Chapter 5
MicroRNAs in Hematologic Malignancies

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Abstract Besides normal hematopoiesis, microRNAs (miRNAs) have been found to be essentially involved in the development of various hematological malignancies. Here, we review the role of miRNAs in lymphoid neoplasias, with focus on lymphomas as well as myeloid malignancies such as acute myeloid leukemia.

Keywords miRNA • Cancer • Leukemia • Lymphoma • Oncogene • Tumor suppressor • Therapy • Survival

5.1 Introduction

Much evidence implicates miRNAs as contributing factors in the pathogenesis of hematological neoplasias. A provocative observation made by Calin et al. was that a large number of known recurrent genomic alterations involved in cancer are in close proximity to miRNA genes, suggesting that these rearrangements affect the expression of miRNAs with tumor suppressive or oncogenic properties. Indeed, multiple miRNAs have been implied in the pathogenesis of various neoplasias. Especially in chronic lymphocytic leukemia (CLL), the first connection between a frequent loss of chromosomal region 13q14.2 containing two miRNAs (miR-15a and miR-16-1) and the pathogenesis of the disease was discovered. Therefore, the pathophysiological role of miRNAs in lymphomas was recognized even before their regulatory role in normal hematopoiesis.

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5.2 Chronic Lymphocytic Leukemia

CLL is the most frequent form of leukemia in adults in the western world, affecting roughly 4 out of 100,000 people per year with a prevalence in men and a median age at diagnosis of 72 years [1]. People affected by CLL are usually not treated right from the time-point of diagnosis but with developing symptoms or progression to advanced stage [2]. Treatment has changed throughout the last decades switching from single substance treatment (with Fludarabine) to combined chemotherapy protocols (including Fludarabine and Chlorambucil) and with the advent of monoclonal antibodies to chemoimmunotherapy (with Fludarabine, Chlorambucil, and Rituximab) showing significant improvement in complete response (CR) rates [3]. Deletion of chromosome 17p and mutation of p53 have been clearly identified as predictive for refractoriness, but a considerable portion of cases with refractory disease or insufficient response and early relapse might not exhibit these established markers [4, 5]. Characterizing the genetic background and clinical presentation of CLL helped to identify risk groups the clinician can use for models to predict the clinical course, for management of follow up and rational treatment choice [5].

Classical features include recurring genomic aberrations and gene mutations such as TP53 [6] and ATM [7], somatic mutations in the variable regions of the immunoglobulin (Ig) heavy chain (IGHV) genes [8, 9], biased IGHV usage and stereotyped B cell receptors (BCRs) [8, 10, 11]. In about 80 % of all CLL cases chromosomal aberrations can be identified, mostly showing deletion of chromosome 13q14 (55 %) or 11q (18 %), trisomy of chromosome 12 (16 %), or deletion of chromosome 17p (7 %) [12]. Central genes identified at the minimal deleted region are the ataxia teleangiectasia-mutated (ATM) gene spanning the chromosome bands 11q22.3–q23.1 [13], the tumor suppressor gene TP53 at 17p13 [14, 15] and the cluster of two miRNAs named miR-15a and miR-16-1 within the DLEU2 gene on chromosome 13q14.2 [16].

The search for a putative target-gene of these miRNAs identified the BCL-2 gene by sequence-complementarity with the seed regions of both miRNAs. Functional validation confirmed the potential for posttranscriptional repression of BCL2 with an increased rate of apoptosis in MEG-01 cells in vitro and decreased tumorigenicity in xenograft mouse-models upon transfection with miR-15/16 [17, 18]. By generating a mouse model with a deletion of the DLEU2/miR-15a/16-1 cluster, Ulf Klein and colleagues proved the pathogenic effect mediated through the loss of these miRNAs. Mice with loss of the minimal deleted region or with sole miR-15a/16-1 deletion both developed clonal B-cell lymphoproliferation with a slightly pronounced effect when DLEU2 was affected as well. The loss of miR-15a and miR-16-1 affected growth, cell-cycle control and apoptosis, though the effect on BCL2 remains controversial [19]. As the involvement of DLEU2 already implicated additional mechanisms beside the loss of miR-15a and miR-16-1 that foster lymphoma development, Lia and colleagues provided another mouse model in which DLEU7 and RNASEH2B were additionally knocked out. Such mice developed

more aggressive lymphomas and presented with a phenotype of CLL or SLL (small lymphocytic lymphoma) [20]. Most interestingly in the context of these two mouse-model studies is the observation that patients with monoallelic 13q14 deletion tend to express higher miR-15a/16-1 levels than patients with a biallelic 13q14 deletion [21] and the growth kinetics of lymphocytes is slower in patients with a monoallelic compared to biallelic 13q14 deletion [22]. Although this phenotypes suggest differences in the clinical course, current studies draw a heterogeneous picture without a clear prognostic difference [23, 24]. With ongoing research, the functional network of miR-15/miR-16 steadily grows in complexity. Central target genes regulated by these miRNAs are involved in cell-cycle, cell-growth and apoptosis. Moreover, a regulatory loop with TP53 has been unmasked in a recent study by Fabbri and colleagues. While p53 can lead to the induction of miR-15a/miR-16-1 through upstream binding sites, the miRNA themselves specifically target TP53 and reduce protein and mRNA-levels [25]. Beside deletions or rare mutations leading to defective precursor transcript processing [26] epigenetic mechanisms have recently been identified as well. In the study by Sampath et al., epigenetic silencing of miR-15a, miR-16, and miR-29b mediated by histone deacetylases has been found in one-third of all investigated CLL samples. Exposure to histone deacetylases inhibitors led to the induction of all of these miRNAs and was associated with declines in the levels of MCL-1 but not BCL-2 [27]. With respect to the underlying (cyto-) genetic and newly identified epigenetic abnormalities and its clinical presentation, specific miRNA expression patterns help to uncover individual mechanims involved in CLL subgroups and to sharpen prognostic models [28–30]. Although the majority of deregulated miRNAs are not located at the commonly deleted regions in CLL, the regulatory changes seem to converge in similar functional routes as found for the p53-pathway. MiRNAs found to be specifically deregulated in conditions with dysfunctional p53 include miR-151-3p, miR-29c, miR-34a (downregulated) [28], miR-21, miR-155, miR-15a (upregulated) miR-34a, miR-181b (downregulated) [30], miR-34a, miR-29c, miR-17-5p (downregulated) [31]. Changes of miR-34a levels seem crucial, since this miRNA has been identified as a direct target of p53, taking a central part in the DNA-damage response [32–34]. The functional role and clinical relevance in CLL has been confirmed in a recent study showing that irradiation of CLL cells without functional p53 did not lead to induction of miR-34a. Low levels of miR-34a were found in association with fludarabine-refractory disease and impaired DNA-damage response even in cases without 17p-deletion or TP53 mutation.

Profiling studies aiming to discover miRNAs that could be further used as surrogate or prognostic markers were able to identify specific patterns of deregulation.

Initial studies using supervised approaches generated characteristic profiles based on the IGHV mutation status and ZAP-70 expression [26, 35]. Subsequent studies were able to confirm the association of decreased miR-223 levels and members of the miR-29 family with unmutated IGHV genes and disease progression [11, 21, 29, 36]. Shorter treatment free survival and reduced overall survival was shown for cases with low miR-223 and miR-29c. By using a specifically developed score based on the expression levels of these two miRNAs, ZAP-70 and LPL levels, Stamatopoulos et al. were even able to distinguish prognostic subgroups [29].

With the focus on miRNAs that correlate with 17p-deletion in CLL, one study was able to identify two miRNAs with prognostic relevance irrespective of other clinical-pathologic factors. Low miR-181b expression and high miR-21 expression were identified as poor prognostic features and significantly associated with OS and PFS [30]. Confirmation of the prognostic relevance of miR-181b came from a subsequent study that analyzed miRNA expression changes in patients with stable and progressive CLL. By investigating patient-matched and sequentially sampled leukemic cells, miR-181b was found to decrease over time only in samples derived from patients with progressive disease [37]. Putative targets of miR-181b include the myeloid cell leukemia sequence 1 gene (MCL-1) [37], a member of the BCL-2 family with anti-apoptotic function, and the pleomorphic adenoma gene 1 (PLAG1) oncogene [38]. Of note in this context is the observation that miR-181 together with miR-29c have previously been shown to be downregulated in cases with 11q deletion and found to inversely correlate with the TCL1-oncogene [39]. Interestingly, the miR-29 family also downregulates MCL1 [40], which itself is associated with unfavorable prognostic factors and disease course [41]. The example of concomitant downregulation of miR-181 and miR-29 highlights the functional synergism miRNAs can generate in pathogenic circumstances.

5.3 Follicular Lymphoma

Follicular lymphoma (FL) represents one of the most common non-Hodgkin lymphomas in the western world. Its incidence approximates 2.6 per 100,000 with an median age ranging between 60 and 70 years at diagnosis with a slight predominance in females: FL typically exhibits the t(14;18)(q32;q21) chromosomal translocation with subsequent proximity of the BCL2 gene on chromosome 18 and the immunoglobulin heavy chain gene locus which result in high levels of the anti-apoptotic protein BCL-2. Despite its frequency, literature covering the relevance of miRNAs in this disease is rare. Roehle et al. investigated the lymphoma specific expression signature in DLBCL, FL and non-neoplastic lymph nodes and developed a classification tree consisting of four miRNAs (miR-330, miR-210, miR-17-5p, and miR-106b) with which most cases were assigned to the correct entity [42].

Though FL usually shows a slow and indolent clinical course transformation to more aggressive DLBCL takes place in a considerable portion of cases [43, 44]. To detect transformation associated changes in miRNA expression levels, Lawrie et al. compared transformed DLBCL cases with de novo DLBCL and FL cases with subsequent transformation to cases without transformation at a median follow-up of 5 years.

Of note, prediction of transformation for FL cases was possible by utilizing six miRNAs (miR-223, miR-217, miR-222, miR-221, and let-7i and let-7b) and therefore highlights the potential as novel prognostic marker. In addition, de novo DLBCL and transformed cases were differentiated based on a 12 miRNA signature

[45]. Despite FL mostly evolves through its characteristic translocation, a subset of approximately 10 % of cases do not exhibit the t(14;18)(q32;q21) and mostly BCL2 is not expressed. Analysis of differences in miRNA levels of t(14;18)-positive and t(14;18)-negative FL identified 17 miRNAs to be downregulated in FL lacking t(14;18). Using a highly sophisticated approach, the authors succeeded to correlate five downregulated miRNAs (miR-16, miR-26a, miR-101, miR-29c, and miR-138) in the t(14;18)-negative FL subset with significant mRNA expression changes of their predicted targets. Validation of these miRNAs using qPCR confirmed the downregulation of miR-26a, miR-29c, miR-138, and most significantly miR-16. The investigation of putative miR-16 targets like CHEK1 and CDK6 by immunohistochemistry revealed an inverse correlation with the respective protein expression levels [46].

5.4 Mantle Cell Lymphoma

Mantle cell lymphomas (MCL) represent a highly aggressive form of lymphoma and account for 3–10 % of all non-Hodgkin lymphomas that manifest in advanced stage with predominance in male patients at higher age [47, 48]. Outcome with conventional therapies is poor and median survival ranges around 3–4 years. However, novel approaches with intensive regimen, combining immunochemotherapies followed by autologous stem-cell-transplantation currently lead the way to considerable improvement [49]. The central pathogenic event in MCL is t(11;14)(q13;q32) which links the cyclin D1 gene (CCND1) to the immunoglobulin heavy chain promoter and leads to consecutive overexpression of cyclin D1 with subsequent deregulation of the cell cycle control. In addition, cell-cycle regulators like BMI1, INK4a, ARF, CDK4, and RB1 and DNA-damage-pathway members like ATM, CHK2, or p53 are frequently affected by chromosomal alteration or mutation [50, 51].

