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HOST MIRNA EXPRESSION ASSOCIATED WITH EBV INFECTION STATUS: A PILOT STUDY

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ABSTRACT

Epstein–Barr virus (EBV) is a lifelong persistent herpesvirus, usually asymptomatic but associated with several malignancies and autoimmune disorders. EBV encodes viral proteins and microRNAs (miRNAs) that modulate host gene expression and facilitate immune evasion. This pilot study analyzed host cellular miRNA expression in EBV-positive (EBV^+) and EBV-negative (EBV^-) individuals, as well as within EBV infection subgroups, and examined IL-6 promoter methylation and telomere length.

In a cohort of 156 participants, EBV infection was confirmed in 95 individuals via qPCR and categorized as chronic latent, chronic lytic, acute early, or acute recent. miR-328 and miR-21 significantly differentiated EBV^+ from EBV^- individuals, while miR-877 distin- guished acute from chronic infections. IL-6 promoter methylation inversely correlated with miR-328 expression, indicating an association between epigenetic regulation of in- flammation in EBV persistence. No telomere length differences were observed between EBV^+ and EBV^- groups. These findings are hypothesis-generating and support further mechanistic work on miRNA–epigenetic interactions in EBV persistence.

Keywords: Epstein–Barr virus; miRNA; IL-6 methylation; telomere length; immune evasion; viral load; biomarkers

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1. INTRODUCTION

Epstein–Barr virus (EBV) infects over 95% of the global population and persists for life[1]. Primary infection during childhood is typically asymptomatic, whereas infection in adolescence or adulthood often manifests as infectious mononucleosis. EBV primarily infects B-lymphocytes via the CD21 receptor, activating NF-κB signaling and upregulating proinflammatory cytokines such as interleukin-6 (IL-6) [2]. EBV can establish either latent or lytic infections, characterized by distinct viral gene expression patterns: latent membrane proteins (LMP1, LMP2) and Epstein–Barr nuclear antigens (EBNA family) define latency, while immediate-early genes such as BZLF1 and BRLF1 drive lytic reactivation [3].

The immune response to EBV involves both innate and adaptive arms. Pattern recognition receptors detect viral components and activate inflammatory pathways, while cytotoxic T-cells target infected cells [4]. MicroRNAs (miRNAs) contribute to fine-tuning these immune responses and can modulate inflammasome activity [1]. EBV encodes multiple miRNAs, including the miR-BHRF1 and BART clusters, which prolong infected cell survival and 41 promote immune evasion by targeting immune-related host genes such as CXCL11, MICB, and PTEN [5–7]. Furthermore, these miRNAs suppress antigen presentation by downregulating TAP2 and HLA class I/II molecules, effectively reducing immune recognition [8].

Host miRNAs also play a role in EBV-associated pathogenesis. They regulate immunity, inflammation, and oncogenic transformation, and have been implicated in EBV-associated malignancies such as Burkitt lymphoma and EBV-positive gastric carcinoma [9,10]. Recent studies highlight miR-142 as a regulator of EBV reactivation through modulation of B-cell receptor signaling via the ERK/MAPK pathway [11]. EBV viral load, determined by plasma EBV DNA or VCA-IgA titers, has been correlated with multi-cancer risk and relapse prediction in nasopharyngeal carcinoma [12–14].

In addition to immunological effects, EBV infection may alter host epigenetic processes and cellular aging. Viral infections, including EBV, can affect the methylation status of inflammatory cytokine promoters, such as IL-6, thereby modulating immune responses and sustaining chronic inflammation [11,15,16]. Chronic viral burden has also been associated with accelerated immunosenescence, raising the possibility of telomere attrition in long-term EBV infection [17,18]. These molecular consequences of EBV persistence remain underexplored in human cohorts and may provide insight into systemic pathophysiological changes beyond viral reactivation.

