Role of microRNAs in primary central nervous system lymphomas

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Abstract

Primary central nervous system lymphomas (PCNSL) are extranodal non-Hodgkin lymphomas arising exclusively inside the CNS, and account for about 3% of primary intracranial tumours. This tumour lacks systemic manifestations and prognosis of patients with PCNSL remains poor despite recent advancement of chemoradiotherapy. MicroRNAs are small non-coding RNAs that post-transcriptionally downregulate gene expression by binding to target mRNAs, inducing their degradation or translational repression. MicroRNAs play significant roles in almost all malignancy-related biological processes, including cell proliferation, differentiation, apoptosis and metabolism. Many deregulated miRNAs has been identified in PCNSL but their biological significance remains to be fully elucidated. In this review, we summarize current evidence regarding the pathogenic role of PCNSL-associated microRNAs and their potential applications for diagnosis and prognostication of this deadly disease.

Introduction

Primary central nervous system lymphomas (PCNSL) are an aggressive, extra nodal form of non-Hodgkin lymphomas (NHL) that arise exclusively in the CNS, including the brain, leptomeninges, spinal cord and eyes, in the absence of systemic dissemination. PCNSL

accounts for 2–4% of primary intracranial tumours and 1% of all lymphomas (1). The incidence of PCNSL increases with age in immunocompetent populations. Immunodeficiency as a result of human immunodeficiency virus (HIV) infection or immunosuppressive medications for organ transplantation also increases the risk but this form of PCNSL has a different pathogenesis (e.g. association with Epstein–Barr virus (EBV) infection) with distinct therapeutic implications (1–3). In contrast to most primary malignant brain tumours, PCNSL can be curable by aggressive radio-chemotherapeutic approaches, such as high-dose methotrexate followed by whole-brain irradiation (4–6). However, delayed diagnosis and treatment is a common cause of death in PCNSL patients (7) in which early diagnosis is significant for improving survival and prognosis (8). Despite the recent advancement of imaging techniques, the diagnosis of PCNSL is still a clinical challenge (9). Stereotactic needle biopsy is currently the standard diagnostic method for patients with suspected PCNSL (6,10,11). Therefore, identification of novel non-invasive method is required for improving the accuracy and shortening the delay of PCNSL diagnosis.

Molecular pathogenesis and cellular origin of PCNSL

About 90% of PCNSL are classified as diffuse large B-cell lymphomas (DLBCL). The cellular origin of PCNSL-DLCBL remains obscure but recent gene expression profiling studies suggests that it could originate from germinal centre B cells that are destined to become IgM-expressing memory B cells (12). The recent discovery of functional lymphatic vessels lining the dural sinuses that are connected to the deep cervical lymph nodes may also shed new light on the origin of malignant lymphocytes in the CNS (13). Mechanistically, blockade of B-cell differentiation due to *PRDM1*

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mutation, translocation-mediated overexpression of *BCL6*, activation of proto-oncogenes (e.g. *PIM1*, *PAX5*, *RhoH/ITF*, *MYC*) due to somatic hypermutation, and DNA hypermethylation of tumour suppressors (e.g. *DAPK*, *CDKN2A*, *MGMT*) have been proposed to play key roles in the pathogenesis of PCNSL (12). The advent of high throughput platforms, such as array-comparative genomic hybridization and whole exome sequencing, also revealed additional genomic features, including loss of *TNFAIP3*, *PRDM1*, *GNA13*, *TMEM30A*, *TBL1XR1*, *B2M*, *CD58*, *NPFFR2*, *C4orf7*, *OSMR*, *EMCN*, *TPO*, *FNDCl*, *COL12A1* and *MSC*, and activating mutations of *MYD88*, *CD79B*, *CARD11*, *BRAF3* (14,15). In general, several signalling pathways, such as nuclear factor- κ B (NF- κ B), Janus kinase-signal transducers and activators of transcription (JAK-STAT) and adhesion-related pathways, may be involved (14,15). It is noteworthy that the molecular features, clinical behaviours and prognosis of PCNSL and peripheral DLBCL could differ considerably (12,16). For instance, the mutation load of PCNSL is 2- to 5-fold higher than that of its peripheral counterpart (17). The former also harbours some specific genomic features, including recurrent biallelic losses of *TOX* (a regulator of T-cell development) and *PRKCD* (protein kinase C delta) and chromosomal breakpoints in *DLGAP1* (discs large-associated protein 1) (15). In general, the prognosis of PCNSL is worse than that of peripheral DLBCL (16).