Cyclin D1 mRNA transcripts without a full-length 3′ UTR are often detected in more aggressive MCL variants with a high proliferation rate and short clinical course [52, 53]. Highly interesting in this context is the role of miR-15/miR-16 which regulate Cyclin D1 expression by targeting its 3′ UTR. Truncation of the gene therefore renders MCL cases unresponsive to the posttranscriptional regulation of CCND1 [54, 55]. Moreover, other cell-cycle regulators like CDK6 have been identified as miRNA targets. CDK6 belongs to the family of cyclin-dependent protein kinases and, as the name suggests, acts together with Cyclin D1 (and CDK4) to accelerate proliferation. One profiling-study identified the miR-29 family as regulators of CDK6 and found that patients with significant downregulated miR-29 levels had a less favorable clinical course than those with higher expression of miR-29 [56]. Another study performed by Navarro et al., investigated the expression of 86 miRNAs that are located at commonly disrupted genomic regions in MCL. Two clusters characterized by different mutational status of the immunoglobulin genes, proliferation signature, and number of genomic alterations were detected based on

an unsupervised analysis of the generated miRNA expression profiles. Like in DLBCL, overexpression of miR-17-5p/miR-20a was found in aggressive tumors with high MYC levels [57]. Another profiling study, using 23 primary MCL samples and 8 MCL cell lines identified a MCL miRNA-signature consisting of 117 miRNAs when compared to that of 11 reactive lymphoid tissues and CD19þ/IgDþ/CD27 lymph node-sorted B cells, respectively. MiR-617, miR-370 and miR-654 were found among the most significantly upregulated miRNAs whereas miR-31, miR-148a and miR-27b ranged among the most significantly downregulated ones. A subsequent bioinformatic approach by combining regular gene expression and miRNA-profiles with target-prediction databases hinted to several overactive routes including CD40, NF-kB, and mitogen-activated protein kinase (MAPK) pathways. Moreover, the authors provide evidence that downregulation of miR-26a leads to NF-kB activation potentially by targeting MAP3K2. They show that induced expression of miR-26a leads to abrogation of the nuclear translocation of RelA. Similar to other studies on different cancer types, the authors here identify miR-20b as significantly associated with prognosis in MCL. Patients exhibiting low levels of miR-20b had a higher probability for longer survival than patients with high miR-20b levels [58].

5.5 Diffuse Large B-Cell Lymphoma

Diffuse large B-cell lymphoma (DLBCL) belongs to the most frequent aggressive B-cell neoplasms with an incidence of approx. 25,000 cases per year in the US [59]. Significant progress in treatment efficacy has been achieved through the addition of rituximab to CHOP-like regimen [60–63]. However, treatment outcome remains variable due to the heterogeneity DLBCL presents with regards to clinical aspects, biology and pathogenesis. By the use of gene-expression profiling it was possible to link the molecular phenotype of biologically distinct groups to the clinical presentation. DLBCL can be split in three major subtypes, namely, the germinal-center B-cell-like (GCB) DLBCL, the activated B-cell-like (ABC) DLBCL, and the primary mediastinal DLBCL (PMBCL) with survival rates of 59, 30, and 64 % after 5-years [64–66]. Molecular characteristics of ABC-DLBCL include overexpression of BCL2 and amplification of its locus, deletion of the INK4A–ARF locus, trisomy 3 with consecutive upregulation of FOXP1 and a constant activation of the nuclear factor (NF)-κB pathway. GCB-DLBCL show recurrent t(14;18), TP53 mutations, loss of PTEN and amplification of the oncogenic miR-17-92 cluster as well as the proto-oncogene REL. Similar to the ABC-subtype, PMBCL present with overactive NF-κB signaling, in addition PMBCL show frequent amplification of a chromosome region on 9p24 encoding JAK2 and loss or mutation of its suppressor SOCS1 [67, 68]. Extending the molecular characterization of DLBCL to the miRNA level helped to identify further pathogenic mechanisms. The lymphoma specific relevance of the BIC-locus transcript has been known since the end of the 1980s [69]. However, suggestions for the classification and a putative role as noncoding RNA

[70, 71] as well as the observation that miR-155 is encoded in the BIC-transcript were published several years later [72]. Consequently miR-155 has been classified as an oncogenic acting miRNA due to its frequent overexpression in a variety of B-cell neoplasms [72, 73]. Following experiments confirmed its oncogenic potential in transgenic mice that overexpress miR-155 and develop a pre-B-lymphoproliferative disease with consecutive progression to high-grade B-cell neoplasms [74]. Mechanistically, the downregulation of SHIP, a negative regulator of PI3K-signaling, and C/EBPβ have been attributed to the lymphoma mediating effects of this miRNA [75, 76]. MiR-155 shows higher levels in PMBCL and ABC- than in GCB-DLBCL which may be attributed to the constitutive activation of the (NF-κB) pathway in these DLBCL subtypes [66, 77, 78], beside AP1 and MYB, NF-κB has been identified as central regulator of miR-155 expression [79, 80] and sustained upregulation of miR-155 was found to happen in response to autocrine stimulation by the tumor necrosis factor α (TNFα) [76]. GCB-DLBCL have lower levels of miR-155, however, the GCB-type specific loss of PTEN [81, 82] or amplification of the miR-17-92 cluster [82] which targets PTEN [83] point to the observed importance of maintaining PI3K-signaling in DLBCL [84]. Overexpression of the miR-17-92 cluster in lymphomas [85] and a MYC driven overexpression in DLBCL has been confirmed in independent studies [82, 86]. By using an integrative approach through combining the results of miR specific array CGH and microarray based miRNA expression profiling, Li et al. were able to generate a detailed map of commonly disrupted miRNA-loci in the DLBCL genome [86]. Hierarchical clustering of the investigated miRNAs separated the analyzed DLBCLs in three subsets independent of the hitherto identified DLBCL subclasses but with respect to the transcriptional level of MYC. Generated subgroup profiles were associated with transcriptional levels of MYC, influenced by genomic abnormalities and showed significant overlap with the discriminating miRNA profiles of B-cell subsets [86]. The central role for malignant transformation has been shown in a mouse B-cell lymphoma model where enforced expression of the miR-17-92 cluster acted with MYC expression to accelerate tumor development [87]. This miRNA cluster was identified to regulate the cell cycle and inhibit apoptosis that takes place at a higher rate if the miR-17-92 cluster is not expressed. Essentially, this effect was attributed to miR-17 and miR-20a by targeting the E2F family members [88–90]. With respect to the seed sequence homology the miR-17-92 cluster consists of the families miR-17/miR-20a, miR-18a, miR-19a/1miR-19b, and miR-92a. The selective deletion or overexpression of single family members of this cluster helped to identify the miR-19 family as most relevant for MYC-induced lymphomagenesis with PTEN as its main target [91, 92]. Moreover the miR-17-92 cluster was found to target the cyclin-dependent kinase inhibitor CDKN1A/p21 with consecutive increase in cell growth and to regulate the proapoptotic protein Bim, leading to overexpression of BCL-2 [93]. Uncontrolled expression of the clusters miR-17-92/miR-106b-25 and/or other family members in the miR-106a-363 cluster may also guide malignant cells to escape from TGFβ-dependent cell cycle arrest and apoptosis as previously exemplified [94]. Since miR-155 targets SMAD5 and renders DLBCL resistant to growth inhibitory effects that are mediated through cytokines of the bone morphogenetic

protein (BMP) family and transforming growth factor (TGF)-β [95], the cooperative action of these miRNAs represents an exemplary model on how different molecular routes may converge in pathogenic effects. Clinical relevance was found by the observation that DLBCL cases with upregulation of miR-17-92 and its paralog miR-106a-363 had the worst overall survival (OS) in one study [86].

5.6 Primary CNS Lymphoma

Beside the frequent occurrence of DLBCL without involvement of the central nervous system, a rare subtype of lymphoma presents with isolated manifestation in the brain, spinal cord or related structures and is therefore called primary CNS lymphoma (PCNSL). The majority of these cases can be classified as DLBCL and show an invariably poor outcome [96]. Data on differential regulation of miRNAs in this lymphoma-subtype and a specific pathogenic role is scarce due to the rare occurrence and difficult sampling procedure. A recent study investigated the miRNA expression in 11 samples of PCNSL compared to 10 samples of nodal DLBCL. 18 miRNAs turned out to be differentially regulated. Upregulated miRNAs in PCNSL were associated with the Myc-pathway (miR-17-5p, miR-20a, miR-9), blocking of terminal B-cell differentiation (miR-9, miR-30b/c) and inflammatory cytokines (miR-155), whereas downregulated miRNAs were found to involve miRNAs with ascribed tumor-suppressor function (miR-199a, miR-214, miR-193b, miR-145). Amongst brain specific miRNAs, only miR-9 was found to be upregulated in PCNSL cases [97]. Another study analyzed the differential expression of 15 miRNAs (miR-15a, miR-15b, miR-16, miR-17-3p, miR-17-5p, miR-18a, miR-19a, miR-19b, miR-20a, miR-21, miR-92, miR-127, miR-155, miR-181a, and miR-221) in 19 nodal cases without extranodal dissemination, 9 cases of PCNSL, 11 cases of primary testicular and 11 cases of other primary extranodal DLBCL and identified a significantly higher expression level of miR-17-5p in the cases with CNS manifestation [98]. Both studies did not identify differential expression between germinal and non-germinal center DLBCL cases of any of the investigated miRNAs [97, 98].

Investigations on the prognostic value of miRNAs in DLBCL identified several miRNAs that may help to predict the clinical course. Montes-Moreno et al. retrospectively analyzed a series of 258 de novo cases of DLBCL treated with standard protocols (243 Patients of this cohort were treated with R-CHOP) and identified a set of 9 miRNAs with prognostic relevance. Seven of these miRNAs (miR-221, miR-222,miR-331, miR-451, miR-28, miR-151, and miR-148a) were identified with respect to the putative cellular origin as previously described [99]. Two additional, independent prognostic miRNAs were miR-93 and miR-491. The authors succeeded to identify a high-risk group of patients with a 2-year OS and a progression free survival (PFS) probability of <50 % by applying a combined model including the IPI score [100]. Lawrie et al. who evaluated three miRNAs (miR-21, miR-155, or miR-221) which were differentially expressed between ABC and GCB-DLBCL identified miR-21 as independent prognostic marker. In this

retrospective series of 49 de novo DLBCL, high miR-21 expression was associated with longer relapse free survival [101]. The specific evaluation of three miRNAs (miR-21, miR-155, and miR-222) in another study on 106 DLBCL cases uniformly treated with R-CHOP therapy found a correlation of high levels of miR-222 and shorter OS and PFS [102]. 11 miRNAs that had been previously identified as variably expressed in DLBCL were investigated in an independent study in patients uniformly treated with R-CHOP, high levels of miR-18a were correlated with shorter OS, high levels of miR-181a were associated with longer PFS and increase expression miR-222 with shorter PFS [103].

5.7 Burkitt's Lymphoma

Burkitt's Lymphoma (BL) represents a high-grade B-cell neoplasm belonging to the class of Non-Hodgkin's lymphoma. BL has a highly aggressive clinical phenotype and is one of the most rapidly dividing tumors in humans with an approximate doubling time of 24 h [104]. With respect to its epidemiological presentation BL is subdivided in three different groups, namely, endemic BL, HIV-associated BL, and sporadic BL. Epstein–Barr Virus genome (EBV) is found in nearly all cases with endemic BL with its geographic hot-spot found in equatorial Africa, whereas the minority of sporadic BL and less than half of the HIV-associated BL are tested positive for EBV. Endemic BL in equatorial Africa is prevalent in children of the younger age, has distinct predilection sites like the jaw and shows an incidence that is 50 times higher than in the US. Unlike endemic BL sporadic BL mostly manifests with abdominal bulks in young adults and, with an incidence of 1–2 %, belongs to the less frequent form of lymphoma in Western Europe and the United States. Mortality shows a close correlation with age, rising consistently from pediatric patients to older adults [105]. The current basis of BL treatment consists of high intensity, brief-duration regimens, with which 65–100 % of adults achieve a CR and 47–86 % of patients maintaining these remissions at least 1 year following therapy (reviewed in [106]). The combination of high intensity regimen with the monoclonal antibody Rituximab has increased response rates in BL patients [107]. The major pathogenic event in BL is the translocation of the MYC gene to the immunoglobulin (Ig) heavy-IgH t(8;14) or light-chain (Ig-κ, Ig-λ) t(2;8) or t(8;22) locus with subsequent overexpression of MYC [108]. Similar to mRNA-based gene expression profiling that can reliably classify classic BL and might even more reliably distinguish borderline cases [109], miRNA based approaches succeed to accurately classify cases with DLBCL or BL regardless to the sometimes overlapping morphology [110]. However, subtypes of BL show a rather homogenous miRNA profile and might therefore be more similar with respect to underlying pathogenic mechanisms than one would assume from the epidemiologic distribution [110]. Transcriptional activity of Myc is central to differences in miRNA profiles between BL and other lymphoma entities [110, 111]. Especially members of the miR-17-92 cluster were identified as targets of Myc with a significant overexpression in Myc driven

lymphomas [87]. In contrast, activation of Myc may also leads to a widespread repression of miRNAs with tumor suppressive function. MiR-22, miR-26a, miR-29c, miR-30e, miR-146a, let-7, miR-15a, miR-29a, miR-34a, miR-195, and miR-150 were identified in one study by microarray screens as specifically downregulated by Myc. Enforced expression of these miRNAs reduced the tumorigenic potential of lymphoma cells [112]. Myc-dependent deregulation of miR-26a, miR-181a, and miR-16 has been associated with altered cell proliferation and loss of miR-26a leads to overexpression of its targeted oncogene EZH2 [113]. In addition let-7a, which targets and suppresses Myc is similarly downregulated in this genetic entity and therefore represents a blocked autoregulatory mechanism for the control of Myc [114]. However, deregulated miRNA expression is not only induced on the basis of the transcriptional activity of Myc itself. The closer analysis of t(8;14) negative BL cases and translocation-positive BL provides evidence for a specific role of miR-9* in this context. Of note is the finding of significant downregulation of miR-9* in cases without Myc-translocation and a strong methylation of the miR-9-1 gene. Mechanistically, miR-9* can target E2F1 (which itself is able to induce Myc) and by this indirectly leads to changes in Myc expression levels [115].