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2. MATERIALS AND METHODS

2.1. Study Population

Data and blood samples have been collected from 156 participants in total. Participants were recruited as apparently healthy adults without acute infectious symptoms at the time of sampling. Exclusion criteria were current fever, acute inflammatory disease, im-munosuppressive therapy, pregnancy, and known active malignancy. MiRNA gene ex-pression analysis was done from capillary blood drops collected on Whatman® protein saver cards (Sigma Aldrich, St. Louis, MO, USA), further procedure described in the next section. Additionally, whole blood was taken from the participants for detection of EBV, immunoglobulins, different B-cell receptors and cytokines by the medical supervi-sor Dr. Jacob.

2.2. EBV DNA Detection and Quantification

EBV status was determined by qPCR (EBV DNA detectable vs. not detectable). EBV-positive participants were further classified using a combined pattern of serological markers (IgM, IgG) and B-cell co-stimulatory markers (CD80, CD86), and the lytic anti-gen gp350. Chronic latent infection was defined by detectable EBV DNA together with an IgG-dominant pattern and reduced CD80/CD86 expression without evidence of lytic activity. Chronic lytic infection was defined by detectable EBV DNA with additional evidence of lytic activity (elevated gp350 and/or IgM). Acute infection was defined by an IgM-positive pattern with increased CD80 and/or CD86. Within acute infection, an

'early-stage' subgroup was defined by detectable EBV DNA and gp350 positivity in the presence of serological and cellular markers still within the reference range. [19–21]. Be-cause standardized clinical cut-offs were not available for all markers, subgrouping should be interpreted as a pragmatic classification for exploratory analyses. miR-24 was used as the reference miRNA for normalization, as recommended by the assay manufac-turer (Thermo Fisher Scientific) for TaqMan® Advanced miRNA assays in blood-de-rived samples.

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2.3. Total DNA/RNA extraction and miRNA expression

DNA and RNA were sequentially extracted using the MagMAXTM FFPE DNA/RNA Ultra Kit (Thermofisher, Waltham, MA, USA) and the KingFisher Duo Prime System

(Thermofisher, Waltham, MA, USA). cDNA synthesis and qRT-PCR were performed using the TaqMan® Advanced miRNA cDNA Synthesis Kit (Thermofisher, Waltham, MA, USA), the Applied Biosystems QuantStudio 3 Real-Time PCR System (Ther-mofisher, Waltham, MA, USA), and the ExpressionSuite Software (Thermofisher, Wal-tham, MA, USA), The protocol, TaqMan® Advanced miRNA Assays Single-tube assays, Catalog Number A25576, (Thermofisher, Waltham, MA, USA), was used without excep-tions. miR-24 was used as a housekeeping and reference gene for the other target miR-NAs, which were miR-let-7g, miR-let-7a, miR-877, miR-155, miR127-3p, miR-151a, miR-328 and miR21-5p (Thermofisher, Waltham, MA, USA). These miRNAs were selected in a pilot study upon a broad miRNA Array from Qiagen analyzing 360 miRNAs out of 4 EBV infected samples and four healthy controls. Given the small size of the pre-screen-ing (4 EBV-positive vs. 4 controls), miRNA selection was exploratory and aimed at hy-pothesis generation rather than definitive biomarker discovery. Reference miR-24 was used, following the manufacturer's recommendation for TaqMan® Advanced miRNA assays in blood-derived samples (Thermo Fisher Scientific).

2.4. IL-6 Promoter Methylation Analysis

Genomic DNA was extracted from peripheral blood mononuclear cells (PBMCs). Bisul-fite conversion was performed, followed by methylation-specific PCR targeting the IL-6 promoter region. Methylation percentages were calculated based on the relative abun-dance of methylated versus unmethylated CpG sites.

2.5. Telomere Length Measurement

Relative telomere length was determined in genomic DNA, isolated from the dried blood spots using a StepOne Plus real time PCR Detection System (Applied Biosysteme). For PCR, single-copy gene primers, telomere primers (Biomers, Germany) and a Light-Cycler® 480 Sybr®Green I master mix (Roche) were used.

Methylation status, qPCR and high-resolution melt analysis were applied. Bisulfit con-version was done using the EpiTect bisulfite kit (Qiagen) following the manufacturer's protocol and using a maximum of 2

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µg of genomic DNA. EpiTect HRM PCR kit (Qi-agen) and primers for IL-6, was carried out in a Rotor Gene Q (Qiagen). Standards were generated with REPLI-g Mini Kit and mixed accordingly, to generate standards with 0, 25, 50, 75 and 100% methylation and compared to the samples.

