Chapter 6
MicroRNAs and Blood Cancers

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Contents

Abstract Despite having been only formally recognized for just over 10 years, microRNAs (miRNAs) have become one of the trendiest topics in biology. It is now clear that dysfunctional expression of miRNAs is a characteristic of many, if not all, hematological malignancies. Many of the miRNAs aberrantly expressed in hematological malignancies also play a crucial regulatory role in normal hematopoietic

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function. In this chapter we review the evidence for this assertion in particular focusing on the use of miRNAs as novel tools for biomarkers and therapeutic agents against hematological malignancies.

Keywords Hematological malignancies • Leukemias • Lymphomas • MicroRNA • Biomarker

1 Introduction

MicroRNAs (miRNAs) are a recently discovered class of naturally occurring short non-coding (18–24 nt) RNA molecules that regulate eukaryotic gene expression post-transcriptionally. There are now nearly 2,000 human miRNAs that have been identified through cloning and/or sequence analysis (http://www.mirbase.org) (Griffiths-Jones et al. 2006), and it is believed some 60 % of all human genes are a target for miRNA regulation (Friedman et al. 2009). MiRNAs have been shown to play key regulatory roles in virtually every aspect of biology including developmental timing, cell differentiation, apoptosis, cell proliferation, metabolism organ development, and hematopoiesis (Kim 2005). The potential importance of miRNAs in cancer is implied by the finding that the majority of human miRNAs are located at cancer-associated genomic regions (Calin et al. 2004b). The first indication that dysregulation of miRNAs was associated with hematological malignancies came from the seminal publication by Calin et al in 2002 (Calin et al. 2002), that made the connection between 13q14, a frequently deleted locus in chronic lymphocytic leukemia (CLL), and down-regulation of the miR-15a/16 cluster that is encoded within this region. There is now overwhelming evidence that dysfunctional expression of miRNAs is a common, if not ubiquitous, hallmark of cancer in general including haematological malignancies (Lawrie 2008; Iorio and Croce 2009).

The reasons for aberrant expression of miRNAs in hematological malignancies (and other cancers) are numerous, and can include chromosomal aberrations, epigenetic deregulation, aberrant expression of transcription factors that regulate promoter regions of miRNAs, and factors that change miRNA biosynthesis or function (Croce 2009; Babashah et al. 2012). Many of the miRNAs that are aberrantly expressed in hematological malignancies are also key regulators of hematopoiesis (Table 6.1, Fig. 6.1), and in order to fully understand the role of these miRNAs in the pathogenesis of these cancers it is crucial that we first understand their role under physiological conditions.

2 Role of MicroRNAs in Hematopoiesis

The process by which hematopoietic stem cells (HSC) maintain their pluripotency whilst at the same time responding to lineage determining signals to differentiate into the various hematopoietic lineages is a finely balanced process tightly

Table 6.1 Major microRNAs involved in hematological malignancies showing known roles in hematopoiesis, validated target genes and representative animal model

MicroRNA	Hematopoiesis	Malignancy	Target	Animal model
miR-155	B/T-cell development	DLBCL, BL, AML	HGAL, RTKN2 (Dagan et al. 2012); SMAD5 (Rai et al. 2010); PIK3R1 (Huang et al. 2012); SHIP (Pedersen et al. 2009); PU.1, CD10 (Thompson et al. 2011); AID (de Yebenes et al. 2008; Teng et al. 2008)	Eμ-enhancer expression → lymphoma (Costinean et al. 2006); Inducible miR-155 knock-in model (Babar et al. 2012) Engraftment of miR-155 HSCs → myeloid (O'Connell et al. 2008)
miR-17-92	B-cell development	B-cell lymphoma, CML, ALL, MCL	BIM, PTEN (Xiao et al. 2008); E2F1 (Woods et al. 2007); PP2A, PRKAA1 (Xiao et al. 2008; Ventura et al. 2008; Mu et al. 2009; Mavrakis et al. 2010); PHLPP2 (Rao et al. 2012); CCND1 (Chen et al. 2008; Deshpande et al. 2009)	miR-17-92 expression alone → lymphoproliferative/autoimmunity (Xiao et al. 2008) miR-17-92 along with MYC (Eμ-MYC) → lymphoma (He et al. 2005)
miR-34a	B-cell development	B-cell lymphoma	SIRT1 (Yamakuchi and Lowenstein 2009); MYC (Sotillo et al. 2011); FOXP1 (Craig et al. 2011a)	Xenotransplant model of ABC-type DLBCL inoculated with synthetic miR-34a (Craig et al. 2012)
miR-125	Myelopoiesis	DLBCL, ALL, MDS, AML	IRF4, PRDM1 (Malumbres et al. 2009); TNFAIP3 (Kim et al. 2012); LIN28A(Chaudhuri et al. 2012)	Eμ-enhancer expression → lymphoblastic leukemia/lymphoma (Costinean et al. 2006)
miR-223	Myelopoiesis, erythropoiesis, granulopoiesis, B-cell development	MALT, SzS	MEF2C (Johnnidis et al. 2008); LMO2 (Malumbres et al. 2009); NFIA, CEBPA (Fazi et al. 2005); E2A(Liu et al. 2010)	
miR-150	Myeolopoiesis, Megakaryopoiesis, B/T-cell development, NK cell development	MDS, MALT, NK/T-cell lymphoma	MYB (Zhou et al. 2007; Monticelli et al. 2005) NOTCH3 (Ghisi et al. 2011); DKC1, AKT2 (Watanabe et al. 2011)	

(continued)

Table 6.1 (continued)

