is plays a crucial role in preventing myeloid differentiation and preventing cellular apoptosis through the repression of the pro-apoptotic gene BIM. Interestingly, HOXB8 targets BIM through the upregulation of the miRNA cluster miR-17-92, The exact mechanisms of HOXB8 regulation of miR-17-92 are elusive but are believed to be indirect via c-Myc function [8]. miRNA signatures were also identified from patients with cytogenetically normal AML, where 13 miRNA had lower expression (miR-126, miR-203, miR-200c, miR-182, miR-204, miR-196b, miR-193, miR-191, miR-199a, miR-194, miR-183, miR-299 and miR-145) and 10 were upregulated (miR-10a, miR-10b, miR-26a, miR-30c, let-7a-2, miR-16-2, miR-21, miR-181b, miR368, and miR-192 [7]. Together these studies correlated miRNA expression to different subtypes of AML suggesting that one day some subtypes of AML could be diagnosed on the miRNA pattern alone.

Moreover, miRNA expression is also a useful marker to identify disease progression and prognosis. Garzon *et al* correlated miRNA expression to prognosis they identified high expression of miR191 and miR-199a to poor prognosis in AML[7]. Another study in CN-AML identified miR-181a as another prognostic marker, higher levels of miR-181a was a good indication for a less severe prognosis and a lower chance of relapse [9].

Outside of the microarray studies already discussed, several miRNA families have been implicated in AML. miR-155 is a known oncomiR, which is a miRNA that promotes carcinogenic mechanisms in cells, usually by repressing tumor suppressor genes. The converse of this is a tumor suppressor miRNA, which is anti-oncogenic in nature by inhibiting expression of cellular oncogenes. In AML, miR-155 is processed from its parent gene miR155HG, which is located on chromosome 21 [10]. One study identified miR-155 upregulation in subtypes of AML

patients (acute myelomonocytic leukemia and acute monocytic leukemia, of FAB subtypes M4 and M5), and ectopic overexpression in mice resulted in a myeloproliferative (pre-leukemic)-like disease. The study went on to identify several mRNA targets thought to be important in AML, including PU.1, CEBPα and Picalm [11]. This is important as PU.1 is an AML tumour suppressor thatis mutated in 7% of AML patients (primarily monocytic or undifferentiated leukemia) leading to inhibition of differentiation [12].

As with most miRNA, the role of the miR-125 family is tissue-specific, however it has been characterised as an oncomiR in leukemia (13). The miR-125 family exists as three homologues (miR-125a,b, and c) all on different chromosomes. miR-125b exists as two paralogs, miR-125b1 and miR-125b2 (both contain the same seed region but are located on different chromosomes and therefore can be regulated independently) [13]. To date miR-125b remains the most well characterised member of the miR-125b family in leukemia. miR-125b-1 is overexpressed in AML cells, in particular patients with the t(2:11)(p21:q23) translocation, which showed up to a 90 fold increase in miR-125b-1 levels [14]. Ectopic overexpression of miR-125b in mice lead to them developing leukemia. The specific leukemic subtype developed was dependent on the level of miR-125b. Furthermore, its upregulation is sufficient to shorten the latency of the BCR-ABL protein in mice. While this finding on BCR-ABL is less important in the context of AML, it helps to highlight miR-125b's role as an oncomiR in blood cancers [15].

Conversely, miR-29b is a well characterised tumour suppressor miRNA in AML. The miR-29 family exists as three homologues (miR-29a/b/c) on different chromosomes.miR-29b also exists as two paralogs (miR-29b1 and miR-29b2). Members of the miR-29 family were found to be downregulated in a range of AML samples [7], and ectopic overexpression of miR-29b in both primary AML samples and in AML cell lines caused their apoptosis. Furthermore, when synthetically injected into xenografts, their resultant tumour size was reduced, again showing its tumour suppressor role [16]. miR-29b targets anti-apoptotic genes such as MCL-1, which is itself usually upregulated in AML, thus providing one mechanism for miR-29b's role as a tumour suppressor miRNA[16].