5.8 Multiple Myeloma

Multiple myeloma is characterized by uncontrolled clonal expansion of malignant plasma cells. Usually, the clinically defined stages in the supposed sequential development of myeloma include monoclonal gammopathy of undetermined clinical significance (MGUS), consecutive progression to smoldering myeloma and at the end to symptomatic myeloma [116]. The approximate incidence per year is 5–6 cases per 100000 persons, with a median age of 70 years. Post-germinal-center B-cells with constant proliferation are considered as basis for further transformation triggered by genetic and microenvironmental changes [116, 117]. On the molecular level multiple myeloma is usually characterized by a complex karyotype. Recurrent genomic changes are regularly found and include hyperdiploidy, deletion of chromosome 13, gain of chromosome 1q, translocations with IgH on chromosome 14q, deletion of chromosome 17p and indicate variable clinical course [116, 118–120]. Translocations of 14q involve specific partner regions with consecutively deregulated genes on 11q13 (CCND1) [121, 122] and 6p21 (CCND3) [123], 4p16 (MMSET and FGFR3) [124–126], 16q23 (MAF) [126, 127], and 20q11 (MAFB) and are additionally used as subgroup discriminators [119]. Beside cytogenetic changes, NRAS and KRAS have been found mutated in approximately one-third of investigated MM cases [128] and differentiate between MM and MGUS to a certain extend as mutations are found only in 5 % in MGUS [116, 129, 130]. Profiling of miRNAs with respect to the underlying cytogenetic changes in MM identified expression patterns mainly linked with the major IGH translocations [131, 132]. Especially in cases with t(4;14) the miR-let-7e, miR-125a-5p, and miR-99b from the cluster region at 19q13.33 were specifically overexpressed. Allelic imbalances

and LOH was associated with changes in expression levels of miRNAs located in the affected regions and included miR-let-7b (22q13.31) and miR-140-3p (16q22) [132]. A global assessment aiming to detect differential miRNA expression between samples from MM and MGUS patients compared to healthy donors identified several discriminating miRNAs with specific regulatory function [133]. Most upregulated miRNAs in MGUS and MM samples involved miR-181a/b, cluster miR-106b-25, and miR-21. MiRNAs predominantly upregulated in MM involved miR-32 and the miR-17-92 cluster. Functional investigations on these miRNAs revealed a potential role in controlling p53 activity by targeting the p300-CBP-Associated Factor (PCAF). MiR-19a and b were almost exclusively upregulated in MM and shown to target SOCS-1 which suggests a functional interconnection to the Il-6R/STAT-3 pathway. Moreover the miR-17-92 cluster was confirmed as specific regulator of the pro-apoptotic gene BIM [133]. MiRNA profiles derived from samples of relapsed or refractory patients exhibit an overexpression of miR-222, miR-221, miR-382, miR-181a and b and decrease of miR-15a and miR-16. Functional investigation of miR-15a and miR-16 implicated these two miRNAs as regulators of growth and proliferation by interacting with BCL2 (which has been identified in CLL [18]) and AKT3, the ribosomal protein S6 and MAP kinases. Specific inhibition has further been demonstrated on the NF-kB pathway, probably by regulating TAB3 [134] which has previously been found to activate NF-kB signaling [135, 136]. Myeloma cell surrounding osteoclasts, bone marrow stromal cells or osteoblasts secrete numerous factors including IL-6 and MM cells with amplifications of chromosome 1q21 show overexpression of the IL-6 receptor [137]. Both mechanisms therefore build the ground for steady or enhanced upregulation of IL-6 dependent genes as was shown for Stat3 mediated and dependent miR-21 expression [138]. Increase of miR-21 levels in the absence of IL-6 significantly reduce apoptosis in myeloma cells [138]. Like miRNA expression can be influenced by factors derived from surrounding cells as reported for IL-6 [138], miRNAs themselves can shape the microenvironment by regulating the release of mediators like vascular endothelial growth factor (VEGF) [134] which induces neo-angiogenesis and again IL-6 secretion [139]. Overexpression of miR-15a and miR-16-1 can diminish VEGF release by direct interaction and decreases consecutive capillary formation in vivo and in vitro [134]. Increased angiogenesis has been shown to promote disease progression and to render MM cells more resistant to conventional therapeutic approaches [140–143]. Decrease or loss of miR-15a and miR-16-1, as found in 13q deleted cases, therefore confers advantage in MM and represents an example on how pathogenic axes can be interconnected on different levels. However, the exact role of miR-15a and miR-16-1 in MM currently remains unclear. While miR-15a has been found to be upregulated in newly diagnosed cases [133, 144], other authors report low levels of 15a in advanced stages [134]. Similar to MM with deletion 13q, cases with 17p deletion or TP53 mutation show a very poor outcome. Inactivation of the p53 pathway by deletion or mutation is usually found at advanced stages [128] though, p53 inactivation has been suggested in the context of MDM2 overexpression in MM [145, 146]. A recent study identified a p53 dependent miRNA feedback-loop that regulates the expression levels of MDM2 expression. As previously

shown for miR-34a (reviewed in [147]) the miRNA cluster miR-194-2-192 and miR-194-1-215 are direct p53 targets. Activation of p53 induces upregulation of these miRNAs with a subsequent downregulation of their mutual target MDM2 and finally leads to cell-cycle arrest or apoptosis in a p53-dependent manner [148]. Moreover the authors identify the miR-192 and miR-215 dependent inhibitory effect on the MDM2 mediated ubiquitination of IGF-1R and its consecutive influence on the IGF-1 dependent mobility and invasion of MM cells as previously described [148–150]. Of note is the observation that these miRNAs show different expression levels in plasma-cells (highest), samples derived from MGUS-patients and MM cells (lowest). Aberrant promoter methylation of the miR-194-2-192 cluster, which has been identified in MM cell lines, might serve in part as explanation for this deregulated miR-expression and consecutive clonal selection [148].

5.9 Hodgkin Lymphoma

Hodgkin Lymphoma (HL) is a hematologic malignancy with an approximate incidence in the western world of 3 new cases per 100,000 persons and year. Effectiveness of treatment has consistently increased over the last years and therapy with current protocols achieves 5-year survival rates for patients with early-stage Hodgkin's lymphoma of at least 90 %. With regard to this development, reduction of long-term complications affecting the heart or lung and prevention from secondary malignancies gains importance [151]. The main groups of HL consist of the frequently diagnosed classical Hodgkin's lymphoma (cHL) and the rare nodular lymphocyte-predominant Hodgkin's lymphoma (NLPHL), which account for 95 % and 5 % of all HL cases. The classification is based on differences in the morphology, specific aspects of lymphoma cells and cellular infiltration pattern. With the diagnosis of cHL, subclassification into nodular sclerosis, which accounts for the majority of cHL cases, mixed cellularity, lymphocyte depletion, and lymphocyte-rich HL is applied. The hallmark of HL is the typical presentation of Hodgkin and Reed–Sternberg (HRS) cells and the extensive surrounding of these cells with a reactive, inflammatory environment consisting of putatively nonmalignant B- and T-lymphocytes, eosinophils, and plasma cells [152].

Though research currently considers HRS cells as derived from germinal center (GC) or post-GC-B-cells, it seems controversial that HRS cells have lost most of their B-cell-specific gene expression [152]. HRS cells show constitutive activation of NF-κB, JAK–STAT, PI3K–AKT, ERK, AP1, and NOTCH1 signaling and several recurrent genetic lesions have been found to majorly involve members of the NF-κB and Jak–Stat signaling pathways [152]. Moreover, the *TNFAIP3* tumor suppressor gene, a negative regulator of NF-κB signaling, has been identified to be affected in up to 40 % by inactivating mutations [153, 154]. HRS cells are latently infected by Epstein–Barr virus (EBV) in about 40 %. The pathogenic relevance for this finding is attributed to two latent membrane proteins expressed by EBV, which are able to mimic active BCR and CD40 receptors [155, 156]. Revelations from miRNA

mediated pathogenic effects perfectly fit into the hitherto delineated pathogenic traits that have been identified in HL. Studying microdissected HRS cells from cHL patients revealed a specific miR expression pattern when compared to CD77+ GC-B-cells. Putative targets of these miRNAs (overexpressed: miR-20a, miR-21, miR-9, miR-155, miR-16, miR-140, miR-18a, miR-30b, miR-30a-5p, miR-196a, miR-374, miR-186 and downregulated: miR-520a, miR-614, miR-200a) include numerous members of the SOCS family [157] which might lead to inactivation of SOCS with consecutively activated JAK/STAT signaling as previously described [158]. In addition, this miRNA expression pattern includes multiple well known miRNAs from studies on HL [73, 159, 160] or other lymphoma entities and different cancers as previously outlined. Beside the activation of the JAK/STAT-signaling pathway other miRNA mediated mechanisms have been revealed that may have a role in HL. Amongst these is the regulation of PRDM1 that is centrally involved in the process of plasma cell differentiation and is a target of miR-9 which itself is overexpressed in HL [159]. In addition high levels were found for miR-155 [73] which have been attributed to its specific induction through NF-κB, based on the EBV mediated expression of LMP1 [161]. In contrast, the study of Navarro et al. could not identify miR-155 as significantly upregulated based on the EBV status. Ten miRNAs (miR-96, miR-128a, miR-128b, miR-129, and miR-205 (low levels), miR-28, miR-130b, miR-132, miR-140, and miR-330 (high levels)) were differentially expressed in EBV+ cHL compared with EBV− cHL [162].

Amongst the signature based on 25-miRNAs that could be used to differentiate between classic HL and reactive lymph nodes, miR-138 expression levels were found in relation with the Ann Arbor stage of investigated Hodgkin cases. Interestingly, chromosomal mapping locates differentially expressed miRNAs to regions of frequent loss or gain in cHL that in part explains the observed deregulation. Exemplarily, gains were found for 17q harboring miR-21, 2p and miR-216, 22q and miR-185 and 14q with miR-134. Losses are found for 4q with miR-302a, miR-302b, and miR-302c and 3p with miR-135a [162]. A subsequent analysis by the same group showed that low levels of miR-135a expression were associated with shorter disease-free survival and more frequent relapse in patients with cHL. Transfection experiments of cell lines with pre-miR-135 increased apoptosis and reduced proliferation. The specific evaluation of the predicted target JAK2 confirmed its downregulation when miR-135a was overexpressed and in addition revealed that JAK2 is coordinatively downregulated together with the antiapoptotic protein BCL-XL [163].

5.10 Chronic Myelogenous Leukemia

Chronic myelogenous leukemia (CML) is a clonal myeloproliferative disorder of the pluripotent stem cell and affects approximately 1–2 per 100,000 persons and year with a slight predominance in men at a median age around 65 years. Usually the disease manifests with a sudden onset of symptoms caused by progressive

splenomegaly, marrow hypercellularity and resulting anemia, thrombocytopenia, and leukocytosis. The pathogenic reason is cytogenetically identified by the presence of the Philadelphia (Ph) chromosome that is caused by the reciprocal translocation t(9;22)(q34;q11) in 90–95 % of CML patients.

The involved genes ABL1 and BCR are coupled to the fusion gene BCR–ABL with sustained kinase activation of ABL which leads to the uncontrolled expansion of the malignant clones. If untreated, the disease typically follows a biphasic or triphasic course with an initial chronic phase changing to the accelerated phase after an average of 5–5.5 years and finally to the so called blast crisis [164, 165].

Approaches using miRNA-profiling have integrated the miRNAs into the concepts of pathogenesis and disease progression of CML. Similar to other hematological malignancies the miR-17-92 cluster was identified as Myc dependent in CML and in addition has been found to be regulated by BCR–ABL. Modes of specific inhibition of BCR–ABL through either using Imatinib or RNA interference resulted in decreased expression of miRNAs encoded in the miR-17-92-cluster. Coordinate signaling through a BCR–ABL–MYC–miR-17-92 pathway has therefore been suggested for enhanced miRNA expression in early chronic phase in CML [166]. Similar to this, another independent study reported about the relevance of another miRNA involved in the regulation of the BCR–ABL pathway. Initially miR-203 was identified by characterizing the fragile region on the mouse chromosome 12 that harbored about 12 % of the known miRNAs and was mostly lost in γ-radiation-induced T cell lymphomas. Though, downregulation of this miRNA was caused in a considerable portion of cases not through deletion of the chromosomal region but through the hypermethylation of the corresponding promoter region of Ph+ malignancies like B-ALL and CML. Most significantly, the authors identified ABL as the specific target of miR-203 and showed that expression of miR-203 leads to the inhibition of proliferation in malignant cells [167]. Comparative analysis of cells from healthy donors and newly diagnosed CML patients identified miR-96 as overexpressed and miR-10a, miR-150, and miR-151 as selectively downregulated in CML samples. BCR–ABL independent downregulation of miR-10a was found to correlate with upregulation of the putative target gene upstream stimulatory factor 2 (USF2), which itself leads to increased cell growth upon overexpression [168].