MicroRNAs (miRNAs) are small (18–24 nucleotides in length) non-coding RNAs that post-transcriptionally downregulate gene expression by binding to target mRNA, triggering their degradation or translational repression (18,19). miRNAs play significant roles in critical biological processes, including cell proliferation, differentiation, metabolism, apoptosis and tumorigenesis (20–25). In particular, deregulated expression of miRNAs is frequently observed in human cancers (26,27). miRNAs can also function as tumour suppressors or oncogenes through their extensive crosstalk with intracellular signalling network (28,29). Moreover, miRNA expression signatures have diagnostic, prognostic and therapeutic implications in some cancers (30–32).

Differentially expressed miRNAs in PCNSL as compared with DLBCL

Three studies have been published so far to compare miRNA expression of PCNSL with that of peripheral DLBCL. Using quantitative reverse transcription-PCR, Fischer *et al.* demonstrated that 18 miRNAs were differentially expressed in PCNSL compared with nodal DLBCL (33). Among them, the expression of 13 and 5

miRNAs was significantly upregulated and downregulated, respectively, in PCNSL compared with nodal DLBCL. In addition, miRNAs upregulated in PCNSL were implicated in various molecular functions. For example, miR-17-5p, miR-20a and miR-9 were associated with the Myc pathway, miR-9 and miR-30b/c with blocking of terminal B-cell differentiation, and miR-155 with upregulation by inflammatory cytokines. Furthermore, miRNAs downregulated in PCNSL were potential tumour-suppressor miRNAs. In conclusion, PCNSL showed a distinct miRNA expression compared with nodal DLBCL (33). In another study, Zheng *et al.* using miRNA hybridization demonstrated that expressions of 28 (e.g. miR-122, miR-513b, miR-552) and 33 (e.g. miR-363, miR-196a, miR-192) miRNAs/segments increased and decreased by more than 10-fold in PCNSL compared with that of non-germinal centre DLBCL (34). As compared with germinal centre DLBCL, the number of >10-fold upregulated and downregulated miRNAs/segments were 11 (e.g. miR-513b, miR-802, miR-512-3p) and 13 (e.g. miR-135a, miR-592, miR-582-5p) respectively (34). Robertus *et al.* compared the miRNA expression profile in DLBCL from different primary sites (35). miR-17-5p expression levels were significantly higher in PCNSL than in testicular and nodal DLBCL. In addition, miR-127 was significantly downregulated in PCNSL and nodal DLBCL compared with the testicular type (35). Therefore, expressions of miRNAs are different in different primary sites of DLBCL. Differentially expressed miRNAs between PCNSL and peripheral DLBCL were shown in Table 1.

Deregulated miRNAs and their putative functions in PCNSL

miR-21

miR-21 was upregulated in various cancers, acting as a well-established oncogenic miRNA (36–39). Importantly, miR-21 has been shown to contribute to pre-B-cell lymphomagenesis in which inhibition of miR-21 led to regression of tumours via apoptosis and cell cycle arrest in a mouse model (40). miR-21 also played a significant role in the chemosensitivity of DLBCL cells (40). The confirmed targets of miR-21 in DLBCL include FOXO1 (a transcription factor), PDCD4 (a positive regulator of apoptosis) and PTEN (an inhibitor of oncogenic phosphoinositide 3-kinase/Akt pathway) (40,41). The levels of serum miR-21 were significantly higher in PCNSL than in other brain tumours and normal controls (42). Whether miR-21 was actively secreted from PCNSL cells via the exosome pathway