The transcription factor nuclear factor (erythroid-derived 2)-like 2 (NRF2) plays an important role in protecting cells from reactive oxygen species (ROS). In AML, NRF2 is constitutively activated and has shown to play an important role in protecting cells from front-line chemotherapeutic agents through its regulation of antioxidant genes [17]. Our recent study has shown NRF2 can positively regulate miR-125b1 and negatively regulate miR-29b1 in both AML cell lines and primary patient samples (18). NRF2 regulation of miRNA was shown to increase resistance to front-line chemotherapy drugs. This chemo-resistance was nullified when these cells were treated with a miR-125b antagomiR and miR-29b mimic. AntagomiRs and miR-mimics are short sequence RNAs that can be used as tools to inhibit or mimic cellular miRNA functions respectively. Interestingly, the most significant increase in sensitivity towards chemotherapy was shown when both miRNA were simultaneously targeted at the same time, suggesting NRF2 synergistically regulates both miRNA classes. We believe the downstream miRNA pathways that are most likely being targeted are AKT2 and BAK1 signalling pathways [18].

Chronic Myeloid Leukemia

Chronic Myeloid Leukemia (CML) disease is caused by the excess proliferation of myeloid cells, of a more defined cytogenetic profile. CML is primarily characterised by the BCR-ABL chromosomal translocation that results in uncontrolled proliferation. Briefly, the breakpoint cluster region (BCR) on chromosome 22 translocates with the Abelson (ABL) tyrosine kinase gene on chromosome 9, thereby creating the BCR-ABL fusion gene (known as the Philadelphia chromosome).BCR-ABL oncoprotein is also a tyrosine kinase with constitutive activity, which drives myeloid cellular proliferation as well as repressing apoptosis [19]. Unlike AML, CML is a relatively slow developing disorder and is characterised by three phases: chronic, accelerated and blast crisis. Blast crisis is the final stage of CML, where myeloid cells accumulate and cause differentiation arrest (more similar in nature to AML). Unlike chronic phase CML, once blast crisis has been reached patients become unresponsive to chemotherapy agents and prognosis is unfavourable. Before blast crisis, Philadelphia chromosome-positive CML, is treated tyrosine kinase inhibitors, such as imatinib, nilotinib or dasatinib[19].

One study by Rokah *et al* used a miRNA array to characterise miRNA expression in CML cell lines and patient samples. Several dysregulated miRNAs were identified in cell lines. After their further analysis to ensure that the dysregulation was CML-specific with confirmation in primary patient cells, three miRNA were identified (miR-31, miR-155 and miR-564) to be downregulated. After 30 days of BCR-ABL inhibition (by imatinib) upregulation was observed in all three miRNA indicating BCR-ABL must at least partly play a role in repressing these miRNA. Target analysis identified several genes that these miRNAs can regulate including KRAS, AKT2, E2F3, CBL and cyclin D1. These target genes also showed increased expression in

CML, suggesting an inverse correlation between the miRNA and their targets (as would be expected). All four gene targets are well characterised oncogenes thus giving insight into a mechanism that would promote a more aggressive CML phenotype [20].

Another study identified miR-96 upregulation, and miR-120, miR-151 and miR-10 downregulation in CML. Conversely, miR-10 downregulation was shown to be independent to BCR-ABL signalling, the method of miR-10 inhibition remains elusive, with no evidence of methylation or mutation that could be found. USF2 was however identified as a downstream target of miR-10, when miR-10 was overexpressed in CML cells both a decrease in USF2 and a lack of cell proliferation was found indicating miR-10 plays an important role in CML [21]. miR-10 is also downregulated in most AML subtypes with the exception of patients with NPM1 mutations in which it curiously overexpressed [22,23].