Progenitors of CML blast crisis have been shown to lose their ability for differentiation by suppression of the transcription factor CEBPα, which controls myeloid differentiation. Interestingly CEBPα protein levels are regulated by hnRNP E2 through interacting with the UTR of CEBPα, correspondingly upregulation of hnRNP E2 diminishes CEBPα protein levels. Of note is the observation that changes in posttranscriptional gene regulation induced by hnRNP E2 have been found as central mechanism for the transition to blast crisis in CML [164, 169–171]. Investigations on the role of miRNAs this context identified miR-328 as specifically modulated through the MAPK-hnRNPE2 pathway with decreased miR-328 levels in blast crisis CML [169, 170]. Analysis of the molecular architecture of miR-328 uncovered a high similarity between this miRNA and the binding site for hnRNP E2 contained in the CEBPα mRNA region. As expected, functional investigation identified miR-328 as competitive target and therefore decreases hnRNP E2 binding and

association of hnRNP E2 to CEBPα, respectively. Reconstitution of miR-328 expression was found to recover the ability of maturation in BCR–ABL positive cells with subsequently higher rates of apoptosis [167].

5.11 Acute Lymphoblastic Leukemia

Acute lymphoblastic leukemia (ALL) is the most common childhood leukemia with a peak incidence at 2–5 years of age. Cure is a realistic goal, as ≥94 % of children have continuous disease-free survival for 5 years and appear cured [172]. In contrast, only 25 % of adults in the age group of 45–54 have continuous disease-free survival for 5 years [172]. Recurring genetic abnormalities with prognostic and therapeutic relevance involve hyperdiploidy, MLL and BCR–ABL translocations, HOX genes as well as PAX5 and IKZF1 [173]. The potential of miRNAs to distinguish between related hematological diseases was shown in the study by Mi et al., demonstrating that four miRNAs, including miR-223, miR-128a, miR-128b (miR-128a and miR-128b were later found to be identical) and let-7b were the most discriminatory between acute myeloid leukemia (AML) and ALL, regardless of leukemia subtype [174]. A combination of any two of these miRNAs could discriminate ALL from AML cases with an overall diagnostic accuracy of 97–99 %. However, it is not clear if this study was performed on solely on ALL and AML samples from adults. Comparing exclusively pediatric AML and ALL, Zhang et al. found miR-100, miR-125b and miR-335 more abundant in AML samples compared to the healthy donors [175]. Subsequently, Fulci et al. identified a three-miRNA signature of miR-148, miR-151, and miR-424 as discriminative of adult T-lineage versus B-lineage ALL [176]. Furthermore, the authors described a set of six miRNAs, miR-425-5p, miR-191, miR-146b, miR-128, miR-629, and miR-126, that distinguished between B-ALL subgroups harboring distinct molecular lesions such as BCR-ABL, MLL-AF4, and E2A-PBX1 fusions [176]. These findings were extended by Schotte et al., who quantified 397 miRNAs in pediatric precursor B-ALL patients, demonstrating that miRNA expression profiles vary between leukemic cells, normal bone marrow, and sorted $CD34^+$ cells [177]. Based on ALL cytogenetics, Schotte et al. were also able to identify characteristic miRNA expression signatures [177]. Differences were found for 11q23/MLL-rearranged precursor B-ALL cases, which exhibited a downregulation of miR-708 and increased levels of miR-196b as well as t(12;21)/TEL–AML1-positive precursor B-ALL cases, which displayed an upregulation of miR-383, miR-99a, miR-100, and miR-125b [177]. Signatures that associate with prognosis, include high expression of miR-33, miR-215, miR-369-5p, miR-496, miR-518d, and miR-599 for a worse outcome and high abundance of miRNAs such as miR-10a, miR-134, miR-214, miR-484, miR-572, miR-580, miR-624, and miR-627 with a more favorable prognosis in pediatric ALL [177]. Central nervous system (CNS) involvement is a common and prognostic relevant feature of ALL. Therefore, Zhang et al. have identified a blood miRNA signature in pediatric ALL complicated by central nervous system (CNS) relapse [175]. They found

significant upregulation of miR-7, miR-198, and miR-633 and a downregulation of miR-126, miR-345, miR-222, and miR-551a in ALL patients with CNS relapse versus non-CNS relapsed ALL. In contrast, Kaddar et al. found miR-16 to be of prognostic relevance for ALL patients [178]. The authors describe that high miR-16 levels were associated with hyperleukocytosis and poor cytogenetic subgroups. Disease-free survival (DFS) was shown to be significantly shorter for miR-16 levels above the 75th quartile in all analyzed B-cell ALL samples. Considering the prominent role of miR-16 in CLL, these findings might point towards a dual role of miR-16 in both diseases and even a shared mechanism in their pathogenesis.

5.12 Acute Myeloid Leukemia

The incidence of acute myeloid leukemia (AML) is 3–5 cases/100,000 [179]. Its prognosis and subtypes are mainly determined by cytogenetics and molecular genetics as reflected in the WHO classification [180]. Before the first comprehensive miRNA profiling studies in AML were published, the role of individual miRNAs has preferentially been studied based on their expression in normal hematopoiesis [181, 182]. Therefore, miR-223 became one of the most investigated miRNAs in myelopoiesis (and AML) due to its specific expression in differentiated myeloid cells [181]. Although, its role in the pathogenesis of AML is not clear, profiling miRNA expression in hematopoietic subpopulations as well as in a human APL cell line (NB4) upon differentiation with ATRA revealed miR-223 to be expressed at low levels in the stem cell compartment with increasing expression throughout myeloid differentiation [182, 183]. Lentiviral overexpression of miR-223 in an AML cell line as well as in AML patient samples induced myeloid differentiation [183, 184], demonstrating that changes in the miRNA transcriptome can promote reprogramming of AML cells.

Gain and loss of miR-223 was shown to have distinct effects, as genetic depletion of miR-223 led to a significant increase of myeloid progenitor cells as well as hyper-mature circulating neutrophils [185]. However, AML profiling studies did not connect miR-223 expression to a particular leukemia subtype [186–189 {Marcucci, 2008 #272}]. Contradicting the prevailing view that only one strand of the miRNA:miRNA* duplex is actively silencing genes, it was further shown that both strands miR-223 and miR-223* are functionally relevant in myeloid cells [190].

Multiple miRNA expression studies of AML patient samples have been performed using different methodological approaches and different patient subgroups [186–188, 191, 192]. Recently, Garzon and colleagues applied custom DNA microarrays to quantify miRNA expression levels in 240 AML patient samples with intermediate and poor cytogenetics. Based on this approach, miRNA signatures associated with 11q23 translocations`, trisomy 8 and FLT3 mutations (FLT3-ITD) were identified, demonstrating that cytogenetics drive miRNA profiles [191]. The same group further investigated the role of miRNAs in AML carrying NPM1 and FLT3-ITD mutations, the two most frequent molecular aberrations in AML [187]. A signature

distinguishing mutated *NPM1* from wildtype cases included the upregulation of miR-10a, miR-10b as well as let-7 and miR-29 family members. The correlation of the presence of FLT3-ITD and miR-155 upregulation was further confirmed by several works [187, 188, 191, 193–195] although FLT3 inhibitor studies showed that the upregulation of miR-155 was independent from FLT3 signaling [187]. However, only little overlap was found between the different miRNA signatures published for NPM1+ AML, which might depend on the applied technology, patient samples and the comparisons made within the study. For example, Jongen-Lavrencic et al. and Cammarata et al. used a similar multiplexing RT-PCR approach, whereas Garzon et al. profiled their AML samples with a custom made miRNA microarray [188, 191, 192]. In each study a different number of patients, ranging from 9 to 68 was analyzed and different comparisons were made: Garzon et al. profiled cNPM1+ and cNPM1− NK-AML, whereas Cammarata et al. compared their AML miRNA profiles to CD34$^+$ bone marrow cells. Jongen-Lavrencic et al. applied unsupervised ordering to create subgroups with similar expression patterns of miRNAs. A total of three miRNAs, miR-10a, miR-10b, and miR-9 were consistently deregulated in all three studies. This indicates that they might not only be important for the pathogenesis of cNPM1+ AML, but also reflect the minimum phenotype of this AML subgroup.

In addition, multiple studies exploring the expression of miRNAs by quantitative RT-PCR in AML patient cohorts could also associate miRNA expression patterns with cytogenetic and molecular subtypes [188, 196]. However, for a miRNA based prediction of AML subtypes the necessary number of miRNAs varied drastically. In the study of Jongen-Lavrencic et al. a class predictor of only ten miRNAs predicts AML with t(8;21) and a set of seven miRNAs AML with t(15;17). In contrast, a predictor comprising 72 miRNAs was necessary for AML with inv(16), thereby suggesting that not all cytogenetic aberrations might have a quite unique miRNA expression pattern and indeed some of the heterogeneity may stem from the fact that current subgroups may need to be further subdivided. In addition, miRNA expression levels might mainly be influenced by the differentiation stage of the leukemic cells, and thus for example inv(16) might be hard to distinguish form other inv(16)-negative AML cases with an identical morphology. In contrast to the complexity of AML subgroups, a signature of only two miRNAs (miR-128 and miR-223) is highly discriminate between AML and acute lymphoblastic leukemia [174].

Similarly, smaller genome-wide miRNA expression studies using bead-based miRNA profiling approaches, microarrays and quantitative RT-PCR confirmed miRNA expression patterns characteristic of cytogenetic subgroups such as t(15;17), t(11q23), t(8;21) and inv(16) [192, 197], as well as molecular subtypes like AML with *CEBPA* and *NPM1* mutations or deregulated *MN1* expression [198]. Interestingly, almost all studies pointed towards the deregulation of miRNAs located in the *HOX* gene cluster, including miR-10a/b and miR-196a/miR-196b, as well as miR-221, let-7 family members, miR-155, miR-29, miR-125b, miR-181 and members of the miR-17-92 cluster in AML. This suggests that a defined group of miRNAs, possibly associated with normal hematopoietic stem cells might be involved in leukemogenic processes such as impaired differentiation and increased self-renewal.

Being correlated with altered gene expression and cytogenetic and molecular genetic aberrations, miRNA expression signatures have been shown to also confer prognostic information. While the study of Garzon and colleagues could identified two miRNAs, miR-191 and miR-199a to be significantly correlated with overall (OS) and disease-free survival (DFS) [191], Sun et al. could show that miR-212 expression correlates with OS, DFS and relapse-free survival independent of cytogenetic subgroup in AML [199]. Within cytogenetically normally AML (CN-AML), Schwind et al. described an association of high miR-181a levels with favorable OS, especially CN-AML with FLT3-ITD and NPM1 wildtype [200]. The same group also found that the combination of high BAALC expression and a BAALC-hosted miRNA, miR-3151 identified CN-AML patient subset with a poor outcome [201]. However, in the future additional studies are needed to determine the impact of miRNAs as reliable biomarkers for diagnosis as well as prognosis in AML.

So far, only few studies investigated the role of miRNAs in leukemic stem cells (LSC) as well as leukemia development. Recently, Wong et al. showed that the miR-17-92 polycistron regulates LSC activity through p21 in a murine MLL model [202]. In a more direct approach, Han and colleagues showed that retroviral overexpression of miR-29a can induce AML in mice [203], and O'Connell and colleagues demonstrated similar findings through overexpression of miR-155 in primitive hematopoietic cells that led to a myeloproliferative syndrome [204]. In contrast to miRNAs that can function as proto-oncogenes, there also has been evidence that distinct miRNAs can function as tumor-suppressor in AML. For example, recently Garzon and colleagues highlighted the potential of miR-29b as tumor suppressor by inducing apoptosis and reducing tumorgenicity in a xenograft AML model [205]. Furthermore, miRNAs have also been shown to represent both targets and effectors of the epigenetic machinery. In accordance to other genes, miRNA expression can be affected by DNA promoter methylation and histone modifications. As mentioned above AML1-ETO can lead to heterochromatic silencing of the miR-223 genomic region and demethylation can restore miR-223 expression followed by differentiation of leukemic blasts [184]. On the other hand, miRNA expression can impact the epigenetic modifications as for example miR-29b targets DNA methyltransferases in AML [205].

5.13 Summary

Here, we show that our knowledge about miRNAs in aberrant hematopoiesis has dramatically advanced since their discovery in CLL. However, most of the studies are descriptive and the functional relevance for many potential oncogenic miRNAs is still questionable. Functional approaches, especially animal models might significantly add to the understanding how miRNAs contribute to the development of cancer, by revealing novel miRNAs, miRNA isoforms, mutations, and absolute sequence counts, thereby highlighting additional miRNAs that might serve as future therapeutic targets in hematological neoplasias.

