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In silico prediction of cellular gene targets of herpesvirus encoded microRNAs

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ABSTRACT

Herpesviruses have evolved to encode multiple microRNAs [viral miRNAs (v-miRs)], a unique feature of this family of double stranded DNA (dsDNA) viruses. However, functional role of these v-miRs in host-pathogen interaction remains poorly studied. In this data, we examined the impact of oral disease associated v-miRs *viz*., miR-H1 [encoded by herpes simplex virus 1 (HSV1)] and miR-K12-3 [encoded by Kaposi sarcoma-associated herpesvirus (KSHV)] by identifying putative targets of viral miRNAs. We used our published microarray data (GSE107005) to identify the transcripts downregulated by the v-miRs. The 3′ untranslated region (UTR) of these genes were extracted using BioMart tool on Ensembl and subjected to RNA:RNA interaction employing RNA Hybrid. We obtained hundreds of potential and novel miR-H1 and miR-K12-3 binding sites on the 3′UTR of the genes downregulated by these v-miRs. The information can provide likely regulatory mechanisms of the candidate v-miRs through which they can exert biological impact during herpesvirus infection and pathogenesis.

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Specifications Table

Subject area	Biology
More specific subject area	Molecular Virology
Type of data	Text file
How data was acquired	Microarray and Bioinformatics
Data format	Filtered and analyzed
Experimental factors	Cells were transfected with v-miRs or control mimics
Experimental features	Genes downregulated by v-miRs were scanned for putative miRNA binding sites on the 3'UTR using RNA Hybrid tool.
Data source location	NA
Data accessibility	Data is presented as supporting file text with this manuscript. Microarray data of transcriptome wide changes in miR-H1 and miR-K12-3 overexpressing human oral keratinocytes compared to control mimics is deposited in the Gene Expression Omnibus public database under Accession Number GSE107005 (https://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE107005).

Value of the data

The data presented is valuable for the reasons listed below:

- The data provided here enlists human genes that were downregulated by herpesvirus derived miRNAs viz., miR-H1 (Herpes simplex virus 1) and miR-K12-3 (Kaposi sarcoma-associated herpesvirus) and harbor potential v-miR binding sites.
- These genes can provide new avenues to begin focused research on the role of viral miRNAs *viz*., miR-H1 and miR-K12-3 in the pathogenesis of oral mucosal diseases.
- Due to lack of online tools that can predict viral miRNA binding sites with high confidence, this methodology can provide a starting point to share large datasets examining global impact of v-miRs to identify more reliable candidate targets or facilitate development of algorithms to predict v-miR targets with a high degree of confidence.

1. Data

Human Herpesviruses (HHV) are dsDNA viruses that are highly prevalent worldwide [1]. A key feature of all herpesviruses is their capability to encode microRNAs [2]. These small non-coding RNAs are implicated in wide range of biological functions that govern host-pathogen interaction [2]. Recent evidences show a likely association of herpesvirus in oral diseases, however a role of viral components in the oral pathogenesis remains unknown [3,4]. We recently identified four viral miRNAs that were upregulated in human subjects with inflamed pulps and diseased gingival biopsies compared with healthy tissues [5,6]. Our recent transcriptome and miRnome analysis showed v-miRs can profoundly impact a specific set of genes in oral keratinocytes which are targeted by herpesviruses [6,7]. However, the direct gene targets of these viral miRNAs will shed light on the possible pathways through which viral miRNAs can modulate host cell functions. The data presented here provides a list of potential miR-H1 and miR-K12-3 binding sites on the 3'UTR of host transcripts that were significantly downregulated by these v-miRs in our previously published microarray (GSE107005). Tables 1 and 2 provides list of some representative interaction for miR-H1 and miR-K12-3, respectively, identified in our screening. The remaining interactions are listed as supplementary information in the Supplementary text file 1 (for miR-H1) and Supplementary text file 2 (for miR-K12-3).

