Circulating Epstein-Barr Virus microRNAs Associated with Hodgkin Lymphoma Prognosis

Abstract : 6682

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Background

Hodgkin lymphoma (HL) is a malignant lymphoproliferative disorder that affects the immune system. **Epstein-Barr virus (EBV)** is a ubiquitous human gamma-herpesvirus that persists in B lymphocytes. EBV has been implicated in the pathogenesis of several cancers [1], and is an established causal factor for HL [2].

Studies suggest that EBV-positive HL (EBV+ HL) constitutes a biologically distinct entity with unique clinical and molecular features compared to EBV-negative HL (EBV- HL). However, identifying EBV involvement in HL traditionally requires invasive tissue biopsies, highlighting the need for **noninvasive biomarkers** to aid in early detection, risk assessment, and disease monitoring.

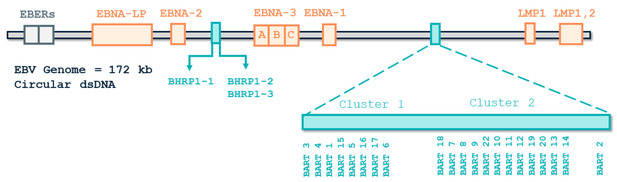


Figure 1. EBV Genome.

MicroRNAs (miRNAs) are small, non-coding RNAs that regulate gene expression at the post-transcriptional level and play critical roles in **cancer development, immune response, and viral pathogenesis** [3]. The EBV genome (**Figure 1**) encodes its own viral miRNAs, which can modulate host cellular pathways and contribute to viral persistence and oncogenesis. More importantly, these EBV miRNAs can be detected in **biofluids**, making them promising candidates for liquid biopsy-based diagnostics [1,3]. The potential role of EBV miRNAs as **noninvasive biomarkers** for **early diagnosis, patient stratification, and therapeutic monitoring** remains largely unexplored.

Aim

To identify circulating expression of EBV-encoded miRNAs in the plasma of HL patients associated with EBV infection, disease severity, or clinical outcome.

Materials & Methods

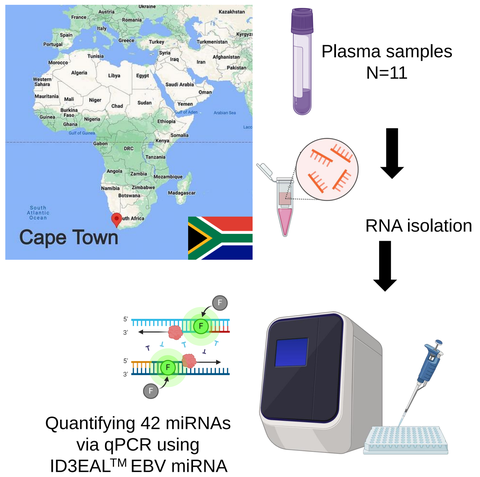


Figure 2. Study workflow.

Plasma was obtained from 11 patients with HL in a tuberculosis and HIV-endemic setting in Cape Town, South Africa. EBV infection in HL tumor cells was confirmed using a clinical PCR assay.

The expression of 42 miRNAs was measured using a qPCR-based ID3EAL™ EBV miRNA panel (**Figure 2**).

Wilcoxon rank-sum test or **Fisher's exact test** were used to compare continuous or categorical data, respectively, between EBV+ HL and EBV- HL cases.

Spearman's rho evaluated associations between EBV miRNA expression levels and disease severity or clinical parameters.

Fold changes in miRNA expression were calculated using the **2^−ΔΔCT method**, normalizing data to endogenous controls.

Results

EBV+ HL patients were **significantly older** than **EBV- HL** patients (***p*=0.04**; **Table 1**).

No miRNA was associated with **EBV status or prognostic factors** at false discovery rate (FDR) <0.05. We highlighted interesting findings at $p<0.05$.

MiR-BART17-3p expression inversely correlated with **disease stage** (rho=-0.61, ***p*=0.047**).

