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REVIEW

Relevance of miR-21 in HIV and non-HIV-related lymphomas

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Abstract The critical role of microRNAs (miRNAs) in cell differentiation, homeostasis and cancer development has been extensively discussed in recent publications. The microRNAs with RISC enzyme complex allow it to find its complementary sequence, which is usually located in the 3′-untranslated region (UTR) of the target messenger RNA (mRNA). This is followed by inhibition of protein translation or promotion, resulting in degradation of the target gene. miR-21 has been mapped at chromosome 17q23.2, where it overlaps with the protein coding gene vacuole membrane protein 1 (VMP1), a human homologue of rat vacuole membrane protein. Recent evidence indicates that miR-21 plays a vital role in tumour cell proliferation, apoptosis and invasion. The inhibition of miR-21 may induce cell cycle arrest and increased chemosensitivity to anticancer agents, providing evidence that miR-21 functions as an oncogene in human cancer. Increased expression levels of miR-21 were observed in tumours arising from diverse tissue types. This also includes tumours of haematological origin, such as chronic lymphatic leukaemia, diffuse large B cell lymphomas (DLBCLs), acute myeloid leukaemia and Hodgkin lymphomas. Recently, it has been shown that high levels of B cell activation were induced by miR-21 in circulating B cells and are seen in HIV-infected individual. Notably, miR-21 is overexpressed in activated B cells, suggesting its assistance in maintaining B cell hyperactivation, which plays a pivotal role in HIV-infected cells. Therefore, miR-21 can be considered as a powerful biomarker in HIV-related lymphomas. The number of studies related to the role of miR-21 in HIV-related lymphomas is sparse; therefore, this mini review highlights the recent publications related to clinical impact and significance of miR-21, specifically in HIV- and non-HIV-related lymphomas.

Keywords B cell lymphoma · MicroRNA · Prognosis · HIV · miR-21 · DLBCL

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Introduction

MicroRNAs (miRNAs) are short non-coding RNA molecules consisting of 21–25 nucleotides (nts) in length. They are transcribed as long primary transcripts in the nucleus and subsequently cleaved to produce stem loop-structured precursor molecules of ~70 nts in length (pre-miRNAs) by Drosha. This is then transported to the cytoplasm, where the RNase III enzyme Dicer further processes them into mature miRNAs (~22 nucleotides). miRNAs can silence their cognate target genes by inhibiting messenger RNA (mRNA) translation or degrading the mRNA molecules by binding to their 3′-untranslated region (UTR) [1]. This critical step plays a central role in the regulation of mRNA expression. miRNAs have been recognized as a key regulator for metastasis of cancer cells, signifying that they may play an important role in the development of many malignancies [2, 3].

Recently, research has shown that miRNAs may play both a suppressive and promoting role in cancer progression [4]. Elevated expression of miRNAs has been shown in many disease states, i.e. cancer, cardiovascular disease, neurodegenerative disease and viral infections [5]. In addition, it is also evident that more than 50 % of miRNA genes are frequently

located at fragile sites and genomic regions involved in many malignancies. This is an early indication of the potential importance of miRNAs in cancer development [6]. Disruptions in the miRNA–target gene relationship have obvious implications for tumorigenesis, metastasis and drug resistance in cancerous cells.

miR-21 is a common microRNA significantly upregulated in many malignancies, suggesting that it plays an important role in tumour cell proliferation, apoptosis and invasion. hsa-miR-21 is located on chromosome 17q23.2, immediately downstream of the vacuole membrane protein 1 (*VMP1*) gene. It is also known as *TMEM49*. VMP1 transcripts, which originate approximately 130 kb upstream of miR-21, are spliced and polyadenylated only a few hundred base pairs upstream of the miR-21 hairpin [7]. miR-21 is an oncogenic miRNA that modulates the expression of multiple cancer-related target genes such as phosphatase and tensin homologue (*PTEN*), *TPM1* and programmed cell death protein 4 (*PDCD4*) and has been shown to be overexpressed in various human tumours [8–10]. Recent evidence demonstrated that lentiviral-transduced human pancreatic ductal adenocarcinoma (PDA) efficiently downregulate miR-21 expression, both in vitro and in vivo. Consequently, cell proliferation was strongly inhibited by apoptosis through the mitochondrial pathway. In addition, in vivo experiments demonstrate that miR-21 depletion stopped the progression of a very aggressive type of PDA, by programmed cell death. Furthermore, targeting miR-21 in combination with chemotherapeutic treatment accelerates tumour regression [11].