2.6. Inflammatory Marker Quantification

Plasma levels of IL1-R, IL12-R, IFNa-R, TNFa-R, and C-reactive protein (CRP) were measured by multiplex bead-based immunoassays. Values were expressed as relative units (for cytokine receptors) or mg/L (for CRP).

2.7. Statistical Analysis

Group comparisons were conducted using Student's t-test or ANOVA with post-hoc Tukey correction, as appropriate. Correlation analyses employed Pearson's correlation coefficient. Statistical significance was set at $p < 0.05$. To account for multiple compari-sons in miRNA analyses, p-values were adjusted using the Benjamini–Hochberg false discovery rate (FDR). Analyses were performed using GraphPad Prism and R software.

3. RESULTS

3.1. subgroup classification

Of the 156 participants, 95 (60.9%) tested positive for EBV via qPCR. These EBV-positive individuals were further subclassified into four groups based on immunoglobulin profiles and B cell markers: chronic latent (n=29), chronic lytic (n=20), acute last months (n=26), and acute early stage (n=20) as summarized in table 1.

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Category	Group	N	Percent	Male	Female	Mean Age	Age Male	Age Female
Total population		156	100%	72	84	48,98	49,43	48,66
	EBV+ EBV-	95 61	60.9% 39.1%	42 30	53 31	47,9 48,67	49,54 48,14	46,64 49,16
EBV+ group	Chronic Acute	49 46	51.6%	20	29	49,14	51,7	47,38
			48.4%	22	24	46,56	45,75	47,48
Chronic subgroup	Latent Lytic	29 20	59.2% 40.8%	11 9	18 11	49,31 48,9	52,27 51	47,5 47,18
Acute subgroup	Last months Early stage	26 20	56.5% 43.5%	10 12	16 8	47,35 45,47	45,4 49,36	48,56 40,13

Table 1. Participant characteristics and EBV subgroup distribution.
Overview of the total study population (N=156), stratified by EBV status (EBV+ vs EBV−) and EBV+ subgroups (chronic latent, chronic lytic, acute last months, and acute early stage). Group sizes, sex dis-tribution, and mean ages are reported for each classification level

3.2. Clinical Inflammatory Marker Differences between EBV+ and EBV- Individuals

To explore inflammatory profiles, multiple cytokine receptors were analyzed. EBV-posi-tive individuals exhibited significantly decreased expression of IL1-R, IL12-R, TNFa-R, and IFNa-R compared to EBV-negative participants ($p<0.05$), while CRP levels were sig-nificantly elevated (Fig. 1a-e). These findings suggest potential immune receptor down-regulation and systemic inflammation in EBV persistence.