MicroRNA	Hematopoiesis	Malignancy	Target	Animal model
miR-181	B/T-cell development	AML, CLL	AID, BCL2, CD69, TCRα, DUSP5, SHP2, PTPN22 (de Yebenes et al. 2008; Teng et al. 2008; Neilson et al. 2007)	
miR-221/222	Erythropoiesis		KIT (Felli et al. 2005)	
miR-15a/16-1		CLL, B-ALL, ALCL	BCL2, MCL1, CDK6 (Cimmino et al. 2005); TP53 (Fabbri et al. 2011); HIF-1A (Dejean et al. 2011); CCND1(Chen et al. 2008; Deshpande et al. 2009)	NZB strain (Raveche et al. 2007); MDR and miR-15a/16-1 deletions (Klein et al. 2010); CDR deletion (Lia et al. 2012)
miR-21		B-cell lymphoma, NK/T lymphoma, SzS	PDCD4, PTEN (Yamanaka et al. 2009); STAT3 (van der Fits et al. 2011); ANP32A, SMARCA4 (Schramedei et al. 2011)	Inducible miR-21 knock-in model (Medina et al. 2010)
miR-29a	Early HSC development	AML, CLL, MCL	HBP1 (Han et al. 2010); TCL1 (Pekarsky et al. 2006)	
miR-124a	Myelopoiesis	AML, ALL	EVI1, CEBPA (Hackanson et al. 2008); CDK6 (Agirre et al. 2012)	

Abbreviations: *AID* activation-induced cytidine deaminase, *ALCL* anaplastic large cell lymphoma, *ALL* acute lymphoblastic leukemia, *AML* acute myeloid leukemia, *ANP32A* acidic nuclear phosphoprotein 32 family member A, *BCL-2* B-cell leukemia/lymphoma-2, *BL* Burkitt lymphoma, *CCND1* Cyclin D1, *CDK6* Cyclin-dependent protein kinase 6, *CEBPA* CCAAT/enhancer binding protein alpha, *CLL* chronic lymphocytic leukemia, *CML* chronic myeloid leukemia, *DKC1* dyskeratosis congenita gene 1, *DLBCL* diffuse large B-cell lymphoma, *DUSP5* dual-specificity phosphatase 5, *E2F1* E2 transcription factor family-1, *EVI1* ecotropic virus integration 1, *FOXP1* Forkhead Box P1, *HBP1* HMG box-containing protein 1, *HGAL* human germinal-center associated lymphoma, *HIF-1A* hypoxia-induced factor 1α, *HSC* hematopoietic stem cells, *IRF-4* interferon regulatory factor 4, *LIN28A* Lin-28 Homologue A, *LMO2* LIM-only protein 2, *MALT* mucosa-associated lymphoid tissue, *MCL1* myeloid cell leukemia 1, *MDS* myelodysplastic syndrome, *MEF2C* myocyte enhancer factor 2C, *MYB* myeloblastosis, *NFIA* nuclear factor I-A, *NK* natural killer, *NZB strain* New Zealand Black strain, *PDCD4* programmed cell death 4, *PHLPP* PH domain leucine-rich repeat protein phosphatase 2, *PIK3R1* phosphatidylinositol 3-kinase regulatory subunit alpha, *PP2A* protein phosphatase 2, *PRDM1* PR domain zinc finger protein 1, *PRKAA1* AMP-activated protein kinase catalytic subunit alpha-1, *PTPN22* protein tyrosine phosphatase, non-receptor type 22, *PTEN* phosphatase and tensin homolog, *RTKN2* rabbit polyclonal anti–Rhotekin 2, *SHIP* the SH2-domain-containing inositol 5-phosphatase, *SIRT1* Sirtuin 1, *SMARCA4* SWI/SNF-related, matrix-associated, actin-dependent regulator chromatin, subfamily A, member 4, *STAT3* signal transducer and activator of transcription 3, *SzS* sézary syndrome, *TCL1* T-cell leukemia 1, *TCRα* T cell receptor alpha, *TNFAIP3* tumor necrosis factor-alpha-induced protein 3

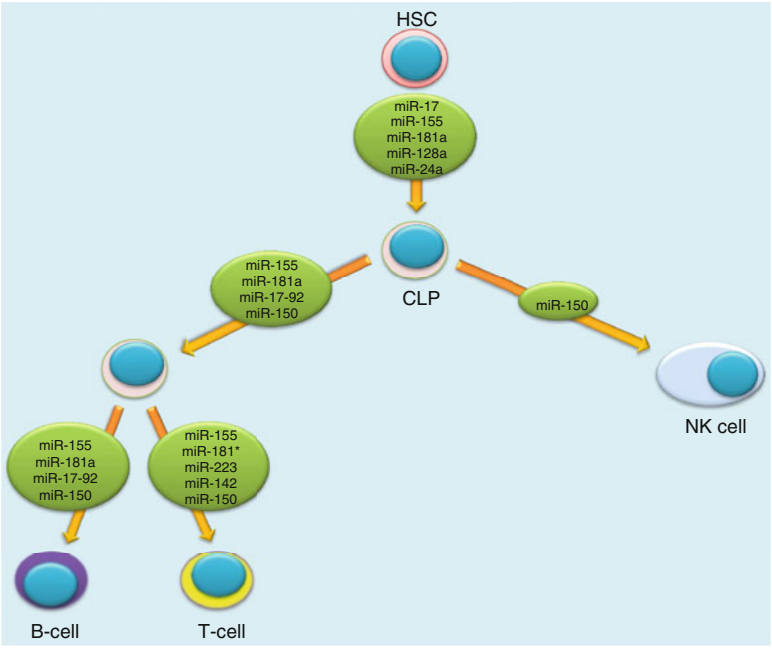

Fig. 6.1 Role of miRNAs in lymphopoiesis. For more details, see the text. *HSC* hematopoietic stem cell, *CLP* common lymphoid progenitor

controlled by a complex network of extrinsic and intrinsic stimuli, signaling pathways, growth factors, cytokines, transcription factors and other molecular components. MiRNAs have can target a great many of these factors and more generally can determine HSC fate, differentiation state and function, self-renewal ability, apoptosis levels as well as the balance of myeloid and lymphoid progenitor cells (Georgantas et al. 2007).