miRNA 21 has also been shown to be an important biomarker in colorectal cancer (CRC). High levels of miR-21 expression in serum and tissue were statistically correlated with tumour size, metastasis and poor survival. Moreover, serum miR-21 was shown to be an independent prognostic biomarker in CRC [12]. Overexpression of miR-21 resulted in enhanced growth and reduced apoptosis in a number of cell culture and animal models. Importantly, elevated miR-21 alone was shown to be sufficient to induce a pre-B malignant lymphoid-like phenotype in animal models, and continuous miR-21 expression was necessary to maintain the tumour phenotype, indicating that miR-21 is a true oncogene [13]. Similarly, miR-21 deletion in mouse cancer models reduced tumour formation [14, 15]. Thus, there is significant evidence that miR-21 is an important gene in the development of cancer.

Recent reviews have explored the role of miR-21 in drug chemoresistance in both myeloid and lymphocytic leukaemias. Furthermore, miR-21 inhibition induced apoptosis in chronic myelogeneous leukaemia cells [6]. Additionally, the mechanism of regulation and deregulation by microRNAs in lymphomas was elucidated from diagnosis to targeted therapy [16]. HIV and non-HIV-related lymphomas can be differentiated by severe immunocompromise [17], and further difference in the pathogenesis of HIV-associated lymphoma (HAL) relative to non-HIV lymphomas could be characterised via high proliferative activity and low incidence of DNA aneuploidy [18]. To date, there is no review demonstrating the role of miR-21 in HIV-related lymphomas. Most of the studies mainly focus on non-HIV-related lymphomas, and the number of studies on HIV-related lymphomas is sparse. Therefore, the main thrust of this review is to provide an overview of the current clinical evidence and significance of miR-21 in HIV and non-HIV-related lymphomas.

Recent studies suggest that dysregulation of other miRNAs also plays a crucial role in the pathogenesis of aggressive transformed, high-grade and refractory lymphomas [19]. miR-21 was found to be normally upregulated in both HIV and non-HIV-related lymphomas; however, we summarize the important research findings surrounding the role of miR-21 in both HIV- and non-HIV-related lymphomas. Figure 1 demonstrates a schematic representation of miR-21 function.

miR-21 in lymphomas

Leukaemia-related lymphomas

Expression of miR-21 in patients with chronic lymphocytic leukaemia (CLL) is dramatically higher (up to tenfold) than that in $CD19^+$ lymphocytes of normal individuals [20]. miR-21 was also upregulated in T cell leukaemic (T-ALL) and T cell lymphoma (ALCL) cell lines [21]. Rossi et al. [22] found that miR-21 expression is associated with survival of CLL patients with 17p deletion. From the above evidence, there is a clear indication that leukaemia-related lymphomas can be characterised by significant upregulation of miR-21.

Assessment of miRNA expression in NK cell lymphomas/leukaemias suggests that miR-21 and miR-155 were overexpressed in NK cell lymphoma/leukaemia. Moreover, using antisense oligonucleotides revealed that miR-21 act as an oncomiR promoting NK cell lymphomagenesis through dysregulation of *AKT* signalling [23].

Hodgkin lymphomas

Recently, Sánchez-Espiridión et al. [24] explained that the overexpression of miR-21 has been reported in classical Hodgkin lymphoma (cHL) and other lymphoma types. Functional silencing of miR-21 and miR-30D in L428 cells showed increased sensitivity to doxorubicin-induced apoptosis, pointing towards abnormalities of mitochondrial intrinsic and TP53–CDKN1A pathways as related to miRNA deregulation in cHL. These results suggest that the clinical outcome in cHL is associated with a specific miRNA signature. Moreover, their functional analyses suggest a role for miR-21 and miR-30D in cHL pathogenesis and therapeutic resistance.