References

1. Dores GM, Anderson WF, Curtis RE, Landgren O, Ostroumova E, Bluhm EC, et al. Chronic lymphocytic leukaemia and small lymphocytic lymphoma: overview of the descriptive epidemiology. Br J Haematol. 2007;139(5):809–19.
2. Hallek M, Cheson BD, Catovsky D, Caligaris-Cappio F, Dighiero G, Dohner H, et al. Guidelines for the diagnosis and treatment of chronic lymphocytic leukemia: a report from the International Workshop on Chronic Lymphocytic Leukemia updating the National Cancer Institute-Working Group 1996 guidelines. Blood. 2008;111(12):5446–56.
3. Hallek M, Fischer K, Fingerle-Rowson G, Fink AM, Busch R, Mayer J, et al. Addition of rituximab to fludarabine and cyclophosphamide in patients with chronic lymphocytic leukaemia: a randomised, open-label, phase 3 trial. Lancet. 2010;376(9747):1164–74.
4. Stilgenbauer S, Zenz T. Understanding and managing ultra high-risk chronic lymphocytic leukemia. Hematology Am Soc Hematol Educ Program. 2010;2010:481–8.
5. Zenz T, Gribben JG, Hallek M, Dohner H, Keating MJ, Stilgenbauer S. Risk categories and refractory CLL in the era of chemoimmunotherapy. Blood. 2012;119(18):4101–7.
6. Dohner H, Fischer K, Bentz M, Hansen K, Benner A, Cabot G, et al. p53 gene deletion predicts for poor survival and non-response to therapy with purine analogs in chronic B-cell leukemias. Blood. 1995;85(6):1580–9.
7. Schaffner C, Stilgenbauer S, Rappold GA, Dohner H, Lichter P. Somatic ATM mutations indicate a pathogenic role of ATM in B-cell chronic lymphocytic leukemia. Blood. 1999;94(2): 748–53.
8. Fais F, Ghiotto F, Hashimoto S, Sellars B, Valetto A, Allen SL, et al. Chronic lymphocytic leukemia B cells express restricted sets of mutated and unmutated antigen receptors. J Clin Invest. 1998;102(8):1515–25.
9. Hamblin TJ, Davis Z, Gardiner A, Oscier DG, Stevenson FK. Unmutated Ig V(H) genes are associated with a more aggressive form of chronic lymphocytic leukemia. Blood. 1999;94(6): 1848–54.
10. Tobin G, Thunberg U, Johnson A, Eriksson I, Soderberg O, Karlsson K, et al. Chronic lymphocytic leukemias utilizing the VH3-21 gene display highly restricted Vlambda2-14 gene use and homologous CDR3s: implicating recognition of a common antigen epitope. Blood. 2003;101(12):4952–7.
11. Stamatopoulos K, Belessi C, Moreno C, Boudjograh M, Guida G, Smilevska T, et al. Over 20% of patients with chronic lymphocytic leukemia carry stereotyped receptors: pathogenetic implications and clinical correlations. Blood. 2007;109(1):259–70.
12. Dohner H, Stilgenbauer S, Benner A, Leupolt E, Krober A, Bullinger L, et al. Genomic aberrations and survival in chronic lymphocytic leukemia. N Engl J Med. 2000;343(26):1910–6.
13. Stilgenbauer S, Liebisch P, James MR, Schroder M, Schlegelberger B, Fischer K, et al. Molecular cytogenetic delineation of a novel critical genomic region in chromosome bands 11q22.3-923.1 in lymphoproliferative disorders. Proc Natl Acad Sci U S A. 1996;93(21): 11837–41.
14. McBride OW, Merry D, Givol D. The gene for human p53 cellular tumor antigen is located on chromosome 17 short arm (17p13). Proc Natl Acad Sci U S A. 1986;83(1):130–4.
15. Isobe M, Emanuel BS, Givol D, Oren M, Croce CM. Localization of gene for human p53 tumour antigen to band 17p13. Nature. 1986;320(6057):84–5.
16. Calin GA, Dumitru CD, Shimizu M, Bichi R, Zupo S, Noch E, et al. Frequent deletions and down-regulation of micro-RNA genes miR15 and miR16 at 13q14 in chronic lymphocytic leukemia. Proc Natl Acad Sci U S A. 2002;99(24):15524–9.
17. Calin GA, Cimmino A, Fabbri M, Ferracin M, Wojcik SE, Shimizu M, et al. MiR-15a and miR-16-1 cluster functions in human leukemia. Proc Natl Acad Sci U S A. 2008;105(13): 5166–71.
18. Cimmino A, Calin GA, Fabbri M, Iorio MV, Ferracin M, Shimizu M, et al. miR-15 and miR-16 induce apoptosis by targeting BCL2. Proc Natl Acad Sci U S A. 2005;102(39):13944–9.

19. Klein U, Lia M, Crespo M, Siegel R, Shen Q, Mo T, et al. The DLEU2/miR-15a/16-1 cluster controls B cell proliferation and its deletion leads to chronic lymphocytic leukemia. Cancer Cell. 2010;17(1):28–40.
20. Lia M, Carette A, Tang H, Shen Q, Mo T, Bhagat G, et al. Functional dissection of the chromosome 13q14 tumor-suppressor locus using transgenic mouse lines. Blood. 2012;119(13): 2981–90.
21. Fulci V, Chiaretti S, Goldoni M, Azzalin G, Carucci N, Tavolaro S, et al. Quantitative technologies establish a novel microRNA profile of chronic lymphocytic leukemia. Blood. 2007; 109(11):4944–51.
22. Pfeifer D, Pantic M, Skatulla I, Rawluk J, Kreutz C, Martens UM, et al. Genome-wide analysis of DNA copy number changes and LOH in CLL using high-density SNP arrays. Blood. 2007;109(3):1202–10.
23. Garg R, Wierda W, Ferrajoli A, Abruzzo L, Pierce S, Lerner S, et al. The prognostic difference of monoallelic versus biallelic deletion of 13q in chronic lymphocytic leukemia. Cancer. 2012;118(14):3531–7.
24. Chena C, Avalos JS, Bezares RF, Arrossagaray G, Turdo K, Bistmans A, et al. Biallelic deletion 13q14.3 in patients with chronic lymphocytic leukemia: cytogenetic, FISH and clinical studies. Eur J Haematol. 2008;81(2):94–9.
25. Fabbri M, Bottoni A, Shimizu M, Spizzo R, Nicoloso MS, Rossi S, et al. Association of a microRNA/TP53 feedback circuitry with pathogenesis and outcome of B-cell chronic lymphocytic leukemia. JAMA. 2011;305(1):59–67.
26. Calin GA, Ferracin M, Cimmino A, Di Leva G, Shimizu M, Wojcik SE, et al. A MicroRNA signature associated with prognosis and progression in chronic lymphocytic leukemia. N Engl J Med. 2005;353(17):1793–801.
27. Sampath D, Liu C, Vasan K, Sulda M, Puduvalli VK, Wierda WG, et al. Histone deacetylases mediate the silencing of miR-15a, miR-16, and miR-29b in chronic lymphocytic leukemia. Blood. 2012;119(5):1162–72.
28. Visone R, Rassenti LZ, Veronese A, Taccioli C, Costinean S, Aguda BD, et al. Karyotype-specific microRNA signature in chronic lymphocytic leukemia. Blood. 2009;114(18): 3872–9.
29. Stamatopoulos B, Meuleman N, Haibe-Kains B, Saussoy P, Van Den Neste E, Michaux L, et al. microRNA-29c and microRNA-223 down-regulation has in vivo significance in chronic lymphocytic leukemia and improves disease risk stratification. Blood. 2009;113(21):5237–45.
30. Rossi S, Shimizu M, Barbarotto E, Nicoloso MS, Dimitri F, Sampath D, et al. microRNA fingerprinting of CLL patients with chromosome 17p deletion identify a miR-21 score that stratifies early survival. Blood. 2010;116(6):945–52.
31. Mraz M, Malinova K, Kotaskova J, Pavlova S, Tichy B, Malcikova J, et al. miR-34a, miR-29c and miR-17-5p are downregulated in CLL patients with TP53 abnormalities. Leukemia. 2009;23(6):1159–63.
32. Chang TC, Wentzel EA, Kent OA, Ramachandran K, Mullendore M, Lee KH, et al. Transactivation of miR-34a by p53 broadly influences gene expression and promotes apoptosis. Mol Cell. 2007;26(5):745–52.
33. He L, He X, Lim LP, de Stanchina E, Xuan Z, Liang Y, et al. A microRNA component of the p53 tumour suppressor network. Nature. 2007;447(7148):1130–4.
34. Raver-Shapira N, Marciano E, Meiri E, Spector Y, Rosenfeld N, Moskovits N, et al. Transcriptional activation of miR-34a contributes to p53-mediated apoptosis. Mol Cell. 2007;26(5):731–43.
35. Calin GA, Liu CG, Sevignani C, Ferracin M, Felli N, Dumitru CD, et al. MicroRNA profiling reveals distinct signatures in B cell chronic lymphocytic leukemias. Proc Natl Acad Sci U S A. 2004;101(32):11755–60.
36. Marton S, Garcia MR, Robello C, Persson H, Trajtenberg F, Pritsch O, et al. Small RNAs analysis in CLL reveals a deregulation of miRNA expression and novel miRNA candidates of putative relevance in CLL pathogenesis. Leukemia. 2008;22(2):330–8.

37. Visone R, Veronese A, Rassenti LZ, Balatti V, Pearl DK, Acunzo M, et al. miR-181b is a biomarker of disease progression in chronic lymphocytic leukemia. Blood. 2011;118(11): 3072–9.
38. Pallasch CP, Patz M, Park YJ, Hagist S, Eggle D, Claus R, et al. miRNA deregulation by epigenetic silencing disrupts suppression of the oncogene PLAG1 in chronic lymphocytic leukemia. Blood. 2009;114(15):3255–64.
39. Pekarsky Y, Santanam U, Cimmino A, Palamarchuk A, Efanov A, Maximov V, et al. Tcl1 expression in chronic lymphocytic leukemia is regulated by miR-29 and miR-181. Cancer Res. 2006;66(24):11590–3.
40. Mott JL, Kobayashi S, Bronk SF, Gores GJ. mir-29 regulates Mcl-1 protein expression and apoptosis. Oncogene. 2007;26(42):6133–40.
41. Pepper C, Lin TT, Pratt G, Hewamana S, Brennan P, Hiller L, et al. Mcl-1 expression has in vitro and in vivo significance in chronic lymphocytic leukemia and is associated with other poor prognostic markers. Blood. 2008;112(9):3807–17.
42. Roehle A, Hoefig KP, Repsilber D, Thorns C, Ziepert M, Wesche KO, et al. MicroRNA signatures characterize diffuse large B-cell lymphomas and follicular lymphomas. Br J Haematol. 2008;142(5):732–44.
43. Lossos IS, Levy R. Higher grade transformation of follicular lymphoma: phenotypic tumor progression associated with diverse genetic lesions. Semin Cancer Biol. 2003;13(3): 191–202.
44. Montoto S, Davies AJ, Matthews J, Calaminici M, Norton AJ, Amess J, et al. Risk and clinical implications of transformation of follicular lymphoma to diffuse large B-cell lymphoma. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2007;25(17):2426–33.
45. Lawrie CH, Chi J, Taylor S, Tramonti D, Ballabio E, Palazzo S, et al. Expression of microRNAs in diffuse large B cell lymphoma is associated with immunophenotype, survival and transformation from follicular lymphoma. J Cell Mol Med. 2009;13(7):1248–60.
46. Leich E, Zamo A, Horn H, Haralambieva E, Puppe B, Gascoyne RD, et al. MicroRNA profiles of t(14;18)-negative follicular lymphoma support a late germinal center B-cell phenotype. Blood. 2011;118(20):5550–8.
47. Anderson JR, Armitage JO, Weisenburger DD. Epidemiology of the non-Hodgkin's lymphomas: distributions of the major subtypes differ by geographic locations. Non-Hodgkin's Lymphoma Classification Project. Ann Oncol. 1998;9(7):717–20.
48. Zhou Y, Wang H, Fang W, Romaguer JE, Zhang Y, Delasalle KB, et al. Incidence trends of mantle cell lymphoma in the United States between 1992 and 2004. Cancer. 2008;113(4): 791–8.
49. Dreyling M, Hiddemann W. Current treatment standards and emerging strategies in mantle cell lymphoma. Hematology Am Soc Hematol Educ Program 2009: 542–51.
50. Jares P, Colomer D, Campo E. Genetic and molecular pathogenesis of mantle cell lymphoma: perspectives for new targeted therapeutics. Nat Rev Cancer. 2007;7(10):750–62.
51. Perez-Galan P, Dreyling M, Wiestner A. Mantle cell lymphoma: biology, pathogenesis, and the molecular basis of treatment in the genomic era. Blood. 2011;117(1):26–38.
52. Wiestner A, Tehrani M, Chiorazzi M, Wright G, Gibellini F, Nakayama K, et al. Point mutations and genomic deletions in CCND1 create stable truncated cyclin D1 mRNAs that are associated with increased proliferation rate and shorter survival. Blood. 2007;109(11): 4599–606.
53. Rosenwald A, Wright G, Wiestner A, Chan WC, Connors JM, Campo E, et al. The proliferation gene expression signature is a quantitative integrator of oncogenic events that predicts survival in mantle cell lymphoma. Cancer Cell. 2003;3(2):185–97.
54. Chen RW, Bemis LT, Amato CM, Myint H, Tran H, Birks DK, et al. Truncation in CCND1 mRNA alters miR-16-1 regulation in mantle cell lymphoma. Blood. 2008;112(3):822–9.
55. Deshpande A, Pastore A, Deshpande AJ, Zimmermann Y, Hutter G, Weinkauf M, et al. 3'UTR mediated regulation of the cyclin D1 proto-oncogene. Cell Cycle. 2009;8(21): 3584–92.