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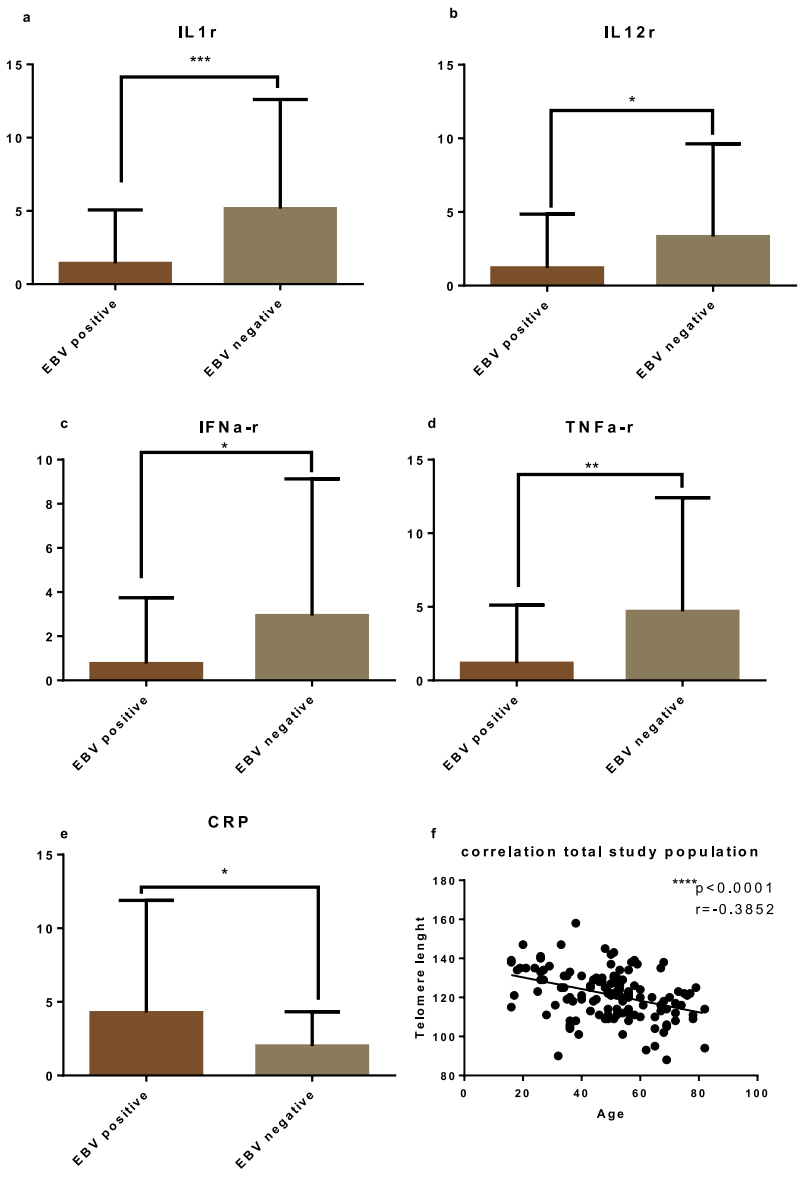

Figure 1. Differences in inflammatory markers between EBV-positive and EBV-negative individu-als (a–e). Correlation between age and telomere length (f). Bars represent mean ± SD; significance was tested using unpaired Student's t-test for approximately normally distributed variables and Wilcoxon rank-sum test for non-normally distributed variables

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3.3. Telomere Length

Consistent with the expected age effect, telomere length inversely correlated with age ($p<0.0001$; $r=-0.3852$), while no differences were detected between EBV^+ and EBV^- groups. This negative finding may reflect limited sensitivity for subtle shifts in heterogeneous whole-blood compartments and the cross-sectional design (Fig.1f).

3.4. Differential Expression of miRNAs between EBV^+ and EBV^- Individuals

Regarding miRNA expression, miR-328 and miR-21 significantly differentiated EBV-positive from EBV-negative individuals. miR-328 was elevated, while miR-21-5p was reduced in EBV-positive subjects (both $p<0.05$). No significant differences were observed in miR-let-7a, miR-let-7g, miR-151, or miR-155 between these groups.

When comparing acute and chronic EBV infections, only miR-877 was significantly ele-vated in acute infections ($p<0.05$). miR-127 and miR-21-5p showed a trend toward higher expression in acute stages, especially in the early phase, though not statistically significant. Further subgroup analysis revealed that miR-21 and miR-127 were most elevated in par-ticipants with early-stage acute infection. miR-155 showed differential expression across subgroups, with higher levels in early acute and chronic latent EBV infections. miR-877 was highest in the acute last-month subgroup and significantly different from chronic groups ($p<0.05$).