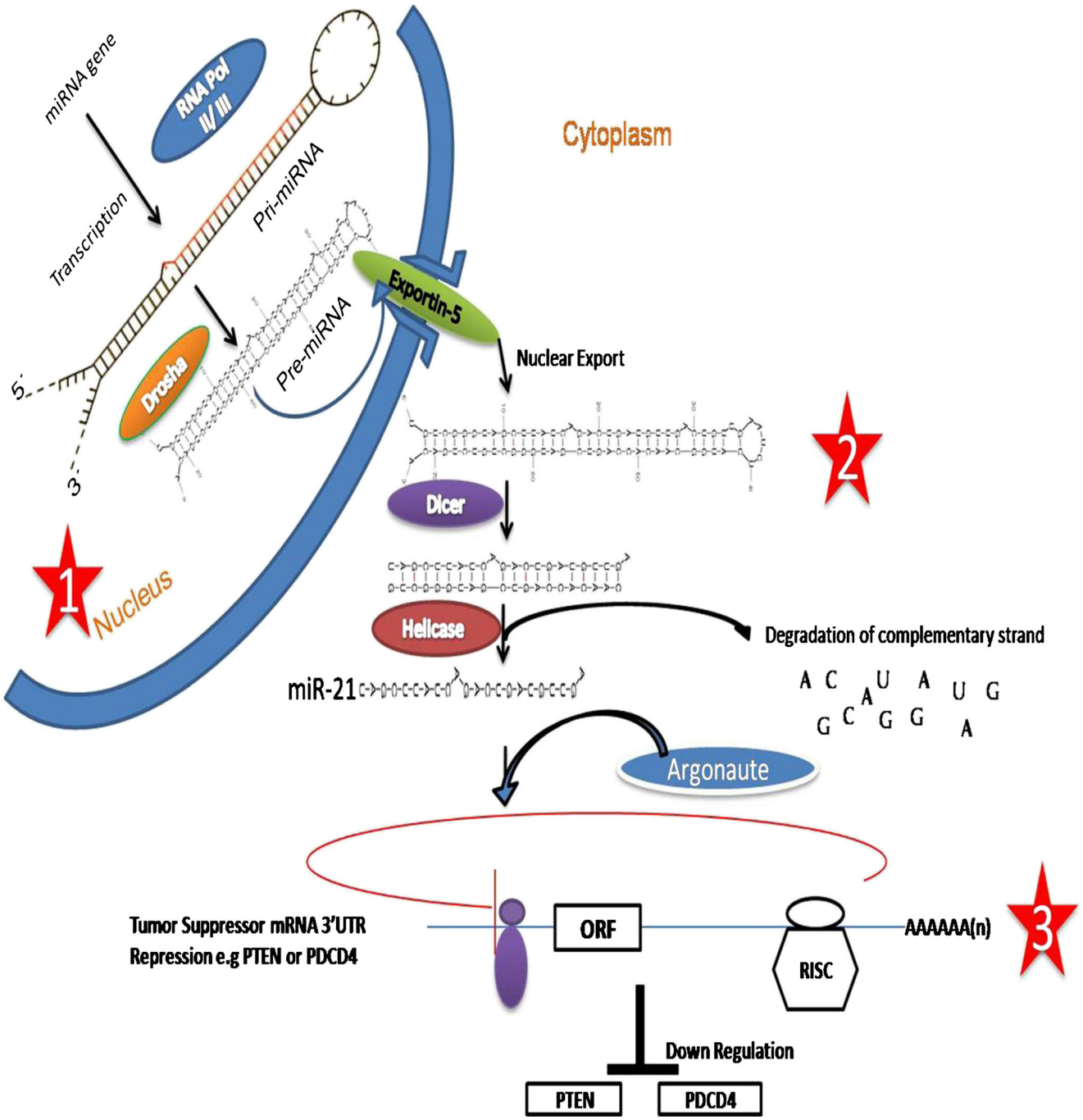

Fig. 1 Describes schematic representation of miR-21 function. *1* Primary miRNA transcription from genes encoding miRNA by RNA polymerase II/III, and primary miRNA was processed by Dorsha to yield pre-miRNA with stem loop structure. *2* Exportin-mediated transport of pre-miRNA via nuclear pore. In the cytoplasm, pre-miRNA is processed by Dicer to yield mature miRNA; further, the single-stranded target complementary single-stranded miRNA was created with helicase. *3* The single-standard complementary miRNA inhibits translation either by competing with ribosome for binding site or by degrading the target mRNA via RISC formation by incorporating argonaute

It has been known that Hodgkin lymphoma (HL) is derived from pre-apoptotic germinal centre B cells, although a general loss of B cell phenotype is noted. In 2009, Gibcus et al. [25] described using quantitative reverse transcription polymerase chain reaction and miRNA microarray, the miRNA profile of HL, and compared this with the profile of a panel of B cell non-Hodgkin lymphomas. In that, they showed a strong correlation for the detection of miRNA expression levels, especially in HL-specific miRNA including miR-17–92 cluster members, miR-16, miR-21, miR-24 and miR-155. Using a large panel of cell lines, they found a differential expression between HL and other B cell lymphoma-derived cell lines for 27 miRNAs.