56. Zhao JJ, Lin J, Lwin T, Yang H, Guo J, Kong W, et al. microRNA expression profile and identification of miR-29 as a prognostic marker and pathogenetic factor by targeting CDK6 in mantle cell lymphoma. Blood. 2010;115(13):2630–9.
57. Navarro A, Bea S, Fernandez V, Prieto M, Salaverria I, Jares P, et al. MicroRNA expression, chromosomal alterations, and immunoglobulin variable heavy chain hypermutations in Mantle cell lymphomas. Cancer Res. 2009;69(17):7071–8.
58. Di Lisio L, Gomez-Lopez G, Sanchez-Beato M, Gomez-Abad C, Rodriguez ME, Villuendas R, et al. Mantle cell lymphoma: transcriptional regulation by microRNAs. Leukemia. 2010;24(7):1335–42.
59. A clinical evaluation of the International Lymphoma Study Group classification of non-Hodgkin's lymphoma. The Non-Hodgkin's Lymphoma Classification Project. Blood. 1997;89(11):3909–18.
60. Coiffier B, Lepage E, Briere J, Herbrecht R, Tilly H, Bouabdallah R, et al. CHOP chemotherapy plus rituximab compared with CHOP alone in elderly patients with diffuse large-B-cell lymphoma. N Engl J Med. 2002;346(4):235–42.
61. Feugier P, Van Hoof A, Sebban C, Solal-Celigny P, Bouabdallah R, Ferme C, et al. Long-term results of the R-CHOP study in the treatment of elderly patients with diffuse large B-cell lymphoma: a study by the Groupe d'Etude des Lymphomes de l'Adulte. J Clin Oncol. 2005;23(18):4117–26.
62. Habermann TM, Weller EA, Morrison VA, Gascoyne RD, Cassileth PA, Cohn JB, et al. Rituximab-CHOP versus CHOP alone or with maintenance rituximab in older patients with diffuse large B-cell lymphoma. J Clin Oncol. 2006;24(19):3121–7.
63. Pfreundschuh M, Trumper L, Osterborg A, Pettengell R, Trneny M, Imrie K, et al. CHOP-like chemotherapy plus rituximab versus CHOP-like chemotherapy alone in young patients with good-prognosis diffuse large-B-cell lymphoma: a randomised controlled trial by the MabThera International Trial (MInT) Group. Lancet Oncol. 2006;7(5):379–91.
64. Alizadeh AA, Eisen MB, Davis RE, Ma C, Lossos IS, Rosenwald A, et al. Distinct types of diffuse large B-cell lymphoma identified by gene expression profiling. Nature. 2000; 403(6769):503–11.
65. Rosenwald A, Wright G, Chan WC, Connors JM, Campo E, Fisher RI, et al. The use of molecular profiling to predict survival after chemotherapy for diffuse large-B-cell lymphoma. N Engl J Med. 2002;346(25):1937–47.
66. Rosenwald A, Wright G, Leroy K, Yu X, Gaulard P, Gascoyne RD, et al. Molecular diagnosis of primary mediastinal B cell lymphoma identifies a clinically favorable subgroup of diffuse large B cell lymphoma related to Hodgkin lymphoma. J Exp Med. 2003;198(6):851–62.
67. Lenz G, Staudt LM. Aggressive lymphomas. N Engl J Med. 2010;362(15):1417–29.
68. Lenz G, Wright G, Dave SS, Xiao W, Powell J, Zhao H, et al. Stromal gene signatures in large-B-cell lymphomas. N Engl J Med. 2008;359(22):2313–23.
69. Clurman BE, Hayward WS. Multiple proto-oncogene activations in avian leukosis virus-induced lymphomas: evidence for stage-specific events. Mol Cell Biol. 1989;9(6):2657–64.
70. Tam W. Identification and characterization of human BIC, a gene on chromosome 21 that encodes a noncoding RNA. Gene. 2001;274(1–2):157–67.
71. Tam W, Ben-Yehuda D, Hayward WS. bic, a novel gene activated by proviral insertions in avian leukosis virus-induced lymphomas, is likely to function through its noncoding RNA. Mol Cell Biol. 1997;17(3):1490–502.
72. Eis PS, Tam W, Sun L, Chadburn A, Li Z, Gomez MF, et al. Accumulation of miR-155 and BIC RNA in human B cell lymphomas. Proc Natl Acad Sci U S A. 2005;102(10):3627–32.
73. Kluiver J, Poppema S, de Jong D, Blokzijl T, Harms G, Jacobs S, et al. BIC and miR-155 are highly expressed in Hodgkin, primary mediastinal and diffuse large B cell lymphomas. J Pathol. 2005;207(2):243–9.
74. Costinean S, Zanesi N, Pekarsky Y, Tili E, Volinia S, Heerema N, et al. Pre-B cell proliferation and lymphoblastic leukemia/high-grade lymphoma in E(mu)-miR155 transgenic mice. Proc Natl Acad Sci U S A. 2006;103(18):7024–9.

75. Costinean S, Sandhu SK, Pedersen IM, Tili E, Trotta R, Perrotti D, et al. Src homology 2 domain-containing inositol-5-phosphatase and CCAAT enhancer-binding protein beta are targeted by miR-155 in B cells of Emicro-MiR-155 transgenic mice. Blood. 2009;114(7):1374–82.
76. Pedersen IM, Otero D, Kao E, Miletic AV, Hother C, Ralfkiaer E, et al. Onco-miR-155 targets SHIP1 to promote TNFalpha-dependent growth of B cell lymphomas. EMBO Mol Med. 2009;1(5):288–95.
77. Davis RE, Brown KD, Siebenlist U, Staudt LM. Constitutive nuclear factor kappaB activity is required for survival of activated B cell-like diffuse large B cell lymphoma cells. J Exp Med. 2001;194(12):1861–74.
78. Savage KJ, Monti S, Kutok JL, Cattoretti G, Neuberg D, De Leval L, et al. The molecular signature of mediastinal large B-cell lymphoma differs from that of other diffuse large B-cell lymphomas and shares features with classical Hodgkin lymphoma. Blood. 2003;102(12):3871–9.
79. Vargova K, Curik N, Burda P, Basova P, Kulvait V, Pospisil V, et al. MYB transcriptionally regulates the miR-155 host gene in chronic lymphocytic leukemia. Blood. 2011;117(14):3816–25.
80. Yin Q, Wang X, McBride J, Fewell C, Flemington E. B-cell receptor activation induces BIC/miR-155 expression through a conserved AP-1 element. J Biol Chem. 2008;283(5):2654–62.
81. Siebert R, Gesk S, Harder S, Plotz S, Matthiesen P, Grote W, et al. Deletions in the long arm of chromosome 10 in lymphomas with t(14;18): a pathogenetic role of the tumor supressor genes PTEN/MMAC1 and MXI1? Blood. 1998;92(11):4487–9.
82. Lenz G, Wright GW, Emre NC, Kohlhammer H, Dave SS, Davis RE, et al. Molecular subtypes of diffuse large B-cell lymphoma arise by distinct genetic pathways. Proc Natl Acad Sci U S A. 2008;105(36):13520–5.
83. Xiao C, Srinivasan L, Calado DP, Patterson HC, Zhang B, Wang J, et al. Lymphoproliferative disease and autoimmunity in mice with increased miR-17-92 expression in lymphocytes. Nat Immunol. 2008;9(4):405–14.
84. Kloo B, Nagel D, Pfeifer M, Grau M, Duwel M, Vincendeau M, et al. Critical role of PI3K signaling for NF-kappaB-dependent survival in a subset of activated B-cell-like diffuse large B-cell lymphoma cells. Proc Natl Acad Sci U S A. 2011;108(1):272–7.
85. Ota A, Tagawa H, Karnan S, Tsuzuki S, Karpas A, Kira S, et al. Identification and characterization of a novel gene, C13orf25, as a target for 13q31-q32 amplification in malignant lymphoma. Cancer Res. 2004;64(9):3087–95.
86. Li C, Kim SW, Rai D, Bolla AR, Adhvaryu S, Kinney MC, et al. Copy number abnormalities, MYC activity, and the genetic fingerprint of normal B cells mechanistically define the microRNA profile of diffuse large B-cell lymphoma. Blood. 2009;113(26):6681–90.
87. He L, Thomson JM, Hemann MT, Hernando-Monge E, Mu D, Goodson S, et al. A microRNA polycistron as a potential human oncogene. Nature. 2005;435(7043):828–33.
88. O’Donnell KA, Wentzel EA, Zeller KI, Dang CV, Mendell JT. c-Myc-regulated microRNAs modulate E2F1 expression. Nature. 2005;435(7043):839–43.
89. Sylvestre Y, De Guire V, Querido E, Mukhopadhyay UK, Bourdeau V, Major F, et al. An E2F/miR-20a autoregulatory feedback loop. J Biol Chem. 2007;282(4):2135–43.
90. Woods K, Thomson JM, Hammond SM. Direct regulation of an oncogenic micro-RNA cluster by E2F transcription factors. J Biol Chem. 2007;282(4):2130–4.
91. Mu P, Han YC, Betel D, Yao E, Squatrito M, Ogrodowski P, et al. Genetic dissection of the miR-17 92 cluster of microRNAs in Myc-induced B-cell lymphomas. Genes Dev. 2009;23(24):2806–11.
92. Olive V, Bennett MJ, Walker JC, Ma C, Jiang I, Cordon-Cardo C, et al. miR-19 is a key oncogenic component of mir-17-92. Genes Dev. 2009;23(24):2839–49.
93. Inomata M, Tagawa H, Guo YM, Kameoka Y, Takahashi N, Sawada K. MicroRNA-17-92 down-regulates expression of distinct targets in different B-cell lymphoma subtypes. Blood. 2009;113(2):396–402.

