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MicroRNAs as Targets and Tools in B-Cell Lymphoma Therapy

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ABSTRACT

MicroRNAs (miRNAs) are posttranscriptional regulators fine-tuning the level of most messenger RNAs (mRNAs) and proteins in mammalian cells. Their expression is dysregulated in neoplastic cells and upregulated or downregulated miRNAs play an important role in tumorigenesis. Changes in the miRNA transcriptome appear to be suitable markers for the differential diagnosis of various B-cell lymphoma types and there are therapeutic attempts to normalize the expression level of key cellular miRNAs involved in lymphomagenesis. In this review we wish to outline the most recent developments in the application of sophisticated, chemically modified antisense oligonucleotides and their nanoparticle complexes to suppress oncogenic miRNAs. These advances form the basis of a new therapeutic approach that may complement current protocols for B-cell lymphoma therapy. Anti-cytokine therapy aiming at the removal of cytokines that activate key oncomirs, and switching on silenced tumor suppressor miRNAs by epigenetic drugs might also be considered, on the long run, in the treatment of well defined B-cell lymphoma types.

Keywords: MicroRNAs; B-Cell Lymphoma Therapy; Antisense Oligonucleotides; Anti-Cytokine Therapy; Epigenetic Drugs

1. Introduction

Recently, microRNAs (miRNAs) emerged as a new class of regulators of a wide variety of physiological processes [1]. miRNAs usually downregulate messenger RNA (mRNA) levels and protein levels by binding to complementary regions on their target mRNAs. miRNA-mRNA association may either facilitate mRNA breakdown or block mRNA translation.

Dysregulated expression of certain miRNAs plays a role in the development of malignant neoplasms [2-4]. Increased level of several miRNAs, called oncomirs, facilitates oncogenesis and tumor progression. Other miRNAs act similarly to the products of tumor suppressor genes: their reduced expression may result in uncontrolled cell proliferation and altered cellular behaviour.

2. miRNAs as Pleiotropic Posttranscriptional Regulators in Normal and Neoplastic Cells

2.1. Biogenesis of MicroRNAs

miRNAs are transcribed in most cases by RNA polymerase II (Pol II) from independent transcription units or they are processed from introns of transcripts (for review see [1,3]). Typically the primary Pol II product (pri-miRNA) is processed in the nucleus by the RNase III Drosha resulting in a stem and loop structure called pre-miRNA. The approximatively 70 nucleotide long pre-miRNA molecule is carried to the cytoplasm by Exportin 5, a nuclear export protein. As a next processing step, DICER1, a cytoplasmic RNAse III enzyme removes the loop of the pre-miRNA and the resulting double stranded RNA is loaded onto an Argonaute (Ago) protein, a component of the RNA-induced silencing complex (RISC). One strand of the approximately 22 nucleotide long duplex RNA represents the guide strand or mature miRNA that remains associated with Ago, whereas the other strand is degraded. As few as 6 nucleotides of the mature single stranded miRNA (nucleotides 2 - 7) form the "seed region" that plays a major role in selecting the 3' untranslated region (3' UTR) of the target mRNA. Because the seed region, where full complementarity is required with the target mRNA for RISC function, is short, a miRNA may potentially recognize multiple mRNA targets. It is also worthy to note, however, that the very

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same 3' UTR may bind more than one miRNA species (reviewed in [1,3]).

2.2. Dysregulation of miRNA Expression in B-Cell Lymphomas

The pattern of miRNA expression in neoplastic cells differs from the miRNA transcriptome (miRNAome) of their normal counterparts (for review see [3]). In addition, the expression signatures of miRNAs appear to be suitable markers for the differential diagnosis of various malignant tumors including the different B-cell lymphoma types [5]. Some of the differentially expressed miRNAs apparently play an important role in the initiation and maintenance of the malignant behaviour, which implies that overexpression or inhibition of key microRNAs may revert the malignant phenotype. The best characterized miRNAs most frequently upregulated or downregulated in the major B-cell lymphoma types are summarized in **Tables 1** and **2** (for a comprehensive review see also [4]). **Tables 1** and **2** also show their target mRNAs and putative role in lymphomagenesis. It is important to note that—depending on the cellular context—the very same miRNA may either facilitate or inhibit tumorigenesis. Thus, miR-155, a multifunctional regulator molecule upregulated in diffuse large B-cell lymphomas (DLBLs) and Hodgkin lymphomas acted as an oncomir in a transgenic mouse model, where its ectopic expression resulted in pre-B cell proliferation and lymphoblastic leukemia/lymphoma [6-8]. All these changes were attributed to a release of the interleukin-6 (IL-6) pathway from its inhibitory control by miR-155 [9]. In gastric cancer cells, however, miR-155 was downregulated and its overexpression suppressed cell migration and invasion. Thus, in gastric cancer cells miR-155 acted as a tumor suppressor targeting SMAD2, a component of the transforming growth factor beta (TGFβ) signalling pathway [10]. In addition, Babar *et al*. observed that although induction of high levels of miR-155 in a tetracycline-controlled knock-in mouse model caused the development of disseminated pre-B cell lymphoma, highly elevated miR-155 expression in the brains of the same mice was insufficient to induce brain tumors [11].