Other studies demonstrated that the comparison of miRNA expression of microdissected Hodgkin/Reed–Sternberg (HRS) cells from cHL patients to $CD77^{+}$ GC B cells showed an upregulation of miR-21 [26]. miR-21 was also overexpressed in seven of the 15 splenic marginal zone lymphoma (SMZL) samples (median=2×8), including three cases with an aggressive clinical presentation and six cases with histological aggressiveness, suggesting that there is an association of miR-21 overexpression with aggressiveness of SMZL [27].

miR-21 in diffuse large B cell lymphoma

Diffuse large B cell lymphoma (DLBCL) is the most commonly diagnosed non-Hodgkin lymphoma (NHL) subtype, comprising of more than a third of NHL cases [28, 29]. It is composed of a heterogeneous group with different clinical, histopathological, molecular and genetic subtypes [30]. This is an aggressive tumour which may be found in lymph nodes or extranodal sites such as the gastrointestinal tract, skin and brain [31]. Diagnosis is made through biopsy which involves surgical removal of the tumour [29], histopathology and immunohistochemistry [32]. DLBCL is the most common type of lymphoma subtype associated with HIV [33]. The chemotherapy (CHOP) regimen has been the standard treatment for HIV-related lymphomas (HRLs) [34], similar to de novo DLBCL. The advantages of adding rituximab to the treatment, however, have not been sufficiently established [35] in patients with HIV-associated DLBCL.

Gu et al. [36] demonstrate suppression of proliferation and invasion, and increased apoptosis is a direct result of the miR-21 inhibition in DLBCL. Moreover, knock-down of miR-21 increased *PDCD4* and *PTEN* expression at the protein level, but not at the mRNA level, suggesting that miR-21 can regulate proliferation, invasion and apoptosis, and thus, it has a potential therapeutic application in DLBCL. Other studies demonstrate that the miR-21 expression level in DLBCL cell lines is relatively high, and miR-21 knock-down can significantly downregulate the expression level of *PTEN* protein and increase the sensitivity of DLBCL cell lines to the chemotherapeutic agents [37]. Strikingly, another report about miR-21 expression in patients with DLBCL suggests that high levels of tumoural miR-21 were associated with a better prognostic outcome [38].

Cerebrospinal fluid (CSF) miRNAs are potentially useful tools as novel non-invasive biomarker for the diagnosis of Primary diffuse large B cell lymphoma (PCNSL). Baraniskin et al. [39] showed that miR-21 was the most abundant miRNA in CSF of patients with PCNSL, and the mean relative expression of miR-21 was 60.0 in the CSF of PCNSL compared with 3.8 in the CSF of controls. This data strongly correlates with that of Lawrie et al. [40] who showed high miR-21 expression levels in samples of diffuse large B cell lymphoma, including PCNSL. Moreover, miR-21 has been shown to be expressed in a variety of tumours and to be associated with the downregulation of *bcl-2* and *PTEN*.

Expression level of miR-21 is an independent prognostic indicator in de novo DLBCL [40]. Further, another study showed that serum miR-21 is significantly increased in PCNSL when compared with other brain tumours with normal controls in both test and validation cohort [41]. This showed that serum miR-21 is an independent and powerful predictor of overall survival. In combination, these results demonstrate that serum miR-21 may represent a diagnostic and prognostic marker for PCNSL.