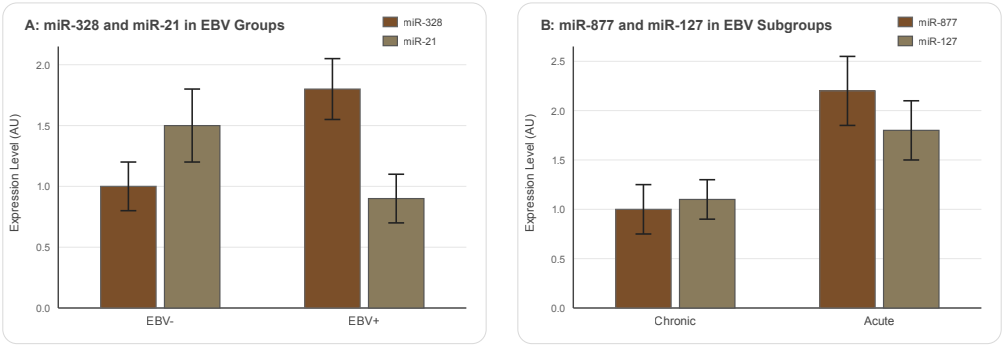

Figure 3. A: Expression levels of miR-328 and miR-21 in EBV^+ and EBV^- individuals. B: Expression levels of miR-877 and miR-127 in chronic versus acute sub groups. Data are presented as mean ± SD. Significant differences between groups are indicated by $p < 0.01$, p values obtained from unpaired t-tests.

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3.5. Correlation of miR-328 with IL-6 Promoter Methylation

We observed a strong inverse association between miR-328 expression and IL-6 promoter methylation in chronic EBV cases ($r = -0.62$, $p < 0.001$). This finding does not establish causality but suggests that inflammatory miRNA patterns may co-occur with epigenetic configurations linked to IL-6 regulation during EBV persistence. Future studies should test whether miR-328 is mechanistically linked to IL-6 transcriptional control, for example via upstream regulators of methylation dynamics or inflammatory signaling pathways (Fig.4).

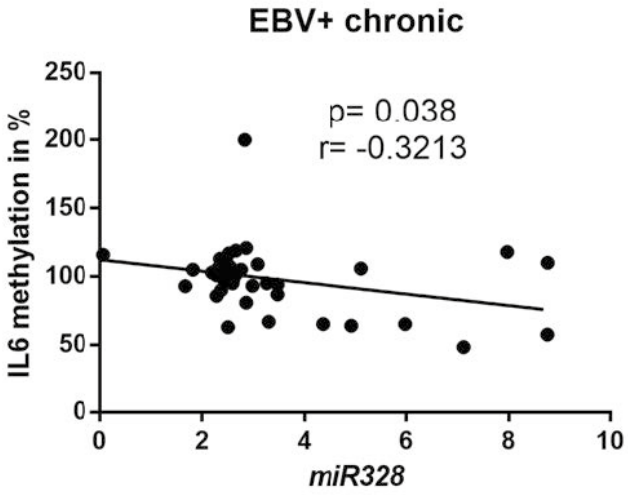

Figure 4. Scatterplot showing inverse correlation between miR-328 expression and IL-6 promoter methylation in chronic EBV cases. Regression line with 95% confidence interval shown; r and p values from Pearson's correlation.

4. DISCUSSION

In this study, we identified distinct host miRNA expression patterns associated with EBV infection status and subtypes. miR-328 and miR-21 clearly differentiated EBV^+ and EBV^- individuals, while miR-877 emerged as a strong discriminator between acute and chronic infection. These findings are consistent with

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previous reports showing that EBV can modulate host miRNA expression to influence immune regulation and viral persis-tence [22,23]

Viral infections like EBV modulate host gene expression, impacting cell survival and immunity. Our study observed decreased expression of IL1-R, IL12-R, TNFa-R, and IFNa-R in EBV+ individuals. This may reflect miRNA-mediated immune modulation. EBV miRNAs such as BHRF1-2-5p are known to target IL1R1 and interfere with NF-κB signaling [10,24]

Recent large-scale studies identified persistently high VCA-IgA antibody titers as pre-dictive markers for EBV-associated cancer risk, especially nasopharyngeal and gastric carcinoma (IARC, 2025). Plasma EBV-DNA is emerging as a clinical marker for relapse risk after radiotherapy in NPC patients [24]

Our findings also indicate dysregulated host miRNAs such as miR-21 and miR-155, which are modulated by EBV proteins like EBNA2 and LMP1. Although miR-21 is com-monly upregulated in cancer, we observed lower expression in EBV+ participants, par-ticularly in latent and chronic reactivation stages. This may reflect impaired immune activation in chronic EBV infection.

miR-127, linked to impaired B-cell differentiation via BCL6 overexpression, was higher in early acute in-fections, suggesting its involvement in early immune evasion. Similarly, tumor-suppressive miR-877 was elevated in acute infections and correlated positively with miR-328, a regulator of phagocytic activity. This correlation, particularly in chronic lytic stages, indicates a role in immune suppression.