Until relatively recently the prognosis for CML patients was poor, with the majority inevitably reaching blast crisis. CML treatment has been revolutionised by tyrosine kinase inhibitors (TKI) most notably imatinibmesylate (Gleevec), which works by inhibiting the BCR-ABL by binding to the ATP docking site of its tyrosine kinase motif, thereby causing apoptosis in the CML cell expressing the Philadelphia chromosome. A small but significant number of patients do however suffer from imatinib resistance[24]. One study aimed to identify miRNA expression in response to imatinib, they found a decrease in (miR-142-3p and miR-199b-5p) and an increase in (miR-146a and miR-150) [25]. miR-150 for example has shown to be involved in Myb regulation (a critical oncogene in CML)[26].miR-146 upregulation targets members of the NF-κB pathway (IRAK1/TRAF6)that are found to be constitutively activated in CML by BCR-ABL [27]. Furthermore, inhibiting the NF-κB pathway in CML results in apoptosis, suggesting that the upregulation of miR-146 post-imatinib treatment makes CML cells more sensitive to apoptotic signalling[28].miR-199b on the other hand is downregulated in response to imatinib treatment. One miR-199b target is HES1 (a target of the notch signalling pathway) which represses proliferation in meduloblastoma cells [29]. However Notch/Hes1 have been implicated in repressing proliferation in CML, which indicates miR-199b-5p may be inhibiting Hes1 to promote cancer growth in CML [26].

As previously mentioned, blast crisis is the most severe stage of CML, and despite advances in treatment, even today prognosis remains poor. One study identified miR-328 as downregulated in blast crisis and when re-expressed causes differentiation by restoring CEBPA expression (through interacting with hnRNP). Interestingly CEBPA expression was able to positively regulate miR-328, thereby indicating the existence of a positive feedback loop, thus in CML hnRNP represses miR-328 via CEBPA silencing thereby aiding the pathogenesis in blast crisis. Conversely miR-328 does not silence hnRNP but instead prevents it from binding to CEBPA protein [30].

Acute Lymphocytic Leukemia

Acute Lymphocytic Leukemia (ALL) is defined by excess proliferation of lymphoid progenitor cells from either a B or T cell lineage. Unlike other leukemic subtypes, ALL primarily affects children and young adults [31]. One study aimed to characterise miRNA expression in the ALL subtype pre B-ALL using a combination approach of microarrays, qRT-PCR and bioinformatics. miR-451 and miR-373* were downregulated, while an increase in miR-222, mIR-339 and miR-142-3p was identified in pre-B-ALL cells compared to control CD19+[32]. Another study focussing in childhood ALL identified dysregulation in several miRNA which included an upregulation in the miR-181 family, miR-34, miR-193 and a downregulation in miR-196, miR-125b, miR-100 [33]. The oncogenic protein c-Myc is a key miR-196 target, which is upregulated in B-ALL due to t(8;14)(q24;32) translocations. In B-ALL miR-196 overexpression results in the decreased expression in c-Myc (and its associated genes) along with a significant increase in apoptosis [34]. Conversely, despite miR-196 being downregulated in T-ALL, it is unable to target c-Myc due to a mutation in the 3'UTR of the miR-196/c-Myc binding region [35]. miR-196 is located between HOXA9 and HOXA10, and has an oncogenic role in leukemia patients characterised by a HOXA mutation, including mixed-lineage leukemia (MLL) and T-ALL. It is also possible to identify between different ALL subtypes (B-ALL and T-ALL) using miRNA signatures: miR-151 (downregulated in T-ALL), miR-148a and miR-424 (both highly expressed in T-ALL) could all be used to discriminate between these two leukemic subtypes [36]. Furthermore, it is possible to distinguish between B-ALL subtypes using miRNA expression, as exemplified by miR-629 having high expression in MLL-AF4, miR-425-5p miR-191 and miR-128 being highly expressed in E2A-PBX1. BCR-Abl also generates higher expression of miR-146b and miR-126.