The general necessity of miRNAs in hematopoiesis has been demonstrated by multiple animal models. For example, deletion of Dicer in the thymus caused severe block in peripheral $CD8^+$ development and reduced numbers of $CD4^+$ cells which when stimulated underwent increased apoptosis and proliferated poorly (Cobb et al. 2005; Muljo et al. 2005). In contrast, when Dicer was deleted in HSCs this led to an increase in apoptosis and a reduction in hematopoietic ability (Guo et al. 2010). At the early progenitor stage, $CD34^+$ HSCs derived either from bone marrow or peripheral blood compartments were found to commonly express 33 different miRNAs (Georgantas et al. 2007). Based on the predicted target genes for these miRNAs, as well as functional validation of 18 of these genes, it was proposed that miR-17, miR-24, miR-146, miR-155, miR-128 and miR-181 prevent the differentiation of early stage progenitor cells, whilst miR-16, miR-103 and miR-107 act later on, and miR-221, miR-222 and miR-223 control the terminal stages of hematopoietic development (Fig. 6.1).

2.1 Myelopoiesis

During the development of hematopoiesis HSCs give rise to lymphoid and myeloid progenitor cells that differentiate into the mature cells of the blood system. It was first noted in 2004 that miR-223 and miR-142 were specifically expressed in myeloid but not lymphoid cells (Chen et al. 2004). MiR-223 is expressed at low levels in $CD34^+$ and common myeloid progenitor (CMP) cells, increasing steadily in the granulocyte compartment, whilst expression is repressed in the monocyte lineage (Fazi et al. 2007). Myeloid transcription factors, PU.1 and CEBPA can activate miR-223 through direct binding to its promoter sequence while the erythroid transcription factor, GATA1 suppresses its expression (Fukao et al. 2007). Granulocytic differentiation regulation by miR-223 is mediated by inhibition of NFIA and CEBPA (Fazi et al. 2005), and miR-223 deficient mice display increased neutrophil numbers through targeting of MEF2 (Johnnidis et al. 2008). Additionally, miR-223 is involved in the regulation of erythropoiesis via LMO2 targeting (Felli et al. 2009). CEBPA can also be targeted by miR-328, which stimulates myeloid differentiation by decoying hnRNP E2 (Eiring et al. 2010). Conversely, miR-124a suppresses the myeloid lineage by inhibiting CEBPA (Hackanson et al. 2008). Ectopic expression of miR-29a in mouse HSC/progenitors resulted in acquisition of self-renewal capacity by myeloid progenitors, and biased myeloid differentiation (Han et al. 2010).

MiR-125 is highly expressed in human myeloblasts and promyelocytes, myeloid progenitor cell line 32D (Gerrits et al. 2012), and bone marrow-derived monocytes in response to antigen stimulation (Monk et al. 2010), but down-regulated in neutrophils (Sun et al. 2011). When miR-125b was inhibited in murine HSCs, lower levels of myeloid cells resulted and this effect could be phenocopied by inhibiting LIN28A (Chaudhuri et al. 2012).

The role of miRNA expression in erythropoiesis first came from a study of Choong et al who identified changes associated with progressing erythroid maturation in $CD34^+$ and K562 models (Choong et al. 2007). Afterwards many miRNA profiling studies have carried out [reviewed in Lawrie (2010)], however little consensus has been reached, primarily due to the many differing models of erythropoiesis used between studies. Felli and colleagues identified miR-221 and miR-222 as being highly expressed in $CD34^+$ cells but down-regulated in response to unilineage erythroid differentiation and targeting KIT (Felli et al. 2005). When miR-150 was expressed in $CD34^+$ cells cultured in the presence of thrombopoietin and Epo, an eight-fold increase of megakaryocytes was observed and transplanted bone marrow cells expressing miR-150 increased levels of megakaryocyte- colony forming units (CFUs) coupled with a decrease in erythroid-CFUs (Lu et al. 2008).

The miR-451/miR-144 cluster has been found to play a crucial role in erythropoiesis, with silencing of mir-451 in zebrafish causing a significant decrease in levels of erythroid markers coupled with severe anemia (Dore et al. 2008). MiR-451 is specifically expressed in erythrocytes and reticulocytes (Merkerova et al. 2008), and is the most highly expressed miRNA in mature erythrocytes, increasing >270-fold during erythroid-CFU culturing (Masaki et al. 2007). Expression of this

cluster is directly regulated by GATA1 binding (Dore et al. 2008). In turn, miR-451 up-regulates levels of β-globin (HBB) (Zhan et al. 2007), and down-regulates GATA2 (Pase et al. 2009).

2.2 Lymphopoiesis

The first indication that miRNAs were important to lymphopoiesis came from Chen et al. in 2004 who showed that reconstitution of lethally irradiated mice with miR-181 expressing HSCs led to a significant increase in B-cells and cytotoxic $CD8^+$ T-cells (Chen et al. 2004). Subsequently, miR-181 has also been shown to regulate levels of CD69, BCL2 and TCRα in T cell development (Neilson et al. 2007), as well as being responsible for T-cell receptor sensitivity (Li et al. 2007).

MiR-155 deletion in mice caused them to become immunodeficient, with B cells that produced reduced levels of immunoglobulins in response to antigen treatment, and T cells that produced decreased levels of IL2 and IFNG. Both of these effects were caused by PU.1 targeting (Rodriguez et al. 2007; Thai et al. 2007). *In vitro* activation of B cells or $CD4^+$ T cells, strongly up-regulates miR-155 expression, whilst miR-155 deficient activated B cells express a third of normal levels of TNF and lymphotoxin, and T cell differentiation becomes biased towards the T_h2 phenotype (Vigorito et al. 2007).