Virus-related lymphomas

Alteration in microRNAs expression is also seen in virally associated cancers via the host–pathogen interactions. Epstein–Barr virus (EBV)-encoded Epstein–Barr nuclear antigen 2 (EBNA2) is indispensable for the capacity of the virus to transform B cells in vitro. Extensive miRNA profiling of the virus-infected and EBNA2-transfected B lymphoma cells revealed that oncomiR miR-21 is positively regulated by this viral protein. Conversely, Burkitt's lymphoma (BL) cell lines infected with EBNA2 lacking P3HR1 strain did not show any increase in miR-21. EBNA2 increased the phosphorylation of *AKT*, and this was directly correlated with increased miR-21. This evidence suggests that EBNA2 might contribute to EBV-induced B cell transformation by altering miRNA expression [42]. A significant increase in miR-21 was also reported in hepatitis C virus (HCV) associated with lymphoma patients [43].

Contrastingly, the miR-21 expression was lower in EBV-associated post-transplant smooth muscle tumours (PTSMTs) than leiomyomas. However, the difference was not significant; therefore, in situ derived results do not reveal a PTSMT-specific deregulated miR-21 signal cascade, but an expression pattern related to smooth muscle phenotype [44]. Garzon et al. [45] found that miR-21 was upregulated in acute myeloid lymphoma patients.

The EBV infection that caused the survival of lymphoid cells may lead to the upregulation of miRNAs including miR-21 and miR-155, as infection with EBV is associated with immortalization of lymphoid cells

HIV-related lymphoma

HIV infects CD4-positive T lymphocytes and destroys the immune system by reducing the number of these lymphocytes. There is a documented correlation between cancer and diseases associated with infectious agents [46, 47]. In persons with compromised immune system, as in people living with

AIDS, the chances of developing lymphoma are 100 times greater [46, 48]. Lymphoma as well as Kaposi's sarcoma have been the late manifestations of HIV infection and, in 1985, were part of the AIDS-defining illnesses [46, 49]. Patients who are HIV positive and are diagnosed with lymphoma are said to have HRL. HRL is said to be a more aggressive malignancy when compared to its non-related counterpart; therefore, patients have a shorter life expectancy [34]. The advent of highly active antiretroviral treatment (HAART) has resulted in a decrease in the incidence of HRL [50], but the incidence is still higher than spontaneous lymphoma.

Patients who receive HAART respond better to CHOP treatment and are less likely to die due to toxicity effects [34]. A study by Chadburn et al. [51] suggested that routine immunohistochemistry biomarkers in the HIV setting do not reveal any information regarding how well the patients will fare during treatment. The only IHC biomarker suggested to reveal information regarding patient survival was Ki-67, a nuclear antigen expressed by dividing cells which is used to determine tumour proliferation index [28]. Patients with a high tumour proliferative index have a higher chance of survival [51] compared to patients with lower proliferative tumours. Although there are no much studies about HIV-related lymphomas, here, we discussed some of the evidence that shows how miR-21 plays a role in HIV-related lymphomas.

Chu et al. [52] investigated the DNA methylation status of 14 oncogenes using methylation-specific PCR in 25 PCNSL patients including 2 HIV-infected patients. DNA methylation was detected in death-associated protein kinase (DAPK) in 84 % of samples, p16 in 64 % and O6-methylguanine-methyltransferase (MGMT) in 52 %, showing that methylation was noted in one of these three genes in 96 % of samples.

Recently, Thapa et al. [53] provided evidence for HIV-related lymphomas which indicate that the levels of miR-21 are significantly elevated in the peripheral B cells of HIV-infected individuals who may develop AIDS-related NHL compared with HIV-negative or HIV-positive controls. Interestingly, miR-21 is overexpressed in activated B cells, suggesting that miR-21 may help to maintain B cell hyperactivation. They also suggested that in HIV individual, several B stimulatory factors such as IL6, IL10, B lymphocyte stimulator (BLyS), LPS and B cell chemokine CXCL13 are elevated in the serum. Moreover, increased surface expression of TNF-α on T lymphocytes and the HIV virions also induce B cell activation. Therefore, it is important to measure miR-21 levels in activated B cells, and upregulation of miR-21 was observed in those activated B cells.

Watanabe et al. [54] showed that in patients with CNS inflammation and other diseases, the levels of miR-21, miR-19 and miR-92a in the CSF were significantly increased in HIV-infected PCNSL patients. It has been reported that HIV-infected PCNSL could be diagnosed at sensitivity and specificity of 95.7 and 96.7 %, respectively, by measuring the expression of these three miRNAs, suggesting that miR-21 plays an important role in HIV-related lymphomas; until now, there are no papers that describe different types of HIV-related lymphomas. Table 1 represents the regulation of miR-21 in different types of HIV- and non-HIV-related lymphomas.