	Method	Sample	Upregulated	Downregulated	Reference
1	Microarray qRT-PCR	PCNSL and nodal DLBCL	miR-9 miR-20b miR-155 miR-340 miR-17-5p miR-148a miR-30b miR-27b miR-26b miR-146b miR-20a miR-30c let-7 g miR-199a miR-214 miR-432 miR-193b miR-145	miR-296 miR-361 miR-301 miR-642 miR-29c	33
2	Microarray qRT-PCR	PCNSL and GC and non-GC-DLBCL	<i>Compared with NGC-DLBCL</i> miR-122 miR-513b miR-522 miR-1973 miR-875-5p miR-513a-5p <i>Compared with GC-DLBCL</i> miR-513b miR-802 miR-512-3p	<i>Compared with NGC-DLBCL</i> miR-363 miR-196a miR-192 miR-10b miR-192 miR-193b miR-1 miR-218 miR-339-3p miR-223 miR-215 miR-374a miR-365 miR-199a-5p miR-497 miR-140-5p miR-135a miR-140-3p miR-199b-5p miR-199a/b-3p miR-503 miR-425 miR-181c miR-424 miR-570 miR-146a miR-194 miR-545 miR-320a miR-454 <i>Compared with GC-DLBCL</i> miR-135a miR-592 miR-582-5p miR-582-3p miR-199b-5p miR-339-3p miR-146a miR-10b	53
3	qRT-PCR	PCNSL and nodal/testicular DLBCL	miR-175p	miR-127 (compared with testicular DLBCL)	34

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Table 2. Functional characterization of the deregulated miRNAs in PCNSL

Name	Up- or downregulation	Role	Reference
miR-21	Up	Oncogene	(40,42)
MiR-17-5p	Up	Oncogene	(35)
miR-127	Down	Tumour suppressor	(35)
miR-17-92	Up	Oncogene	(46)
miR-106a-363	Up	Oncogene	(46)
miR-106b-25	Up	Oncogene	(46)
miR-222	Up	Oncogene	(60)
miR-199a-5p/3p	Down	Tumour suppressor	(50)
miR-143/145	Down	Tumour suppressor	(50)
miRNA-28	Deletion	Unknown	(51)

(43) or continuously released into the circulation through cell death remains unclear.

miR-17-92, miR-106a-363 and miR-106b-25 clusters in HIV-associated PCNSL

The risk for NHL is significantly elevated in population with HIV infection (44). Acquired immune deficiency syndrome (AIDS)-associated NHL includes several B-cell lymphomas, such as Burkitt's lymphoma, DLBCL, PCNSL, primary effusion lymphoma and plasmablastic lymphomas (45). Overexpression of miR-17-92, miR-106a-363 and miR-106b-25 were observed in four AIDS-NHL subtypes, including PCNSL (46). Mechanistically, selected miRNAs from these clusters (miR-17, miR-106a and miR-106b) inhibited p21 (a cyclin-dependent kinase inhibitor) in AIDS-DLBCL samples (46). For miR-17-92 cluster, its member miR-19 has been identified as a key oncogenic component in the genesis of B-cell lymphoma by targeting PTEN and activating Akt-mTOR (mammalian target of rapamycin) pathway (47).

miR-199a-5p/3p and miR-143/145 in primary CNS post-transplant lymphoproliferative disorder

Primary CNS post-transplant lymphoproliferative disorder (PTLD) is a rare complication after solid organ transplantation, with the majority occurring in renal transplant recipients (48,49). EBV infection is the major aetiological factor in the development of PTLD-PCNSL (50). Twenty-eight cellular miRNAs exhibited differential expression in PTLD-PCNSL compared with systemic PTLD, including lower expression levels of miR-199a-5p/3p and miR-143/145 (implicated in NF- κ B and c-Myc signalling) in the former (50). Moreover, EBV played a crucial effect on viral and cellular miRNA expression in PTLD-PCNSL. Several viral and cellular miRNA could distinguish non-EBV-associated

PTLD-PCNSL from EBV-associated PTLD-PCNSL. Moreover, a separate group of EBV-associated PTLD-PCNSL that displayed reduced levels of B-cell lymphoma-associated oncogenic miRNAs (miR-155, miR-21, miR-221 and miR-17-92 cluster) was identified (50).

miR-28 and BCL6

A breakpoint in the BCL6 locus was observed in 38% of the PCNSL evaluated. Among them, a deletion in 3q leads to loss of an 837 kb fragment of the *lipoma-preferred partner (LPP)* gene. As miR-28 gene was located in LPP, the deletion may bring the BCL6 gene under the control miR-28 (51). BCL6 is commonly targeted by genetic aberrations and acts as an oncogene in germinal centre-derived lymphomas. BCL6 is known to prevent terminal B-cell differentiation largely through repression of PRDM1 (52).