Another important regulator of lymphocyte differentiation is the miR-17-92 cluster whose targeted deletion leads to a blockage in pro- to pre-B cell development via BIM targeting (Ventura et al. 2008). As well as BIM, members of this cluster also target PTEN, PP2A and AMP-activated kinase (PRKAA1), all of which play important roles in immune cell development (Xiao et al. 2008; Ventura et al. 2008; Mu et al. 2009; Mavrakis et al. 2010). Similar to the miR-17-92 cluster, ectopic expression of miR-34a in HSCs inhibit the transition of pro- to pre-B cell by FOXP1 inhibition (Rao et al. 2010), as does miR-150 expression via MYB down-regulation (Zhou et al. 2007). miR-150 has also been shown to be down-regulated in response to T-cell stimulation by both T_h1 or T_h2 subsets (Monticelli et al. 2005), and linked to megakaryopoiesis, driving megakaryocyte-erythrocyte progenitor cells to differentiate into megakaryocytes instead of erythrocytes (Lu et al. 2008) (Fig. 6.1).

3 MicroRNA Expression in Myeloid Malignancies

The general importance of miRNA dysregulation to the pathogenesis of myeloid disorders is suggested by the fact that more than 70 % of all human miRNAs are encoded within regions of recurrent copy-number alterations in myelodysplastic syndrome (MDS) and acute myeloid leukemia (AML) cell lines (Starczynowski et al. 2011). Several mouse models have been developed that suggest a direct link between miRNA deregulation and myeloid disorders. Mice with deleted Dicer1 in osteoprogenitor cells developed abnormal hematopoiesis, MDS and eventual AML (Raaijmakers et al. 2010). In another study, two miRNAs (miR-145 and miR-146a) encoded on 5q, a frequently deleted locus in myeloid disorders, were deleted in

murine HSCs. These mice developed mild neutropenia, megakaryocytic dysplasia and a subset progressed to a fatal myeloid malignancy (Starczynowski et al. 2010).

Many studies have demonstrated that miRNAs are abnormally expressed in myeloid malignancies compared to counterpart controls; most commonly in AML [reviewed by Marcucci et al. (2011)], but also in MDS [reviewed by Rhyasen and Starczynowski (2012)] and chronic myeloid leukemia (CML) (Agirre et al. 2008, Babashah et al. 2013).

In AML, in particular, differences in miRNA expression between common cytogenetic subtypes have been widely documented including those harboring favorable-risk abnormalities such as t(8;21) (Jongen-Lavrencic et al. 2008; Li et al. 2008; Dixon-McIver et al. 2008; Cammarata et al. 2010), inv(16), t(15;17) (Jongen-Lavrencic et al. 2008, Li et al. 2008, Dixon-McIver et al. 2008), and inv(16), and those with less favorable-risk subtypes such as t(11q23)/MLL (Jongen-Lavrencic et al. 2008; Li et al. 2008; Dixon-McIver et al. 2008; Garzon et al. 2008b) and trisomy 8 cases (Garzon et al. 2008b). Additionally, karyotype normal AML patients also have distinctive miRNA expression patterns associated with recurrent molecular abnormalities including FLT3-ITD (Jongen-Lavrencic et al. 2008; Cammarata et al. 2010; Garzon et al. 2008a, b) and MLL duplications, mutations in WT1, IDH1, IDH2, NPM1 (Jongen-Lavrencic et al. 2008; Garzon et al. 2008a) and CEPBA (Jongen-Lavrencic et al. 2008), as well as high expression of BAALC (Langer et al. 2008), ERG and MN1 (Langer et al. 2009) genes. Microarray analyses of samples from 122 AML patients were used to define signatures associated with cytogenetically favorable-risk groups (Garzon et al. 2008b). Importantly, these findings were tested in an independent cohort of 60 AML patients using qRT-PCR and levels of miR-191 and miR-199a were found to be independent predictors of prognosis by multivariate analysis. Recently, up-regulation of miR-181a has been linked with a better prognostic outcome for karyotype normal AML patients (n = 187) (Schwind et al. 2010).

In MDS, 12 miRNAs were identified as being differentially expressed between high and low risk MDS patients (Erdogan et al. 2011). Another study found that high levels of miR-150 was associated with good cytogenetic-risk groups in MDS patients (n = 52) (Hussein et al. 2010). Up-regulation of the miR-17-92 cluster was found to be associated with chronic phase but not blast crisis CML patients (Venturini et al. 2007). A miRNA signature was described that could distinguish between CML patients that were responsive and those that were refractory to imatinib treatment (San Jose-Eneriz et al. 2009). miR-203, an epigenetically silenced miRNA in CML, can regulate BCL-ABL expression (Bueno et al. 2008), and miR-138, down-regulated in CML tumor cells but restored in response to imatinib treatment, was recently shown to act as a tumor suppressor in CML cells thorough targeting of BCR-ABL expression (Xu et al. 2012).

It has been reported that the miRNA expression profile of acute promyelocytic leukemia (APL) patients (and cell lines) treated with retinoic acid cause the up-regulation of several miRNAs including miR-223, miR-15a, miR-16, miR-342, miR-107 and let-7a (Garzon et al. 2007). Gauwerky et al. (1989) identified multiple chromosomal aberrations in a patient with APL including a t(8;17) translocation that fused the promoter and 5′ region of miR-142 to a truncated MYC gene.