94. Petrocca F, Vecchione A, Croce CM. Emerging role of miR-106b-25/miR-17-92 clusters in the control of transforming growth factor beta signaling. Cancer Res. 2008;68(20):8191–4.
95. Rai D, Kim SW, McKeller MR, Dahia PL, Aguiar RC. Targeting of SMAD5 links microRNA-155 to the TGF-beta pathway and lymphomagenesis. Proc Natl Acad Sci U S A. 2010;107(7):3111–6.
96. Ferreri AJ. How I, treat primary CNS lymphoma. Blood. 2011;118(3):510–22.
97. Fischer L, Hummel M, Korfel A, Lenze D, Joehrens K, Thiel E. Differential micro-RNA expression in primary CNS and nodal diffuse large B-cell lymphomas. Neuro Oncol. 2011;13(10):1090–8.
98. Robertus JL, Harms G, Blokzijl T, Booman M, de Jong D, van Imhoff G, et al. Specific expression of miR-17-5p and miR-127 in testicular and central nervous system diffuse large B-cell lymphoma. Mod Pathol. 2009;22(4):547–55.
99. Wright G, Tan B, Rosenwald A, Hurt EH, Wiestner A, Staudt LM. A gene expression-based method to diagnose clinically distinct subgroups of diffuse large B cell lymphoma. Proc Natl Acad Sci U S A. 2003;100(17):9991–6.
100. Montes-Moreno S, Martinez N, Sanchez-Espiridion B, Diaz Uriarte R, Rodriguez ME, Saez A, et al. miRNA expression in diffuse large B-cell lymphoma treated with chemoimmunotherapy. Blood. 2011;118(4):1034–40.
101. Lawrie CH, Soneji S, Marafioti T, Cooper CD, Palazzo S, Paterson JC, et al. MicroRNA expression distinguishes between germinal center B cell-like and activated B cell-like subtypes of diffuse large B cell lymphoma. Int J Cancer. 2007;121(5):1156–61.
102. Malumbres R, Sarosiek KA, Cubedo E, Ruiz JW, Jiang X, Gascoyne RD, et al. Differentiation stage-specific expression of microRNAs in B lymphocytes and diffuse large B-cell lymphomas. Blood. 2009;113(16):3754–64.
103. Alencar AJ, Malumbres R, Kozloski GA, Advani R, Talreja N, Chinichian S, et al. MicroRNAs are independent predictors of outcome in diffuse large B-cell lymphoma patients treated with R-CHOP. Clin Cancer Res. 2011;17(12):4125–35.
104. de Leval L, Hasserjian RP. Diffuse large B-cell lymphomas and Burkitt lymphoma. Hematol Oncol Clin North Am. 2009;23(4):791–827.
105. Mbulaiteye SM, Anderson WF, Bhatia K, Rosenberg PS, Linet MS, Devesa SS. Trimodal age-specific incidence patterns for Burkitt lymphoma in the United States, 1973–2005. Int J Cancer. 2010;126(7):1732–9.
106. Blum KA, Lozanski G, Byrd JC. Adult Burkitt leukemia and lymphoma. Blood. 2004;104(10):3009–20.
107. Thomas DA, Faderl S, O'Brien S, Bueso-Ramos C, Cortes J, Garcia-Manero G, et al. Chemoimmunotherapy with hyper-CVAD plus rituximab for the treatment of adult Burkitt and Burkitt-type lymphoma or acute lymphoblastic leukemia. Cancer. 2006;106(7):1569–80.
108. Taub R, Kirsch I, Morton C, Lenoir G, Swan D, Tronick S, et al. Translocation of the c-myc gene into the immunoglobulin heavy chain locus in human Burkitt lymphoma and murine plasmacytoma cells. Proc Natl Acad Sci U S A. 1982;79(24):7837–41.
109. Dave SS, Fu K, Wright GW, Lam LT, Kluin P, Boerma EJ, et al. Molecular diagnosis of Burkitt's lymphoma. N Engl J Med. 2006;354(23):2431–42.
110. Lenze D, Leoncini L, Hummel M, Volinia S, Liu CG, Amato T, et al. The different epidemiologic subtypes of Burkitt lymphoma share a homogenous micro RNA profile distinct from diffuse large B-cell lymphoma. Leukemia. 2011;25(12):1869–76.
111. Robertus JL, Kluiver J, Weggemans C, Harms G, Reijmers RM, Swart Y, et al. MiRNA profiling in B non-Hodgkin lymphoma: a MYC-related miRNA profile characterizes Burkitt lymphoma. Br J Haematol. 2010;149(6):896–9.
112. Chang TC, Yu D, Lee YS, Wentzel EA, Arking DE, West KM, et al. Widespread microRNA repression by Myc contributes to tumorigenesis. Nat Genet. 2008;40(1):43–50.
113. Sander S, Bullinger L, Klapproth K, Fiedler K, Kestler HA, Barth TF, et al. MYC stimulates EZH2 expression by repression of its negative regulator miR-26a. Blood. 2008;112(10):4202–12.

114. Sampson VB, Rong NH, Han J, Yang Q, Aris V, Soteropoulos P, et al. MicroRNA let-7a down-regulates MYC and reverts MYC-induced growth in Burkitt lymphoma cells. Cancer Res. 2007;67(20):9762–70.
115. Onnis A, De Falco G, Antonicelli G, Onorati M, Bellan C, Sherman O, et al. Alteration of microRNAs regulated by c-Myc in Burkitt lymphoma. PLoS One. 2010;5(9):e12960.
116. Kuehl WM, Bergsagel PL. Multiple myeloma: evolving genetic events and host interactions. Nat Rev Cancer. 2002;2(3):175–87.
117. Palumbo A, Anderson K. Multiple myeloma. N Engl J Med. 2011;364(11):1046–60.
118. Avet-Loiseau H, Attal M, Moreau P, Charbonnel C, Garban F, Hulin C, et al. Genetic abnormalities and survival in multiple myeloma: the experience of the Intergroupe Francophone du Myelome. Blood. 2007;109(8):3489–95.
119. Bergsagel PL, Kuehl WM. Molecular pathogenesis and a consequent classification of multiple myeloma. J Clin Oncol. 2005;23(26):6333–8.
120. Calasanz MJ, Cigudosa JC, Odero MD, Ferreira C, Ardanaz MT, Fraile A, et al. Cytogenetic analysis of 280 patients with multiple myeloma and related disorders: primary breakpoints and clinical correlations. Genes Chromosomes Cancer. 1997;18(2):84–93.
121. Chesi M, Bergsagel PL, Brents LA, Smith CM, Gerhard DS, Kuehl WM. Dysregulation of cyclin D1 by translocation into an IgH gamma switch region in two multiple myeloma cell lines. Blood. 1996;88(2):674–81.
122. Gabrea A, Bergsagel PL, Chesi M, Shou Y, Kuehl WM. Insertion of excised IgH switch sequences causes overexpression of cyclin D1 in a myeloma tumor cell. Mol Cell. 1999;3(1):119–23.
123. Shaughnessy Jr J, Gabrea A, Qi Y, Brents L, Zhan F, Tian E, et al. Cyclin D3 at 6p21 is dysregulated by recurrent chromosomal translocations to immunoglobulin loci in multiple myeloma. Blood. 2001;98(1):217–23.
124. Chesi M, Nardini E, Brents LA, Schrock E, Ried T, Kuehl WM, et al. Frequent translocation t(4;14)(p16.3;q32.3) in multiple myeloma is associated with increased expression and activating mutations of fibroblast growth factor receptor 3. Nat Genet. 1997;16(3):260–4.
125. Chesi M, Nardini E, Lim RS, Smith KD, Kuehl WM, Bergsagel PL. The t(4;14) translocation in myeloma dysregulates both FGFR3 and a novel gene, MMSET, resulting in IgH/MMSET hybrid transcripts. Blood. 1998;92(9):3025–34.
126. Chesi M, Bergsagel PL, Shonukan OO, Martelli ML, Brents LA, Chen T, et al. Frequent dysregulation of the c-maf proto-oncogene at 16q23 by translocation to an Ig locus in multiple myeloma. Blood. 1998;91(12):4457–63.
127. Hurt EM, Wiestner A, Rosenwald A, Shaffer AL, Campo E, Grogan T, et al. Overexpression of c-maf is a frequent oncogenic event in multiple myeloma that promotes proliferation and pathological interactions with bone marrow stroma. Cancer Cell. 2004;5(2):191–9.
128. Chng WJ, Glebov O, Bergsagel PL, Kuehl WM. Genetic events in the pathogenesis of multiple myeloma. Best Pract Res Clin Haematol. 2007;20(4):571–96.
129. Corradini P, Ladetto M, Voena C, Palumbo A, Inghirami G, Knowles DM, et al. Mutational activation of N- and K-ras oncogenes in plasma cell dyscrasias. Blood. 1993;81(10): 2708–13.
130. Bezieau S, Devilder MC, Avet-Loiseau H, Mellerin MP, Puthier D, Pennarun E, et al. High incidence of N and K-Ras activating mutations in multiple myeloma and primary plasma cell leukemia at diagnosis. Hum Mutat. 2001;18(3):212–24.
131. Chi J, Ballabio E, Chen XH, Kusec R, Taylor S, Hay D, et al. MicroRNA expression in multiple myeloma is associated with genetic subtype, isotype and survival. Biol Direct. 2011;6:23.
132. Lionetti M, Biasiolo M, Agnelli L, Todoerti K, Mosca L, Fabris S, et al. Identification of microRNA expression patterns and definition of a microRNA/mRNA regulatory network in distinct molecular groups of multiple myeloma. Blood. 2009;114(25):e20–6.
133. Pichiorri F, Suh SS, Ladetto M, Kuehl M, Palumbo T, Drandi D, et al. MicroRNAs regulate critical genes associated with multiple myeloma pathogenesis. Proc Natl Acad Sci U S A. 2008;105(35):12885–90.

134. Roccaro AM, Sacco A, Thompson B, Leleu X, Azab AK, Azab F, et al. MicroRNAs 15a and 16 regulate tumor proliferation in multiple myeloma. Blood. 2009;113(26):6669–80.
135. Kanayama A, Seth RB, Sun L, Ea CK, Hong M, Shaito A, et al. TAB2 and TAB3 activate the NF-kappaB pathway through binding to polyubiquitin chains. Mol Cell. 2004;15(4):535–48.
136. Jin G, Klika A, Callahan M, Faga B, Danzig J, Jiang Z, et al. Identification of a human NF-kappaB-activating protein, TAB3. Proc Natl Acad Sci U S A. 2004;101(7):2028–33.
137. Hideshima T, Mitsiades C, Tonon G, Richardson PG, Anderson KC. Understanding multiple myeloma pathogenesis in the bone marrow to identify new therapeutic targets. Nat Rev Cancer. 2007;7(8):585–98.
138. Loffler D, Brocke-Heidrich K, Pfeifer G, Stocsits C, Hackermuller J, Kretzschmar AK, et al. Interleukin-6 dependent survival of multiple myeloma cells involves the Stat3-mediated induction of microRNA-21 through a highly conserved enhancer. Blood. 2007;110(4):1330–3.
139. Dankbar B, Padro T, Leo R, Feldmann B, Kropff M, Mesters RM, et al. Vascular endothelial growth factor and interleukin-6 in paracrine tumor-stromal cell interactions in multiple myeloma. Blood. 2000;95(8):2630–6.
140. Vacca A, Ribatti D, Roncali L, Ranieri G, Serio G, Silvestris F, et al. Bone marrow angiogenesis and progression in multiple myeloma. Br J Haematol. 1994;87(3):503–8.
141. Singhal S, Mehta J, Desikan R, Ayers D, Roberson P, Eddlemon P, et al. Antitumor activity of thalidomide in refractory multiple myeloma. N Engl J Med. 1999;341(21):1565–71.
142. Hayashi T, Hideshima T, Anderson KC. Novel therapies for multiple myeloma. Br J Haematol. 2003;120(1):10–7.
143. Hideshima T, Chauhan D, Podar K, Schlossman RL, Richardson P, Anderson KC. Novel therapies targeting the myeloma cell and its bone marrow microenvironment. Semin Oncol. 2001;28(6):607–12.
144. Zhou Y, Chen L, Barlogie B, Stephens O, Wu X, Williams DR, et al. High-risk myeloma is associated with global elevation of miRNAs and overexpression of EIF2C2/AGO2. Proc Natl Acad Sci U S A. 2010;107(17):7904–9.
145. Quesnel B, Preudhomme C, Oscier D, Lepelley P, Collyn-d'Hooghe M, Facon T, et al. Overexpression of the MDM2 gene is found in some cases of haematological malignancies. Br J Haematol. 1994;88(2):415–8.
146. Teoh G, Urashima M, Ogata A, Chauhan D, DeCaprio JA, Treon SP, et al. MDM2 protein overexpression promotes proliferation and survival of multiple myeloma cells. Blood. 1997;90(5):1982–92.
147. Hermeking H. The miR-34 family in cancer and apoptosis. Cell Death Differ. 2010;17(2):193–9.
148. Pichiorri F, Suh SS, Rocci A, De Luca L, Taccioli C, Santhanam R, et al. Downregulation of p53-inducible microRNAs 192, 194, and 215 impairs the p53/MDM2 autoregulatory loop in multiple myeloma development. Cancer Cell. 2010;18(4):367–81.
149. Girnita L, Girnita A, Larsson O. Mdm2-dependent ubiquitination and degradation of the insulin-like growth factor 1 receptor. Proc Natl Acad Sci U S A. 2003;100(14):8247–52.
150. Froment P, Dupont J, Christophe-Marine J. Mdm2 exerts pro-apoptotic activities by antagonizing insulin-like growth factor-I-mediated survival. Cell Cycle. 2008;7(19):3098–103.
151. Armitage JO. Early-stage Hodgkin's lymphoma. N Engl J Med. 2010;363(7):653–62.
152. Kuppers R. Molecular biology of Hodgkin lymphoma. Hematology Am Soc Hematol Educ Program 2009: 491–6.
153. Kato M, Sanada M, Kato I, Sato Y, Takita J, Takeuchi K, et al. Frequent inactivation of A20 in B-cell lymphomas. Nature. 2009;459(7247):712–6.
154. Schmitz R, Hansmann ML, Bohle V, Martin-Subero JI, Hartmann S, Mechtersheimer G, et al. TNFAIP3 (A20) is a tumor suppressor gene in Hodgkin lymphoma and primary mediastinal B cell lymphoma. J Exp Med. 2009;206(5):981–9.
155. Kilger E, Kieser A, Baumann M, Hammerschmidt W. Epstein-Barr virus-mediated B-cell proliferation is dependent upon latent membrane protein 1, which simulates an activated CD40 receptor. EMBO J. 1998;17(6):1700–9.