miRNAs as diagnostic markers for PCNSL

miRNAs expression levels have been measured in the cerebrospinal fluid (CSF) from patients with PCNSL compared with other neurologic disorders using TaqMan quantitative real-time PCR assays. Among six candidate miRNAs (miR-15b, miR-19b, miR-21, miR-92a, miR-106b, miR-204) detected, the levels of miR-21, miR-19b and miR-92a were significantly higher in the CSF of patients with PCNSL compared with those from control patients. The combination of these three miRNAs in CSF allowed for a stable diagnostic marker for PCNSL, with a diagnostic accuracy of 95.7% sensitivity and 96.7% specificity (53). These data suggest that CSF miRNAs could be used as non-invasive diagnostic biomarkers for PCNSL. Importantly, these results were confirmed in an enlarged cohort ($n = 39$) of PCNSL patients with a sensitivity of 97.4%. In addition, CSF levels of these miRNAs were significantly correlated with PCNSL status during treatment and/or disease follow-up (54), indicating their potential as biomarkers for treatment monitoring and follow-up. A recent meta-analysis also showed that, as compared with other CNS tumours, CSF-based miRNAs are more accurate and sensitive for diagnosing PCNSL (55).

Apart from measuring miRNA levels in CSF, Mao *et al.* reported that miR-21 levels in serum were significantly elevated in PCNSL as compared with normal controls in two independent cohorts with an area under the curve of 0.930 for the test cohort and 0.916 for the validation cohort. Raised serum levels of miR-21 could also differentiate PCNSL from major brain tumours, including glioblastoma (42). However, it is worthwhile to note that serum miR-21 has been identified as a

diagnostic biomarker for other cancer types (56), including colorectal cancer (57), breast cancer (58) and hepatocellular carcinoma (59). These findings indicate that increased serum miR-21 levels are in general associated with malignancy and not specific for PCNSL. Another study demonstrated that higher serum levels of miR-222 could be a biomarker for early detection of DLBCL and PCNSL among HIV-infected individuals (60). It is propitious that, by combining CSF- and serum-based miRNAs with existing or emerging biomarkers, such as interleukin-10 (61) and U2 small nuclear RNA fragments (62) in CSF, the diagnostic sensitivity and accuracy of PCNSL will be enhanced.

miRNAs as prognostic markers for PCNSL

The current method for prognostication of PCNSL patients remains limited, in which only higher age and low Karnofsky Performance Status have consistently been shown to foreshadow a shorter overall survival (63). Therefore, devising novel prognostic tools for PCNSL could be an important step towards patient-centred therapy. In a recent study, Roth *et al.* profiled circulating miRNAs in PCNSL patients with short-term survival versus long-term survival where levels of 12 miRNAs were significantly different (64). Among these differentially abundant miRNAs, miR-151a-5p and miR-151b demonstrated the most prominent alterations. Importantly, combined analysis of several miRNAs achieved a good separation between short- and long-term survivors with maximal area under curve of 0.75. The prognostic significance of selected miRNAs was also validated in a second cohort by real-time PCR (64). In another study, the investigators demonstrated that serum miR-21 is an independent and powerful predictor of overall survival of PCNSL patients as analysed by Kaplan–Meier curve and multivariable Cox regression (42). In a study determining the treatment efficacy of pemetrexed (a folate anti-metabolite) plus rituximab (a CD20-targeting monoclonal antibody), the median time to progression (PFS) was significantly different in PCNSL patients with different serum levels of miR-21. Higher levels of serum miR-21 predicted a poor survival with PFS of 5.7 months compared with lower serum miR-21 with PFS of 9.0 months (65). In conclusion, circulating miRNAs might serve as prognostic biomarkers and treatment response predictors in PCNSL patients.

Conclusions

PCNSL is a rare malignant tumour with poor prognosis, accounting for approximately 3% of primary intracranial tumours. PCNS-DLBCL is the major subtype of

PCNSL. Our understanding of the cellular origin and pathogenic mechanisms of PCNSL remains fragmented. Pertinent to clinical practice, diagnosis of PCNSL is difficult owing to the lack of specific symptoms. miRNAs are small non-coding RNAs that function as master regulators in many physiological and pathological processes, particularly cancers. Recent studies have revealed the dysregulation of miRNAs in PCNSL using array-based miRNA profiling and real-time PCR. Nevertheless, study on the functional roles of these deregulated miRNAs in PCNSL is still limited. In addition, many reports have demonstrated the potential utilization of miRNAs as novel diagnostic and prognostic markers. Further investigations are warranted to maximize the clinical potentials of miRNA-based diagnostics and therapeutics in PCNSL.

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