4 MicroRNA Expression in Lymphoid Malignancies

4.1 Lymphoid Leukemias

The first report of miRNA dysregulation in CLL, or indeed any cancer, came in 2002 from the laboratory of Carlo Croce who made the observation that CLL patients that harbored a 13q14 deletion, also had lower levels of miR-15a and miR-16, miRNAs that are encoded at this locus (Calin et al. 2002). Subsequent research has demonstrated that down-regulation of these miRNAs results in a myriad of cellular responses mediated by targeting of BCL2, MCL1 and CDK6 (Cimmino et al. 2005). Additionally, a circuit between miR-15a/16-1, miR-34b/c, TP53 and ZAP-70 has been proposed to operate in CLL recently, as TP53 can induce expression these miRNAs, and in turn miR-15a/16-1 targets TP53, whilst ZAP-70 is inhibited by miR-34b/c (Fabbri et al. 2011).

The first *in vivo* functional evidence that CLL was linked to miRNA dysregulation came from the New Zealand Black (NZB) mouse strain that has a propensity to develop a disease akin to human CLL, and consequently was the subject of a genome-wide linkage program in order to identify disease-associated loci (Scaglione et al. 2007). A locus on chromosome 14 that was linked to lymphoproliferative disease in the mice was found to be synteneous with the human 13q14 locus, and to encode for the mir-15a/16-1 cluster. Moreover, levels of miR-16 were decreased in the lymphoid tissue of these mice. Sequencing of this region identified a recurrent point mutation, present in the NZB strain but not other closely-related strains, in a flanking region of the mir-15a/16-1 cluster that was very similar to a mutation previously identified in two CLL patients with a familial history of CLL and breast cancer (Calin et al. 2005).

In order to better define the role of the miR-15a/16-1 cluster *in vivo* mouse models have been created with deletions covering either the miR-15a/16-1 cluster alone, or also encompassing the adjacent DLEU2 gene (Klein et al. 2010). Both sets of homozygous mice developed a disease similar to human CLL, but those mice with the larger deletion had a more aggressive disease phenotype suggesting that components other than miR-15a/16-1 cluster contribute to CLL pathogenesis. Consistent with this idea, when the deletion was extended to include adjacent DLEU7 and RNASEH2B genes, mice developed an even more aggressive disease phenotype (Lia et al. 2012). Recently it has been shown that the miR-15a/16-1 cluster is also epigenetically silenced in 30–35 % of CLL samples, associated with an over-expression of HDAC1-3 perhaps suggesting that these patients could benefit from HDAC-inhibitor based therapies (Sampath et al. 2012).

Many miRNA signatures have been linked to CLL diagnosis and prognosis. For example, a 13 miRNA signature was described that could distinguish between aggressive and indolent forms of CLL (Calin et al. 2004a), and in another study a 32 gene signature was able to discriminate between the most common CLL cytogenetic subgroups (Visone et al. 2009). More recently high miR-21 levels has been associated with poor prognosis in CLL patients harboring the 17p deletion (Rossi et al. 2010), and levels of miR-181b were inversely correlated with disease severity over time

leading to its proposal as a potential treatment biomarker for CLL progression (Visone et al. 2011). It has also been suggested that a miRNA signature can be used to predict those CLL patients that are refractory to Fludarabine treatment (Ferracin et al. 2010), and that these patients are characterized by low miR-34a levels even in the absence of p53 alterations (Zenz et al. 2009).

Similar to other leukemias, B-cell acute lymphoblastic leukemia (ALL) tumor cells have a distinct miRNA expression profile from their healthy counterpart ($CD33^+$) cells (Schotte et al. 2011). High levels of miR-128 are associated with ALL and can distinguish between AML and ALL with >98 % accuracy (Mi et al. 2007). Low levels of miR-16 were linked with better prognosis in pediatric ALL cases (Kaddar et al. 2009). Various cytogenetic subgroups of B-ALL including patients with 11q23/MLL, TEL-AML1, BCR-ABL and E2A-PBX1 translocations, and hyperdiploid patients also have distinct miRNA profiles. Let-7b for example, is down-regulated while the miR-17-92 cluster is over-expressed in B-ALL patients with MLL translocations (Schotte et al. 2011; Mi et al. 2010). Differentially expressed miRNAs have also been identified between T-ALL leukemic cells and healthy thymocytes (Schotte et al. 2011), and mice over-expressing miR-19 (part of the miR-17-92 cluster) in concert with Notch1, developed T-ALL faster than those mice expressing Notch1 alone (Mavrakis et al. 2010).

4.2 Lymphomas

4.2.1 Diffuse Large B-Cell Lymphoma

Diffuse Large B-Cell Lymphoma (DLBCL) was one of the first lymphomas to be linked with aberrant miRNA expression, with several reports observing over-expression of miR-155 in this malignancy (Kluiver et al. 2005; Lawrie et al. 2007; Eis et al. 2005). Forced over-expression of miR-155 in mice caused the development of a high grade B-cell lymphoma similar to DLBCL (Costinean et al. 2006); this oncogenicity was mediated by SHIP1 and C/EBPβ targeting (O'Connell et al. 2009; Pedersen et al. 2009; Yamanaka et al. 2009). When miR-155 was expressed using an inducible rather than a constitutive promoter again mice developed lymphoma, however when miR-155 expression was inhibited the tumor quickly receded and after 1 week remarkably mice had no detectable disease manifestations at all (Babar et al. 2012). Ectopic expression of miR-155 suppresses the *in vitro* growth-inhibitory effects of TGF-β1 and BMP2/4 in DLBCL cells via SMAD5 inhibition (Rai et al. 2010), and can regulate the phosphatidylinositol 3-kinase (PI3K)-AKT pathway via targeting of PIK3R1 in DLBCL (Huang et al. 2012). Furthermore, over-expression of this miRNA promotes TNFα-dependent growth of DLBCL cells *in vivo* in xenotransplant models (Pedersen et al. 2009). Interestingly it has recently been shown that SHIP1 is differentially expressed between the two molecular subtypes of DLBCL [activated B cell-like (ABC) and germinal center B cell-like (GC)] (Alizadeh et al. 2000), consistent with previous studies that identified

differences in miR-155 expression levels between ABC- and GC-type DLBCL (Eis et al. 2005; Lawrie et al. 2007). Additionally, CD10 a marker of GC-type DLBCL (Hans et al. 2004), and constitutive expression of NF-κB, a hallmark of ABC-type DLBCL (Compagno et al. 2009), have been linked via the miR-155/PU.1 pathway (Thompson et al. 2011). When mice were inoculated with U2932, an ABC-type DLBCL cell line, treatment with exogenous miR-34a reduced tumor growth via targeting of Foxp1 (Craig et al. 2012), a molecule associated with ABC-type DLBCL (Choi et al. 2009), and also linked to high grade transformation of lymphoma via myc-mediated miR-34a repression (Craig et al. 2011a).