156. Mancao C, Hammerschmidt W. Epstein-Barr virus latent membrane protein 2A is a B-cell receptor mimic and essential for B-cell survival. Blood. 2007;110(10):3715–21.
157. Van Vlierberghe P, De Weer A, Mestdagh P, Feys T, De Preter K, De Paepe P, et al. Comparison of miRNA profiles of microdissected Hodgkin/Reed-Sternberg cells and Hodgkin cell lines versus CD77+ B-cells reveals a distinct subset of differentially expressed miRNAs. Br J Haematol. 2009;147(5):686–90.
158. Mottok A, Renne C, Willenbrock K, Hansmann ML, Brauninger A. Somatic hypermutation of SOCS1 in lymphocyte-predominant Hodgkin lymphoma is accompanied by high JAK2 expression and activation of STAT6. Blood. 2007;110(9):3387–90.
159. Nie K, Gomez M, Landgraf P, Garcia JF, Liu Y, Tan LH, et al. MicroRNA-mediated down-regulation of PRDM1/Blimp-1 in Hodgkin/Reed-Sternberg cells: a potential pathogenetic lesion in Hodgkin lymphomas. Am J Pathol. 2008;173(1):242–52.
160. Gibcus JH, Tan LP, Harms G, Schakel RN, de Jong D, Blokzijl T, et al. Hodgkin lymphoma cell lines are characterized by a specific miRNA expression profile. Neoplasia. 2009;11(2): 167–76.
161. Gatto G, Rossi A, Rossi D, Kroening S, Bonatti S, Mallardo M. Epstein-Barr virus latent membrane protein 1 trans-activates miR-155 transcription through the NF-kappaB pathway. Nucleic Acids Res. 2008;36(20):6608–19.
162. Navarro A, Gaya A, Martinez A, Urbano-Ispizua A, Pons A, Balague O, et al. MicroRNA expression profiling in classic Hodgkin lymphoma. Blood. 2008;111(5):2825–32.
163. Navarro A, Diaz T, Martinez A, Gaya A, Pons A, Gel B, et al. Regulation of JAK2 by miR-135a: prognostic impact in classic Hodgkin lymphoma. Blood. 2009;114(14):2945–51.
164. Melo JV, Barnes DJ. Chronic myeloid leukaemia as a model of disease evolution in human cancer. Nat Rev Cancer. 2007;7(6):441–53.
165. Sawyers CL. Chronic myeloid leukemia. N Engl J Med. 1999;340(17):1330–40.
166. Venturini L, Battmer K, Castoldi M, Schultheis B, Hochhaus A, Muckenthaler MU, et al. Expression of the miR-17-92 polycistron in chronic myeloid leukemia (CML) CD34+ cells. Blood. 2007;109(10):4399–405.
167. Bueno MJ, Perez de Castro I, Gomez de Cedron M, Santos J, Calin GA, Cigudosa JC, et al. Genetic and epigenetic silencing of microRNA-203 enhances ABL1 and BCR-ABL1 oncogene expression. Cancer Cell. 2008;13(6):496–506.
168. Agirre X, Jimenez-Velasco A, San Jose-Eneriz E, Garate L, Bandres E, Cordeu L, et al. Down-regulation of hsa-miR-10a in chronic myeloid leukemia CD34+ cells increases USF2-mediated cell growth. Mol Cancer Res. 2008;6(12):1830–40.
169. Perrotti D, Cesi V, Trotta R, Guerzoni C, Santilli G, Campbell K, et al. BCR-ABL suppresses C/EBPalpha expression through inhibitory action of hnRNP E2. Nat Genet. 2002;30(1): 48–58.
170. Perrotti D, Neviani P. From mRNA metabolism to cancer therapy: chronic myelogenous leukemia shows the way. Clin Cancer Res. 2007;13(6):1638–42.
171. Chang JS, Santhanam R, Trotta R, Neviani P, Eiring AM, Briercheck E, et al. High levels of the BCR/ABL oncoprotein are required for the MAPK-hnRNP-E2 dependent suppression of C/EBPalpha-driven myeloid differentiation. Blood. 2007;110(3):994–1003.
172. Gaynon PS. Childhood acute lymphoblastic leukaemia and relapse. Br J Haematol. 2005; 131(5):579–87.
173. Mullighan CG. Molecular genetics of B-precursor acute lymphoblastic leukemia. J Clin Invest. 2012;122(10):3407–15.
174. Mi S, Lu J, Sun M, Li Z, Zhang H, Neilly MB, et al. MicroRNA expression signatures accurately discriminate acute lymphoblastic leukemia from acute myeloid leukemia. Proc Natl Acad Sci U S A. 2007;104(50):19971–6.
175. Zhang H, Luo XQ, Zhang P, Huang LB, Zheng YS, Wu J, et al. MicroRNA patterns associated with clinical prognostic parameters and CNS relapse prediction in pediatric acute leukemia. PLoS One. 2009;4(11):e7826.
176. Fulci V, Colombo T, Chiaretti S, Messina M, Citarella F, Tavolaro S, et al. Characterization of B- and T-lineage acute lymphoblastic leukemia by integrated analysis of MicroRNA and mRNA expression profiles. Genes Chromosomes Cancer. 2009;48(12):1069–82.

177. Schotte D, Chau JC, Sylvester G, Liu G, Chen C, van der Velden VH, et al. Identification of new microRNA genes and aberrant microRNA profiles in childhood acute lymphoblastic leukemia. Leukemia. 2009;23(2):313–22.
178. Kaddar T, Chien WW, Bertrand Y, Pages MP, Rouault JP, Salles G, et al. Prognostic value of miR-16 expression in childhood acute lymphoblastic leukemia relationships to normal and malignant lymphocyte proliferation. Leuk Res. 2009;33(9):1217–23.
179. Bloomfield CD, Marcucci G, Dohner K, Dohner H. Acute myeloid leukemia. Introduction. Semin Oncol. 2008;35(4):324–5.
180. Vardiman JW, Thiele J, Arber DA, Brunning RD, Borowitz MJ, Porwit A, et al. The 2008 revision of the World Health Organization (WHO) classification of myeloid neoplasms and acute leukemia: rationale and important changes. Blood. 2009;114(5):937–51.
181. Chen CZ, Li L, Lodish HF, Bartel DP. MicroRNAs modulate hematopoietic lineage differentiation. Science. 2004;303(5654):83–6.
182. Petriv OI, Kuchenbauer F, Delaney AD, Lecault V, White A, Kent D, et al. Comprehensive microRNA expression profiling of the hematopoietic hierarchy. Proc Natl Acad Sci U S A. 2010;107(35):15443–8.
183. Fazi F, Rosa A, Fatica A, Gelmetti V, De Marchis ML, Nervi C, et al. A minicircuitry comprised of microRNA-223 and transcription factors NFI-A and C/EBPalpha regulates human granulopoiesis. Cell. 2005;123(5):819–31.
184. Fazi F, Racanicchi S, Zardo G, Starnes LM, Mancini M, Travaglini L, et al. Epigenetic silencing of the myelopoiesis regulator microRNA-223 by the AML1/ETO oncoprotein. Cancer Cell. 2007;12(5):457–66.
185. Johnnidis JB, Harris MH, Wheeler RT, Stehling-Sun S, Lam MH, Kirak O, et al. Regulation of progenitor cell proliferation and granulocyte function by microRNA-223. Nature. 2008;451(7182):1125–9.
186. Isken F, Steffen B, Merk S, Dugas M, Markus B, Tidow N, et al. Identification of acute myeloid leukaemia associated microRNA expression patterns. Br J Haematol. 2008;140(2):153–61.
187. Garzon R, Garofalo M, Martelli MP, Briesewitz R, Wang L, Fernandez-Cymering C, et al. Distinctive microRNA signature of acute myeloid leukemia bearing cytoplasmic mutated nucleophosmin. Proc Natl Acad Sci U S A. 2008;105(10):3945–50.
188. Jongen-Lavrencic M, Sun SM, Dijkstra MK, Valk PJ, Lowenberg B. MicroRNA expression profiling in relation to the genetic heterogeneity of acute myeloid leukemia. Blood. 2008;111(10):5078–85.
189. Debernardi S, Skoulakis S, Molloy G, Chaplin T, Dixon-McIver A, Young BD. MicroRNA miR-181a correlates with morphological sub-class of acute myeloid leukaemia and the expression of its target genes in global genome-wide analysis. Leukemia. 2007;21(5):912–6.
190. Kuchenbauer F, Mah SM, Heuser M, McPherson A, Ruschmann J, Rouhi A, et al. Comprehensive analysis of mammalian miRNA* species and their role in myeloid cells. Blood. 2011;118(12):3350–8.
191. Garzon R, Volinia S, Liu CG, Fernandez-Cymering C, Palumbo T, Pichiorri F, et al. MicroRNA signatures associated with cytogenetics and prognosis in acute myeloid leukemia. Blood. 2008;111(6):3183–9.
192. Cammarata G, Augugliaro L, Salemi D, Agueli C, La Rosa M, Dagnino L, et al. Differential expression of specific microRNA and their targets in acute myeloid leukemia. Am J Hematol. 2010;85(5):331–9.
193. Faraoni I, Laterza S, Ardiri D, Ciardi C, Fazi F, Lo-Coco F. MiR-424 and miR-155 deregulated expression in cytogenetically normal acute myeloid leukaemia: correlation with NPM1 and FLT3 mutation status. J Hematol Oncol. 2012;5(1):26.
194. Danen-van Oorschot AA, Kuipers JE, Arentsen-Peters S, Schotte D, de Haas V, Trka J, et al. Differentially expressed miRNAs in cytogenetic and molecular subtypes of pediatric acute myeloid leukemia. Pediatr Blood Cancer. 2012;58(5):715–21.
195. Whitman SP, Maharry K, Radmacher MD, Becker H, Mrozek K, Margeson D, et al. FLT3 internal tandem duplication associates with adverse outcome and gene- and microRNA-

expression signatures in patients 60 years of age or older with primary cytogenetically normal acute myeloid leukemia: a Cancer and Leukemia Group B study. Blood. 2010;116(18): 3622–6.
196. Zhu YD, Wang L, Sun C, Fan L, Zhu DX, Fang C, et al. Distinctive microRNA signature is associated with the diagnosis and prognosis of acute leukemia. Med Oncol. 2012;29(4): 2323–31.
197. Li Z, Lu J, Sun M, Mi S, Zhang H, Luo RT, et al. Distinct microRNA expression profiles in acute myeloid leukemia with common translocations. Proc Natl Acad Sci U S A. 2008; 105(40):15535–40.
198. Langer C, Marcucci G, Holland KB, Radmacher MD, Maharry K, Paschka P, et al. Prognostic importance of MN1 transcript levels, and biologic insights from MN1-associated gene and microRNA expression signatures in cytogenetically normal acute myeloid leukemia: a Cancer and Leukemia Group B study. J Clin Oncol. 2009;27(19):3198–204.
199. Sun SM, Rockova V, Bullinger L, Dijkstra MK, Dohner H, Lowenberg B, et al. The prognostic relevance of miR-212 expression with survival in cytogenetically and molecularly heterogeneous AML. Leukemia. 2013;27(1):100–6.
200. Schwind S, Maharry K, Radmacher MD, Mrozek K, Holland KB, Margeson D, et al. Prognostic significance of expression of a single microRNA, miR-181a, in cytogenetically normal acute myeloid leukemia: a Cancer and Leukemia Group B study. J Clin Oncol. 2010;28(36):5257–64.
201. Eisfeld AK, Marcucci G, Maharry K, Schwind S, Radmacher MD, Nicolet D, et al. miR-3151 interplays with its host gene BAALC and independently affects outcome of patients with cytogenetically normal acute myeloid leukemia. Blood. 2012;120(2):249–58.
202. Wong P, Iwasaki M, Somervaille TC, Ficara F, Carico C, Arnold C, et al. The miR-17-92 microRNA polycistron regulates MLL leukemia stem cell potential by modulating p21 expression. Cancer Res. 2010;70(9):3833–42.
203. Han YC, Park CY, Bhagat G, Zhang J, Wang Y, Fan JB, et al. microRNA-29a induces aberrant self-renewal capacity in hematopoietic progenitors, biased myeloid development, and acute myeloid leukemia. J Exp Med. 2010;207(3):475–89.
204. O'Connell RM, Rao DS, Chaudhuri AA, Boldin MP, Taganov KD, Nicoll J, et al. Sustained expression of microRNA-155 in hematopoietic stem cells causes a myeloproliferative disorder. J Exp Med. 2008;205(3):585–94.
205. Garzon R, Liu S, Fabbri M, Liu Z, Heaphy CE, Callegari E, et al. MicroRNA-29b induces global DNA hypomethylation and tumor suppressor gene reexpression in acute myeloid leukemia by targeting directly DNMT3A and 3B and indirectly DNMT1. Blood. 2009;113(25): 6411–8.