2.3. Attempts to Normalize the Expression of Key Cellular miRNAs in Various B-Cell Lymphoma Types

As illustrated above, miR-155 has emerged as a pleiotropic regulator of numerous biological processes. Thus, it became a logical therapeutic goal to attenuate its oncogenic functions to complement, on the long run, current protocols for lymphoma treatment. High affinity binding of anti-miR oligonucleotides to distinct microRNAs may sequester their target without causing its degradation, whereas a lower-affinity binding promotes miRNA degradation [12]. Early *in vivo* attempts of sequence specific silencing by short hairpin RNAs failed due to the activation of the immune system, toxic off-target effects, and saturation of the endogenous microRNA pathway (reviewed in [13,14]). However, more sophisticated, chemically modified antisense oligonucleotides including locked nucleic acid (LNA) oligonucleotides, peptide nucleic acids (PNAs) conjugated either to a cell-penetrating peptide or polylysine, and cholesterol-conjugated RNAs called "antagomirs" proved to be effective inhibitors of microRNAs both *in vitro* and *in vivo* [14-18]. Fabani *et al*. reported that a peptide nucleic acid (PNA) oligonucleotide containing four D-lysine residues to ensure proteolytic stability and enhanced cellular uptake could inhibit miR-155 both *in vitro* and in the spleens of experimental mice receiving 50 mg PNA/kg/day for 2 days [16].

To explore the advantages of the nanoparticle delivery systems that permit targeting of miRNA inhibitors to selected cells and tissues, anti-miR-nanoparticle complexes were constructed and tried successfully in clinically acceptable and therapeutically affordable doses in mice [11, 19,20]. Babar *et al*. demonstrated that in spite of the potential difficulties of cellular internalization, antisense peptide nucleic acids encapsidated into biodegradable poly (lactic-co-glycolic acid) (PLGA) particles coated with penetratin inhibited miR-155 and decreased the growth rate of pre-B-cell tumors in a knock-in mouse model [11]. Although penetratin facilitates uptake into various cell types, it was observed that the systematically administered nanoparticles showed preferential targeting to tumor tissue.

miR-155 is indispensable for the development of an optimal T cell dependent antibody response and controls T helper cell differentiation by regulating cytokine production [21]. miR-155 expression leads to elevated tumor necrosis factor alpha (TNFα) levels whereas TNFα induces miR-155 expression. In a subgroup of diffuse large B cell lymphoma, called activated B cell-like or non-germinal centre (ABC or non-GC) DLBC, augmented miR-155 expression was found due to an increased TNFα production. The high miR-155 level could be reduced in non-GC DLBC cell lines cultured *in vitro* by adding eternacept, a soluble TNFα receptor or infliximab, a neutralized humanized monoclonal antibody against TNFα, to the culture medium [22]. These observations indicate that *anti-cytokine therapy* could potentially be used to normalize the expression of miR-155, a cytokine-regulated microRNA, in a subset of patients with DLBC. Such a treatment may improve the prognosis and relapse-free survival of the ABC/non-GC group of DLBC. Reactivating silenced genes coding for miRNAs that inhibit cell proliferation similarly to tumor suppressor proteins appears to be a promising strategy in lymphoma

Table 1. MicroRNAs upregulated in B-cell lymphomas.