MiR-34a is a well described tumor suppressor miRNA that is closely connected with the p53 network in solid tumors (He et al. 2007), and a positive feedback loop exists whereby p53 induces miR-34a expression and in turn miR-34a activates p53 through SIRT1 inhibition (Yamakuchi and Lowenstein 2009).

Over-expression of the miR-17-92 cluster in conjunction with MYC accelerates lymphoma development and increased tumor aggressiveness (He et al. 2005; Tagawa et al. 2007). This effect is believed to be the result of the MYC/miR-17-92/E2F circuit (O'Donnell et al. 2005). MYC up-regulates the miR-17-92 cluster which targets E2F1, whilst conversely pro-proliferative E2F3 regulates the miR-17-92 cluster (Woods et al. 2007). Recently, miR-19 was identified as the key oncogenic component of the miR-17-92 cluster and in the Eμ-myc model was shown activate the Akt-mTOR pathway via antagonizing PTEN leading to promotion of cell survival (Olive et al. 2009).

4.2.2 Follicular Lymphoma

Despite being the most common form of indolent lymphoma, there are relatively few studies dedicated to miRNA expression in follicular lymphoma (FL). The expression levels of 153 miRNAs were measured in 46 FL samples compared to normal lymph nodes or DLBCL cases (Roehle et al. 2008). Our group looked at expression levels of 464 miRNAs in eighteen FL cases in comparison with 80 DLBCL cases and derived a 26-miRNA signature that could differentiate between FL cases and de novo cases of DLBCL (Lawrie et al. 2009). We also identified six miRNAs (miR-223, miR-217, miR-222, miR-221, let-7i and let-7b) that could distinguish FL cases that underwent high grade histological transformation from those that did not.

The miR-17-92 cluster has recently been suggested to be a useful diagnostic differentiator between the potentially confounding diagnostic classifications of GC-DLBCL and grade 3 FL cases (Fassina et al. 2012). Other studies have compared FL with nodal marginal zone lymphoma (NMZL) (Arribas et al. 2012), and follicular hyperplasia patients (Wang et al. 2012). The latter study also identified miRNAs associated with FL patients responsive to PACE chemotherapy, and demonstrated that p21 and SOCS2 were regulated by miR-20a/b and miR-194 in FL cell lines contributing to cell proliferation.

Although most FL cases harbor the t(14;18) translocation, others (~10 %) do not. Recently a study identified 17 miRNAs that distinguished between t(14;18) positive and negative cases including miR-16, miR-26a, miR-101, miR-29c and miR-138

that were associated with increased expression of CHEK1 and decreased expression of TCL1 in t(14;18) negative cases suggesting a late GC-type phenotype for this form of FL (Leich et al. 2011).

4.2.3 Mantle Cell Lymphoma

A number of miRNA signatures have now been described for mantle cell lymphoma (MCL) (Zhao et al. 2010; Di Lisio et al. 2010; Navarro et al. 2009a; Iqbal et al. 2012). The loss of potential miRNA target sites for miR-15/16 and members of the miR-17-92 cluster in the 3′UTR of CCND1 have been suggested to contribute to the pathogenic over-expression of Cyclin D1 in MCL (Chen et al. 2008; Deshpande et al. 2009). Over-expression of members of the miR-17-92 cluster has been associated with high MYC levels in aggressive MCL (Navarro et al. 2009a), and high proliferation gene signature (Iqbal et al. 2012), as well as activation of the PI3K/AKT pathway, and inhibition of chemotherapy-induced apoptosis in MCL cell lines (Chaudhuri et al. 2012). PHLPP2, an important regulator of the PI3K/Akt pathway, was also shown to be a target of the miR-17-92 cluster in addition to PTEN and BIM in MCL (Rao et al. 2012). Inhibition of miR-17-92 expression in an MCL xenotransplant model suppressed the PI3K/Akt pathway and resulted in decreased tumor growth. Also down-regulation of miR-29 was shown to activate CDK4/CDK6, and serve as a potential prognostic marker for this malignancy (Zhao et al. 2010).

4.2.4 Burkitt Lymphoma

The importance of miRNAs to the pathogenesis of Burkitt lymphoma (BL) is suggested by the fact that mice carrying a mutation in the 3′-UTR binding sequence for miR-155 in the activation-induced cytidine deaminase (AID) gene have increased levels of MYC-IgH (t(8;14)) translocations; the characteristic genetic hallmark of BL (Dorsett et al. 2008). MYC regulates and is itself regulated by a large set of miRNAs, leading to a complex regulatory loop that can contribute to lymphomagenesis (Gao et al. 2009; Chang et al. 2008; Bueno et al. 2011). It has even been suggested that MYC over-expression in BL cases that lack the classical t(8;14) translocation could be the result of miRNA deregulation (Leucci et al. 2008). In addition to a functional role, miRNAs may also be useful for a more accurate classification of the group of B-cell lymphomas with intermediate features between DLBCL and BL (Leucci et al. 2008). It has also recently been shown that the different epidemiologic subtypes of BL share a homogenous miRNA profile distinct from that of DLBCL (Lenze et al. 2011). It has been reported that miR-155 is not over-expressed in adult BL cases (Kluiver et al. 2005, 2006; van den Berg et al. 2003), but is in paediatric cases of BL (Metzler et al. 2004). Over-expression of miR-155, in Burkitt lymphoma and post-transplantation lymphoproliferative disorder (PTLD) at least, was proposed to be associated with EBV latency type-III infections (Jiang et al. 2006; Kluiver et al. 2006).