Future perspectives and clinical impacts for HIV- and non-HIV-related lymphomas

The current treatment options for lymphoma do not factor the different underlying molecular and genetic profiles of patients [28, 55]. For example, patients with the same disease subtype and identical calculated survival score may respond differently to treatment based on their molecular and genetic differences [28]. In patients with HIV-related lymphomas, the standard immunohistochemistry biomarkers do not demonstrate any prognostic value [51]; therefore, new biomarkers need to be discovered, especially in the HIV/AIDS setting. Normally, the diagnosis of lymphomas is based on the integration of clinical and histopathological data together with chromosomal alterations and gene/protein expression data. In recent years, there have been many significant advances in lymphoma classification; nevertheless, additional molecular markers will enable a better distinction of specific lymphoma types and provide a more accurate prediction of response to therapy [56].

Since miR-21 is upregulated in many lymphomas, their unique molecular signatures can be used as prognosis and therapeutic targets. Consistent evidence suggested that miR-21 is an important oncogene which plays an important role in the regulation of all types of lymphomas. miR-21 upregulations enhance tumorigenicity in HIV-infected individuals through activation of additional signalling pathways. It is established that common therapeutic strategies involved antisense-mediated inhibition of oncogenic miRNAs and miRNA mimics, including viral vector-encoded overexpression of tumour suppressor miRNAs. At high doses, synthetic anti-miRNA oligonucleotides (AMOs), which have 2-*O*-methyl modification, provide an effective inhibition of miRNAs in cell culture and xenograft mouse models [57]. It has been reported that targeting the miR-21 by 2-*O*-methyl AMOs in glioblastoma and breast cancer has been achieved in in vitro and xenograft mice model [58, 59]. However, further validation is required for the above studies in order to demonstrate that AMOs can function as therapeutic agents against lymphomas, and it is, therefore, important to have future functional studies for miR-21 with distinct HIV-related lymphomas subtypes.

Table 1 Regulation of miR-21 in different types of HIV- and non-HIV-related lymphomas

Types of lymphoma	Status of miR-21 expression	Gene target	References	Organs or tissue/cells
Splenic marginal zone lymphoma (SMZL)	Upregulated		Bouteloup et al. [27], 2012	Normal spleen (aggressive SMZL)
Natural killer/T cell lymphoma (NK/T)	Upregulated	PDCD4, PTEN	Yamanaka et al. [23], 2009	NK cell lymphoma cell lines
Classical Hodgkin lymphoma (NK/T)	Upregulated		Gibcus et al. [25], 2009	HL and B cell lymphoma cell lines
			Sánchez-Espiridión et al. [24], 2013	cHL-derived cell lines
Diffuse large B cell lymphoma (DLBCL)	Upregulated	PDCD4, PTEN	Bai et al. [37], 2013 Gu et al. [36], 2013	DLBCL cell lines
Hepatitis C virus-associated lymphomas	Upregulated		Fognani et al. [43], 2013	HCV-associated non-Hodgkin lymphomas
Epstein–Barr virus-associated lymphomas	Upregulated	EBNA2, AKT	Rosato et al. [42], 2012	B lymphoma cell lines
HIV/AIDS-related lymphomas	Upregulated		Thapa et al. [53], 2012	Peripheral B cells of HIV-infected individuals
			Watanabe et al. [54], 2011	AIDS-related PCNSL patients

Conclusion

The above findings suggest that miR-21 plays a novel and important role in non-HIV- and HIV-related lymphomas. Inhibition of miR-21 could decrease cell proliferation, induce apoptosis and inhibit tumour growth in numerous lymphomas cell lines and mouse models, indicating that it may serve as an excellent prognostic, diagnostic and therapeutic marker. Furthermore, high expression levels of miR-21 are widely believed to be associated with HIV-infected individuals; however, this requires further investigations. Nevertheless, the applicability of miR-21-targeted strategies for the clinical treatment of HIV- and non-HIV-related lymphomas still remains elusive. Further studies are required to validate and elucidate the mechanism by which miR-21 and its emerging targets impact in HIV-infected individuals. In addition, new investigations will determine the future direction and clinical applications of miR-21 in this disease.

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