Lymphoma type	miRNA (references)	Comment
Diffuse large B-cell lymphoma (DLBCL)	miR-19b [35]	component of the miR-17-92 cluster that promotes cell proliferation and angiogenesis, represses apoptosis
	miR-17-5p [36]	component of the miR-17-92 cluster
	miR-143 [37]	miR-145 or miR-143 play a tumor-suppressive role in various cancers; Ras activation represses the miR-143/145 cluster
	miR-145 [37]	
	miR-155 [5,38]	oncomir, regulates proliferation, promotes to cell survival
	miR-29b [5,39]	regulates P53
	miR-146a [5]	down-regulates TRAF6, IRAK1, the Toll-like and cytokine receptor pathway adaptor molecules
	miR-365 [5]	direct negative regulator of IL-6
	miR-30b [5,40]	blocks terminal B-cell differentiation
	let-7f [5]	let-7 family member, tumor suppressor
	miR-9 [5]	activated by MYC/MYCN; regulates E-cadherin
	miR-34b [5]	tumor suppressor, its promoter is methylated in melanoma
	miR-197 [5,41]	represses the tumor suppressor gene FUS1
	miR-206 [5]	inhibits the TGF-β-mediated up-regulation of HDAC4
	miR-370 [5]	targets TRAF4
Chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL)	miR-19a [35]	component of the miR-17-92 cluster
	miR-20a [35]	
	miR-92 [35]	
	miR-483 [5]	cooperates with IGF2; upregulated in various carcinomas
	miR-485 [5]	putative down-regulator of Nuclear factor (NF)-YB
	miR-150 [5,42]	targets c-Myb; plays a key role in B-cell differentiation
Nodal marginal zone B-cell lymphomas	miR-221 [43]	required for angiogenesis; promotes endothelial cell migration and proliferation
	miR-223 [43]	suppresses cell proliferation by targeting IGF
	let-7 family [5]	tumor suppressor
	let-7f [43]	
Splenic marginal zone B-cell lymphoma	miR-144/451 family [5]	regulates erythroid development and susceptibility to oxidative stress
Marginal zone B-cell lymphoma/MALT	miR-200 cluster [5,44]	inhibits metastasis formation, blocks epithelial–mesenchymal transition (EMT); maintains the epithelial phenotype through targeting the repressors of E-cadherin
	miR-429 [5]	targets MYC
	miR-141 [5]	targets p38α, modulates the oxidative stress response
	miR-138 [5]	regulates P53
	miR-9, miR-9* [5,36]	NF-κB regulators induced by MYC; target E-cadherin
	miR-155 [36]	oncomir, regulates cell proliferation, enhances cell survival
	miR-210 [36	targets the apoptosis-inducing factor AIFM3
Follicular lymphoma (FCL)	miR-301 [36]	mediates proliferation via NF-κB
	miR-143 [37]	tumor-suppressor Ras activation represses the miR-143/145 cluster
	miR-145 [37]	
	miR-221 [37]	required for angiogenesis; promotes endothelial cell migration and proliferation.
	let-7b, let7i [37]	let-7 family members, tumor suppressors
	miR-494 [43]	regulates PTEN expression

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	miR-183 [5]	targets EGR1, a tumor suppressor
	miR-200c [5,44]	inhibits metastasis formation and epithelial–mesenchymal transition (EMT), by maintaining the epithelial phenotype through directly targeting the transcriptional repressors of E-cadherin, ZEB1 and ZEB2
Mantle cell lymphoma	miR-182 [45]	facilitates metastasis formation
	miR-181 [45]	mediates proliferation, overexpression can be apoptotic
	miR-155 [25]	oncomir; regulates proliferation, enhances cell survival
	miR-210 [25]	targets apoptosis-inducing factor, mitochondrion-associated, 3, (AIFM3)
	miR-17-3p [5]	
	miR-17-5p [46]	
	miR-18a [5]	
Burkitt's lymphoma (BL)	miR-19a [5,35]	component of the miR-17-92 cluster
	miR-19b [5,35]	
	miR-20a [46]	
	miR-92 [5]	
	miR-17-5p [40]	component of the miR-17-92 cluster
	miR-20a [40]	
Primary central nervous system lymphoma (PCNSL)	miR-9 [40]	activated by MYC/MYCN; regulates E-cadherin
	miR-30b/c [40]	blocks terminal B-cell differentiation
	miR-155 [40]	oncomir, regulates cell proliferation, enhances cell survival
	miR-29a, b [39,47]	regulates P53
	let-7a, f, g [47]	let-7 family member, tumor suppressor
	miR-21 [47]	modulates tumorigenesis through regulation of BCL-2
Lymphoplasmocytic lymphoma (Waldenström's macroglobulinemia, WM)	miR-125b [47]	inhibits cell proliferation
	miR-181a [47]	miR-181a overexpression can be apoptotic
	miR-155 [48,49]	oncomir, regulates proliferation, enhances cell survival
	miR-206 [48]	increases histone acetylation, and transcription
	miR-223 [47]	suppresses cell proliferation by targeting IGF