4.2.5 Hodgkin Lymphoma

A number of functional experiments have demonstrated the potential involvement of miRNAs to the pathogenesis of Hodgkin lymphoma (HL). A ribonucleoprotein chromatin immunoprecipitation (RIP-ChIP) approach was used to identify the target genes of aberrantly expressed miRNAs in HL cell lines, and identified an over-representation of genes associated with cell proliferation, apoptosis and the p53 pathway (Tan et al. 2009). In a more focused example, it was demonstrated that JAK2 is directly targeted by miR-135a, and that over-expression of this miRNA in HL cell lines increases apoptotic levels and decreases cell growth via Bcl-xL inhibition (Navarro et al. 2009b). Furthermore, patients with low miR-135a levels were found to have significantly poorer prognostic outcome. Inhibition of let-7 and miR-9 in HL cell lines resulted in reduced levels of PRDM1/BLIMP1 preventing plasma cell differentiation (Nie et al. 2008). miR-9 was also shown to target Dicer and HuR in HL, and inhibition of this miRNA led to a decrease in cytokine production and an impaired ability to attract inflammatory cells (Leucci et al. 2012). Ectopic administration of a miR-9 antagomir led to decreased tumor growth in a xenotransplant model.

4.2.6 Other B-Cell Lymphomas

A number of studies have recently investigated the role of miRNAs in mucosa-associated lymphoid tissue (MALT) lymphoma. For example, a 27-miRNA signature was able to distinguish gastric DLBCL from MALT lymphoma (Craig et al. 2011a), and the same researchers also proposed that transformation from gastritis to MALT lymphoma is epigenetically regulated by methylation of miR-203, consequently suggesting ABL1 as a potential target for treatment of this malignancy (Craig et al. 2011b). In another study a set of five miRNAs (miR-150, miR-550, miR-124a, miR-518b and miR-539) were identified as being differentially expressed in gastritis as opposed to MALT lymphoma (Thorns et al. 2012), and finally high miR-223 levels were found to correlate with increased E2A expression in gastric MALT lymphoma (Liu et al. 2010). Recently a miRNA signature of splenic marginal zone lymphoma (SMZL) cases was reported (Bouteloup et al. 2012).

4.2.7 T-Cell Lymphomas

Compared with B-cell lymphomas, relatively little is known of the role of miRNAs in T-cell lymphoma. Our group provided the first evidence for a functional role of miRNAs in T-cell lymphomas in a study that identified >100 aberrantly expressed miRNAs in the cutaneous T-cell lymphoma (CTCL), Sézary syndrome (SzS) (Ballabio et al. 2010). We identified miR-223 as a potential diagnostic marker (>85 % accuracy) by qRT-PCR for SzS, in both the training cohort and a separate validation cohort that contained patients with a confounding diagnosis [i.e. non-erythrodermic mycosis fungoides (MF)]. We also demonstrated a potential role for

miR-342 in the pathogenesis of SzS through its targeting of RANKL which was associated with the protection of SzS cells from apoptosis. The identity of several of these aberrantly expressed miRNAs has now been validated in other independent studies (Narducci et al. 2011; Qin et al. 2012). Our group have also more recently carried out profiling studies on tumor stage MF (van Kester et al. 2011), and cutaneous anaplastic large cell lymphoma (cALCL) (Benner et al. 2012). Subsequently a qRT-PCR based classifier (miR-155, miR-203 and miR-205) has been proposed that can distinguish between the various forms of cutaneous T-cell lymphomas and related benign disorders (Ralfkiaer et al. 2011). Importantly both training (n = 90) and blinded test (n = 58) sets were used in this study. Besides its role in B-cell development, miR-150 also regulates natural killer (NK) cells via Myb targeting, (Bezman et al. 2011) as well as other T-cell subsets via NOTCH3 inhibition (Ghisi et al. 2011). Transduction of miR-150 into NK/T cell lymphoma cells increased apoptotic levels and decreased cell proliferation, effects mediated via targeting of DKC1 and AKT2, leading to a decrease in levels of BIM, p53 and phosphorylated AKT levels. Additionally, over-expression of miR-21 and miR-155, has been demonstrated to activate the PI3K-Akt pathway in NK/T-cell lymphomas (Yamanaka et al. 2009), and over-expression of miR-122 in CTCL induced AKT phosphorylation coupled with a decreased sensitivity to chemotherapy-induced apoptosis as well as inhibition of p53 (Manfe et al. 2012). Additionally miRNAs have been found to be encoded in the avian T cell lymphoma-causing virus, Marek's disease virus (MDV) (Yao et al. 2007; Burnside et al. 2006).