Prognosis can be tested by miRNA expression. For example, miR-223 and miR-27a were upregulated in patients who were in ALL remission while miR-708 was upregulated in relapsed patients [37]. Target analysis suggested miR-27a may be targeting protein BMI-1, which has been implicated in survival and self-renewal in leukemic stem cells [38]. It can also target MDR1 (multidrug-resistance gene) [39]. Their repression by miR-23a would be detrimental to leukemic cell

survival. miR-708 will also repress FOXO3 expression, which has a dual oncogene/tumour suppressor role in cancer. Curiously, this study identified low levels of FOXO3 in patients with a high risk of relapse but high levels in patients who have actually relapsed [37]. Studies in CML has identified FOXO3 as critical for maintaining the leukemic initiating cells in that disease, with its removal decreasing the ability of leukemic initiating cells [40]. The interaction between miR-708 and FOXO3 still remains speculative.

Chronic Lymphocytic Leukemia

Chronic Lymphocytic Leukemia (CLL) is the most common leukemia subtype worldwide. CLL comes about by the excessive proliferation and accumulation of lymphocytes in the bone marrow, blood and lymph nodes. CLL is characterised usually with abnormal B cell receptor (BCR) signalling function. Briefly, antigen binding to BCR causes signal transduction by phosphorylating ITAMs and recruitment of SYK tyrosine kinase, which activates Bruton's Tyrosine Kinase (BTK) through PI3K.BTK can activate downstream targets such as NF-κB, which is done through PLCγ2 activation. Various prognostic markers exist for CLL including mutational status of IGHV and expression levels of ZAP70. High expression of ZAP70 and/or no mutation in IGHV results in a poorer prognosis in patients [41].

miRNA expression could be a useful tool for diagnosis in CLL. One study aimed to identify miRNA expression between CLL patients and control cells, finding changes in expression levels of several miRNA including miR-123, miR-10b, miR-181b, miR-192, miR-220, miR-155 and miR-213.This study also suggested miRNA can be used to distinguish between both IgHv mutations and ZAP70 levels [42].

Several miRNA have been functionally implicated in CLL. miR-15a/16 is a tumour suppressor miRNA that is downregulated in CLL[43]. It is located on 13q14.3 (an area commonly deleted in CLL as well as various other cancers).Using a bioinformatics approach, the mitochondrial integrity protein BCL2 has been identified as a miR15a/16 target, being confirmed via reporter assays [44]. In CLL, BCL2 is a well characterised oncogene that represses apoptosis in cancer. The luciferase reporter assay used showed miR-15a/16 have the ability to inhibit BCL2, and when miR-15a/16 is artificially overexpressed a marked increase in apoptosis was seen [44]. Conversely, one study identified a proportion of CLL cases without 13q14.3 deletion, yet miR-15a/16 were still poorly expressed [45]. This may however be due to HDAC-mediated silencing of the miR15a/16 region (along with miR-29b) [46].

As in AML, miR-155 is overexpressed in CLL [42], and is highly expressed in patients who respond poorly to treatment or are unresponsive to fludarabine chemotherapy[47].miR-155 can be regulated by several proteins including the Myb (an oncogene involved in CLL) and Smad4 (a member of the TGFβ family) [48,49]. miR-155 can target the tumour suppressor PU.1 which in addition to being a key tumour suppressor in AML (as discussed above) is additionally important in CLL. miR-155 can also target the phosphatase SHIP1, which reduces BCR sensitivity. Indeed, miR-155 inhibition in CLL resulted in a decreased sensitivity in BCR ligation, thus providing an interesting relationship between miR-155 and BCR. Furthermore, this study identified miR-155 as upregulated in the lymph nodes of CLL patients, but down-regulated when the CLL lymphocytes egress into the bloodstream [50].

Conclusions

In summary, we have highlighted a broad network of miRNA expression in human leukemia. Some have oncogenic activity while others a have tumor suppressive role. What needs to be explored next is whether we have the technology to target these dysregulated miRNA in a clinical disease setting such as leukemia. Alternatively, if this is an unworkable strategy we could use the expression profiling to inform the clinic on diagnosis and prognosis of the disease, or maybe allow for more targeted chemotherapy treatment.

Conflict of interest

The authors declare no conflict of interest.

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