treatment [23]. Gastric marginal zone B-cell lymphoma of MALT type (MALT lymphoma), an indolent disease, may progress to a more aggressive disease, gastric diffuse large B-cell lymphoma (gDLBCL) due to overexpression of the Myc oncoprotein [24]. Myc transcriptionally represses a series of miRNAs including miR-34a, that has antiproliferative properties when overexpressed in DLBCL cells. This effect could be attributed to the suppression of FoxP1, a pioneer transcription factor and miR-34a target. Craig *et al*. speculated that miR-34a *replacement therapy* could be beneficial in miR-34a negative hematopoietic malignancies, including gDLBCL [24]. Transcriptional silencing of miR-29 in mantle cell lymphoma is also associated with Myc [25]). In a study performed by Zhao *et al*., miR-29 levels were associated with prognosis: patients with significantly reduced expression of miR-29 had a short survival compared with those who expressed relatively high levels [26]. It was observed that Myc repressed miR-29 through EZH2, a component of the Polycomb repressor complex that ensures the inheritance of gene expression patterns from cell generation to cell generation, and the histone deacetylase HDAC3, that also marks repressed chromatin domains [25]. Epigenetic drugs inhibiting both EZH2 and HDAC3 could restore miR-29 expression and suppressed lymphoma growth both *in vitro* and *in vivo*. These studies suggest that *epigenetic therapy* might be efficient in the treatment of certain B-cell malignancies. In addition to gDLBCL and mantle cell lymphoma, Burkitt's lymphomas carrying characteristic *c-Myc* translocations may also fall into this category.

2.4. Cellular and Viral miRNAs as Possible Therapeutic Targets in Virus-Associated Lymphomas

The pattern of Epstein-Barr virus (EBV), a human gammaherpesvirus, is associated with a series of malignant tumors, including B-cell lymphomas (reviewed in [27].

Table 2. MicroRNAs down-regulated in B-cell lymphomas.

Lymphoma type	miRNA (references)	Comments
Diffuse large B-cell lymphoma (DLBCL)	miR-145 [36]	tumor suppressor in various cancers; Ras activation represses the miR-143/145 cluster
	miR-150 [36,42]	regulates c-Myb; and plays a key role in B-cell differentiation
	miR-139 [36]	suppresses metastasis and progression of liver carcinoma.
	miR-149 [36]	miR-149* induces apoptosis by inhibiting Akt1 and E2F1
	miR-320 [36]	reduces ERK1/2 protein levels
	let-7e [36]	tumor suppressor
	let-7 family (a, d, e, f, g) [5]	let-7 family member, tumor suppressor effect
	miR-100 [5]	suppresses IGF2 in breast cancer
	miR-125a [5]	targets the negative NF-κB regulator TNFAIP3
	miR-126, miR-126* [5,50]	diagnostic for acute myeloid leukemia cases with common translocations
	miR-143 [5]	tumor-suppressor; repressed by Ras activation.
	miR-146a [5]	targets TRAF6 and IRAK1, the Toll-like and cytokine receptor pathway adaptor molecules
Chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL)	miR-15b [51]	miR-15 and miR-16 are direct transcriptional targets of E2F1
	miR-16 [51]	
	miR-17-5p [5]	component of the miR-17-92cluster
	miR-20a,b [5]	
	miR-182 [5]	facilitates metastasis formation
	miR-223 [5]	suppresses cell proliferation by targeting IGF
	miR-34a [5]	tumor supressor
	miR-365 [5]	direct negative regulator of IL-6
	miR-451 [5]	regulates erythroid development and susceptibility to oxidative stress
	miR-7 [5]	inhibits tumor growth and metastasis
	miR-9, miR-9* [5]	activated by MYC/MYCN, regulates E-cadherin
	miR-98 [5,41]	targets the tumor suppressor FUS1
Nodal marginal zone B-cell lymphoma	miR-370 [52]	down-regulated in gastrointestinal tumors with 14q loss
Splenic marginal zone B-cell lymphoma	miR-141 [5,44]	the miR-200 family inhibits the initiating step of metastasis, the epithelial mesenchymal transition (EMT), by maintaining the epithelial phenotype through directly targeting the transcriptional repressors of E-cadherin, ZEB1 and ZEB2
		apoptosis-inducing factor, mitochondrion-associated, 3 (AIFM3) could be a direct target gene of miR-210
Marginal zone B-cell lymphoma/MALT	miR-126* [5,50]	diagnostic for acute myeloid leukemia cases with common translocations.
Follicular lymphoma (FCL)	miR-320 [36]	reduces ERK1/2 protein levels and glucose induced ERK1/2 phosphorylation
	miR-149 [36]	induces apoptosis by inhibiting Akt1 and E2F1
	miR-139[36]	suppresses metastasis and progression of hepatocellular carcinoma by down-regulating Rho-kinase 2.
	miR-126* [45,50]	it's expression distinguishes acute myeloid leukemia cases with common translocations
Mantle cell lymphoma	miR-29a, b, c [25,39]	regulates P53
	miR-150 [25,42]	regulates c-Myb expression; plays a key role in B-cell differentiation
	miR-15a, b [25]	miR-15 is a direct transcriptional targets of E2F1 cosing proliferation