5 Summary and Future Directions

The miRNA field continues to grow at a phenomenal rate and new biological roles for miRNAs are constantly being uncovered. Whilst great effort has been put into identifying and cataloguing aberrantly expressed miRNAs in disease, very little is known about the functional consequences of this dysregulation, and understanding the biological function of identified miRNAs is perhaps the biggest challenge facing the miRNA field at the moment. The primary reason for this is a lack of knowledge about which genes are actually targeted by individual miRNAs and which of these genes are functionally important in specific cellular settings. With very few functionally annotated exceptions, current approaches to this problem primarily rely upon the use of the many predictive computational algorithms available. However, these algorithms typically predict hundreds or even thousands of target genes for each miRNA and in reality perform very poorly. When the most widely used algorithms were tested against experimentally validated miRNA-target gene interactions, sensitivity ranged from just 1.3 to 48.8 % (Sethupathy et al. 2006). Additionally, the degree of overlap between predictions (three algorithms) was found to range from 3.6 to 28.6 % and surprisingly no commonly predicted genes were identified at all when the five most-commonly used algorithms were compared. Importantly, this study showed that even when all five algorithms were used in union only 72 % of

experimentally validated miRNA-target gene interactions were predicted. For example, KRAS and HRAS targeting by let-7 (Johnson et al. 2005), or E2F2 and MYC targeting by miR-24 (Lal et al. 2009) are not predicted targets of these algorithms. To compound matters further the function of a particular miRNA is dependent upon cellular context. Indeed, the same miRNA can act as both tumor suppressor and oncogene depending upon the cell type. For example, miR-222 is over-expressed in hepatocarcinoma where it targets tumor suppressor PTEN (Garofalo et al. 2009), but is down-regulated in erythroblastic leukemias where it targets the KIT oncogene (Felli et al. 2005). Consequently much effort has been expended to resolve this issue including techniques to directly measure the miRNA:target gene interface, the so-called 'targetome', in cells under physiologically relevant conditions. Particularly promising is the 'PAR-CLIP' technique (Hafner et al. 2010), that has now been used by several groups to elucidate the targetomes of multiple cellular systems (Skalsky et al. 2012; Lebedeva et al. 2011; Gottwein et al. 2011), however it has not yet been extensively applied to hematology.

MiRNAs show perhaps their greatest and certainly most immediate clinical potential, as novel biomarkers. MiRNA expression profiling can distinguish cancers according to diagnosis and developmental stage of the tumor to a greater degree of accuracy than traditional gene expression analysis, even discriminating between cancers that are poorly separated histologically (Lu et al. 2005). An especially useful characteristic of miRNAs is their remarkable stability which means that they can be robustly measured from routinely prepared formalin-fixed paraffin embedded (FFPE) biopsy material (Lawrie et al. 2007). A further manifestation of their stability is their presence in extracellular biological fluids including blood (Lawrie et al. 2008). We demonstrated for the first time that miRNAs were present in the blood (serum/plasma) of lymphoma patients at differential levels from healthy controls (Lawrie et al. 2008). The speed of miRNA biomarker discovery has been quite astonishing with over 5,000 publications in the last 5 years. However, it should be noted that the reliability of much of this data remains contentious and should be treated with some caution as the degree of discordancy between seemingly identical studies is worrisome, and in reality very few of the biomarkers studies published will ever make it into clinical practice. These discrepancies are probably due to the use of different control populations (unsorted cell types, populations sorted in a differing manner etc.), as well as technical variability (e.g. differing array platforms, statistical analyses and varying cytogenetic/molecular profiling techniques) between studies. Consequently there is a clear need for a standardized approach to be taken in future miRNA biomarker studies in order to rationalize these confounding factors. In particular, a systematic approach should be taken in a similar fashion to that achieved for other 'omic disciplines' (i.e. transcriptomics and genomics).

Perhaps the most promising clinical aspect of miRNAs is their potential as novel therapeutic molecules, either as a tool to modulate target genes associated with disease or by correcting dysfunctional expression of the miRNAs themselves (Babashah and Soleimani 2011). The former approach is particularly attractive in that a single agent (i.e. a miRNA) can be used against multiple targets in a disease pathway or even against the whole pathway (Bui and Mendell 2010). There are two major strategies

to therapeutically modulate dysregulated miRNAs in disease; using miRNA mimics to restore physiological levels of miRNAs that are down-regulated (e.g. tumor suppressor miRNAs such as let-7 or miR-34), or the use of miRNA inhibitors targeted against over-expressed miRNAs (e.g. oncomiRs such as miR-21 or miR-155). In addition, indirect methods such as the use of epigenetic drugs like DNA-demethylating agents and histone deacetylase inhibitors may be of potential therapeutic use in re-expressing epigenetically silenced miRNAs (Agirre et al. 2009).

There is now a wealth of *in vivo* animal experiments that have established the proof-of-principle for the therapeutic efficacy of miRNAs in disease, however at present all but a couple of these studies are still at the pre-clinical stage. The major hurdles still to be resolved include the effective targeting of therapy (e.g. tissue-specific delivery, dosage and pharmacodynamics) and safety concerns (e.g. off-target effects, RNA-mediated immunostimulation and the use of viral vectors). That said, this is an area very much still in its infancy that is almost certain to flourish in the near future, and promises to add to the current arsenal of therapies available to the hematologist in their continual fight against disease. Whatever happens, the future for miRNAs in hematology is very promising, and we should remember that we are only at the very beginning of our understanding of non-coding (nc) RNA and that in reality miRNAs represent the tip of the ncRNA 'iceberg'. Indeed, although ~75 % of the human genome is transcribed (Djebali et al. 2012), the protein-encoding portion of the genome only accounts for 1.5 % (Alexander et al. 2010), whilst miRNAs represent another 1.8 % (Djebali et al. 2012). There is now emerging evidence that ncRNA species other than miRNAs are essential for both physiological function and development, as well as playing a fundamental role in disease (Mercer et al. 2009; Esteller 2011). Although relative to miRNAs, the study of other ncRNA molecules is very limited, many classes of ncRNAs are now recognized including short ncRNAs such as miRNAs, piRNAs and tiRNAs; mid-size ncRNAs such as snoRNAs, PASRs, TSSa-RNAs and PROMPTs; and long ncRNAs (lncRNAs) (Harries 2012; Esteller 2011). In particular, lncRNAs have been found to be more cell-type and tissue-type specific than protein coding genes and miRNAs (Cabili et al. 2011). It therefore seems highly likely that these molecules will become the next frontier of ncRNA discovery.

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