MiR-BART2-5p correlated with **International Prognostic Score** (**IPS;** rho=0.72, ***p*=0.01**), a most commonly used risk stratification tool for HL.

MiR-BART14-3p was inversely correlated with the **Eastern Cooperative Oncology Group** (**ECOG**) **performance score** (rho=-0.60**, *p*=0.049**). ECOG score assesses a patient's functional status and ability to perform daily activities.

Four miRNAs were associated with **B-symptoms**, defined as fever, drenching night sweats and loss of more than 10 percent of body weight over 6 months (**Figure 3**):

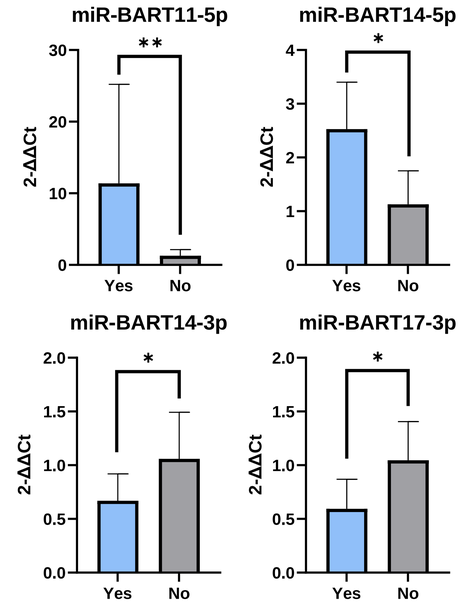
- **Higher** expression of **miR-BART11-5p** and **miR-BART14-5p** expression (11.2-fold ***p*=0.01** and 2.5-fold ***p*=0.02**, respectively).
- **Lower** expression of **miR-BART14-3p** and **miR-BART17-3p** compared to those with no B symptoms (33% and 41% lower, respectively, **both *p*=0.03**).

No association between EBV miRNA expression and **HIV status.**

Table 1. Subject demographics.

		EBV+	EBV-	*p*
n		6	5	
Age (median [IQR])		35.5 [29.2, 49.2]	24.0 [23.0, 27.0]	0.04
Sex (%)	Female	1 (16.7)	1 (20.0)	1.00
	Male	5 (83.3)	4 (80.0)	
Stage (%)	I	0 (0.0)	1 (20.0)	0.45
	II	2 (33.3)	0 (0.0)	
	IV	4 (66.7)	4 (80.0)	
IPS (%)	0	1 (16.7)	0 (0.0)	0.84
	1	1 (16.7)	1 (20.0)	
	2	1 (16.7)	0 (0.0)	
	3	1 (16.7)	3 (60.0)	
	4	1 (16.7)	0 (0.0)	
	5	1 (16.7)	1 (20.0)	
ECOG Score (%)	0	1 (20.0)	4 (66.7)	0.13
	1	4 (80.0)	1 (16.7)	
	2	0 (0.0)	1 (16.7)	
B-Symptoms (%)	Yes	3 (50.0)	3 (60.0)	1.00
	No	3 (50.0)	2 (40.0)	
HIV (%)	Positive	2 (33.3)	1 (20.0)	1.00
	Negative	4 (66.7)	4 (80.0)	

Figure 3. MiRNAs associated with B-Symptoms.



Conclusion

Circulating EBV miRNAs are associated with HL disease severity but not EBV status, suggesting their potential role as non-invasive biomarkers for disease progression and prognostic stratification in HL.

Further investigations into these candidate miRNAs will increase our understanding of HL disease progression as well as explore the potential of these miRNAs as therapeutics or therapeutic targets.

References

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Disclosures

S. Lee, C. S. Bogsan, A. G. Wandoff, M. Wu, E. Verburgh, M. van der Schyff, F. J. Slack, Y. J. Heng, and K Antel declare no conflict of interest. J. T. Howard reports employment with Mirxes US.