A CRISPR/Cas9 screen identified miR-142 as essential in preventing lytic EBV reactiva-tion through ERK/MAPK pathway suppression [25]. EBV also reprograms host metabo-lism, enhancing lipid and nucleotide biosynthesis to support viral persistence and onco-genesis [26]

Interestingly, we observed a strong inverse correlation between miR-328 expression and IL-6 promoter methylation. While miR-328 has previously been implicated in regulating innate immune cell activity and ROS production [27], this association suggests that it may also influence epigenetic regulation of inflam-matory pathways. Hypomethylation of the IL-6 promoter has been linked to increased cytokine expression and chronic in-flammation, both in autoimmune conditions and cancer [28]. Our findings point to a pos-sible mechanism by which EBV-induced miR-328 upregulation could promote inflam-matory signaling via

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IL-6 demethylation, particularly in chronic or reactivated EBV infection.

Although our study found no significant differences in telomere length between EBV+ and EBV– individu-als, in vitro studies suggest that EBV may induce telomeric instabil-ity. EBV-transformed B cells show in-creased telomere fragility and heterogeneity, likely due to oxidative stress and altered telomere regulation [7,29]. These effects may not be detectable in capillary blood under physiological conditions.

5. CONCLUSIONS

EBV manipulates host immunity through viral and host miRNAs. Our results demon-strate differences in key immune-regulatory miRNAs between EBV+ and EBV– individu-als and across infection stages. Host miRNAs such as miR-21, miR-155, miR-127, miR-877, and miR-142 show promise as biomarkers.

Combining host miRNA profiling with established EBV markers (e.g., EBV DNA load and antibody titers) may improve stratification of EBV infection status and support risk-ori-ented follow-up in future studies. Further studies should investigate mechanistic links between host miRNAs, EBV la-tency/reactivation, immune escape, and cancer risk.

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Informed Consent Statement:
Informed consent was obtained from all subjects involved in the study.

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Conflicts of Interest: The authors declare no conflicts of interest.

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ABBREVIATIONS

The following abbreviations are used in this manuscript:

BCL6	B-cell lymphoma 6 (transcription factor)
BRLF1	BamHI R rightward reading frame 1 (EBV lytic transactivator protein)
BZLF1	BamHI Z leftward reading frame 1 (EBV lytic transactivator protein)
CD19	Cluster of Differentiation 19 (B-cell surface marker)
CD21	Cluster of Differentiation 21 (EBV receptor on B cells)
CD80	Cluster of Differentiation 80 (co-stimulatory molecule)
CD86	Cluster of Differentiation 86 (co-stimulatory molecule)
CIC	Circulating Immune Complex
CRISPR	Clustered Regularly Interspaced Short Palindromic Repeats
CRP	C-reactive protein
cDNA	complementary DNA
DNMT	DNA methyltransferase
EBNA	Epstein-Barr Nuclear Antigen
EBVaGC	Epstein-Barr virus-associated gastric carcinoma

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EBV	Epstein-Barr virus
GP350	Glycoprotein 350 (EBV envelope protein)
HRM	High Resolution Melt (analysis)
IFN	Interferon
IgA	Immunoglobulin A
IgG	Immunoglobulin G
IgM	Immunoglobulin M
IL	Interleukin
LMP	Latent Membrane Protein
MAPK	Mitogen-Activated Protein Kinase
m6A	N6-methyladenosine
miRNA	microRNA
NPC	Nasopharyngeal carcinoma
PD-1	Programmed cell death protein 1
PD-L1	Programmed death-ligand 1
qPCR	quantitative polymerase chain reaction

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qRT-PCR	quantitative reverse transcription polymerase chain reaction
ROS	Reactive oxygen species
SYBR	Synergy Brands Green (DNA dye used in PCR)
TAP2	Transporter associated with antigen processing 2
TLR9	Toll-like receptor 9
TNF	Tumor necrosis factor
VCA	Viral capsid antigen

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