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Burkitt's lymphoma (BL)	let-7 family (a, d, e, f, g) [5]	tumor suppressor
	miR-29 family a, b, c [5,39]	regulates P53
	miR-451 [5]	regulates erythroid development, homeostasis and susceptibility to oxidative stress
	miR-146a [53]	down-regulates TRAF6 and IRAK1, the Toll-like and cytokine receptor pathway adaptor molecules
	miR-150 [5,42]	regulates c-Myb; plays a key role in B-cell differentiation
	miR-155 [53]	oncogenic; regulates cell proliferation, enhances cell survival
Primary central nervous system lymphoma (PCNSL)	miR-145 [40]	tumor-suppressor
	miR-214 [40]	targets ATF4
	miR-9 [47-49]	activated by MYC/MYCN; regulates E-cadherin
Lymphoplasmocytic lymphoma (Waldenström's macroglobulinemia, WM)	miR-152 [47]	tumor suppressor
	miR-182 [47]	facilitates metastasis formation
	miR-15a [48]	tumor suppressor
	miR-16 [48]	tumor suppressor

One of the viral oncogenes expressed in nasopharyngeal carcinomas, post-transplant lymphomas, EBV-associated Hodgkin disease and *in vitro* transformed lymphoblastoid cell lines (LCLs) encodes a transmembrane protein called latent membrane protein 1 (LMP1) that affects the levels of certain cellular microRNAs by activating the NF-κB pathway. Cameron *et al.* observed that LMP1 induced miR-146a expression, down-regulating the products of a group of interferon-responsive genes [28]. miR-155, implicated in the development of B cell lymphomas, was also upregulated by LMP1 [29]. These virus-induced cellular miRNAs as well as the EBV-encoded miRNAs (reviewed in [30]) are also potential targets of lymphoma therapy.

2.5. miRNAs as Potential Target Molecules in Radiotherapy and Chemotherapy of Mantle Cell Lymphoma

Mantle cell lymphoma (MCL), comprising 5% - 10% of human B-cell malignancies is considered to be incurable with standard immuno-chemotherapy [31]. For this reason, a novel therapeutic strategy was elaborated, based on the delivery of radioisotopes to the tumor tissue using monoclonal antibodies. Anticipating the development of radioresistant MCL cells, Jiang *et al*. studied the effect of miRNA-17-92, an oncomir upregulated in various neoplasms, on radiosensitivity of a human MCL cell line *in vitro* [32]. They observed that over-expression of miRNA-17-92 increased the survival of irradiated cells by indirectly up-regulating expression of the AKT protein kinase [32]. Thus, suppressing miRNA-17-92 may improve, in principle, the efficiency of MCL radiotherapy. It is worthy to note that another miRNA, miR-155, could be induced by hypoxia and protected lung cancer cells from radiation [33]. Treatment with anti-miR-155 molecules, however, radiosensitized the cells *in vitro*. Over-expression of miRNA-17-92 cluster inhibited chemotherapy-induced apoptosis in MCL cell lines *in vitro* [34]. miR-17-92 targeted a protein phosphatase involved in the negative regulation of the PI3K/AKT pathway, resulting in AKT activation. Rao *et al*. suggested that targeting the miRNA-17-92 cluster could be a plausible approach in MCL chemotherapy [34].

3. Conclusion

Recent developments in the synthesis of sophisticated, chemically modified antisense oligonucleotides targeting oncomirs and the use of anti-miR nanoparticle complexes made possible the development of new therapeutic approaches that may complement current protocols for B-cell lymphoma therapy. Anti-cytokine therapy aiming at the removal of cytokines that activate the biogenesis of key oncomirs might also be considered in case of well defined patient groups. Suppression of oncomir expression may successfully complement, on the long run, radiotherapy and chemotherapy of certain B-cell lymphoma types. In addition, switching on silenced tumor suppressor miRNAs by epigenetic drugs also appears to be a promising strategy in B-cell lymphoma treatment.

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