Table 1
Predicted miR-H1-5p binding sites on the downregulated host genes. Sequence alignment of selected potential miR-H1-5p binding sites is shown. Only the binding sites with mfe < −20 kcal/mol are shown.

v-miRNA	Target gene	vmiR and target gene sequence alignment
hsv1-miR-H1–5p	PREPL	Position 2928 Target 5′ A UU G A 3′ UCAUUUC GU UCUUCUAUU GGUGAAG CA GGAAGGUAG miRNA 3′ GG 5′
hsv1-miR-H1–5p	TTC33	Position 899 Target 5′ U AA AA A 3′ CCA UUUU CCUUUCGUC GGU AGGG GGAAGGUAG miRNA 3′ GA CA 5′
hsv1-miR-H1–5p	ATG16L1	Position 1965 Target 5′ A AG U A A 3′ CUACU C CUG CCUUCCAU GGUGA G GGC GGAAGGUA miRNA 3′ A A G 5'
hsv1-miR-H1–5p	NOTCH2NL	Position 2443 Target 5′ G G G U G 3′ CA U CCC UCCUUCCAUU GU A GGG AGGAAGGUAG miRNA 3′ G G A C 5′
hsv1-miR-H1–5p	ZNF106	Position 1227 Target 5′ G A U 3′ UCGCUUUCC G CCUUUUGUU GGUGAAGGG C GGAAGGUAG miRNA 3′ A 5′
hsv1-miR-H1–5p	CHML	Position 212 Target 5′ A AC AU A 3′ UCAC CUC UUCUUUCAUC GGUG GGG AGGAAGGUAG miRNA 3′ AA C 5′
hsv1-miR-H1–5p	CCDC91	Position 464 Target 5′ A CC AC G 3′ CAUU CCC UCUUUCCAU GUGA GGG AGGAAGGUA miRNA 3′ G A C G 5′
hsv1-miR-H1–5p	RABEP1	Position 88 Target 5′ C A 3′ CCAUUUUUC UUUUUCUGU GGUGAAGGG AGGAAGGUA miRNA 3′ C G 5′
hsv1-miR-H1–5p	TGFBR1	Position 4034 Target 5′ G A 3′ UACUUUCUG UUUUCUGU GUGAAGGGC GGAAGGUA miRNA 3′ G A G 5′
hsv1-miR-H1–5p	TRIM52	Position 453 Target 5′ G C UU A 3′ UACU C GUUUUUCUGUU GUGA G CAGGAAGGUAG miRNA 3′ G A GG 5′
hsv1-miR-H1–5p	DYM	Position 8446 Target 5′A A A G 3′ UACUU UG UCUUUCCAUU GUGAA GC AGGAAGGUAG miRNA 3′ G G 5′
hsv1-miR-H1–5p	NDUFS1	Position 1742 Target 5′ A A CA C 3′ GCUGU UGUUU CAGAGUGUG CGACG GCAGG GUCUUACAC miRNA 3′ AG A U 5′

Table 1 (*continued*)

v-miRNA	Target gene	vmiR and target gene sequence alignment
hsv1-miR-H1–5p	SLC4A7	Position 1345 Target 5′ U UG G G 3′ UACU UUU GUCCUUUUAU GUGA AGG CAGGAAGGUA miRNA 3′ G G G 5′
hsv1-miR-H1–5p	PRRC1	Position 47 Target 5′ G C U 3′ UAC UUCC UCCUUUUGUU GUG AGGG AGGAAGGUAG miRNA 3′ G A C 5′
hsv1-miR-H1–5p	IL1RAP	Position 2670 Target 5′ U A U A 3′ UACUU UU UCUUUCCAU GUGAA GG AGGAAGGUA miRNA 3′ G G C G 5′

2. Experimental design, materials and methods

2.1. Primary gingival human oral keratinocyte (HOK) culture

Primary HOK (human gingival epithelial cells) were purchased from ScienCell Research Laboratories (Carlsbad, CA). Cultures were tested for HOK markers by immunofluorescent methods using antibodies to cytokeratine-8, -18 and -19 and were negative for Human Immunodeficiency Virus 1 (HIV-1), Hepatitis B Virus (HBV), Hepatitis C Virus (HCV), mycoplasma, bacteria, yeast and fungi. Cells were cultured using DermaLife K Keratinocyte Medium Complete Kit (Lifeline Cell Technology, Frederick, MD).

2.2. Transient miRNA transfections and total RNA isolation

Transient viral miRNA (miR-H1 or miR-K12-3) or control mimic transfections in HOK were performed using Lipofectamine 2000 reagent (Life Technologies, San Diego, CA) as described previously [8,9]. Cells were transfected with viral miRNA mimics (Qiagen, Gaithsburg, MD, USA) at a final concentration of 15 nM for 36 h. Total RNA was isolated using the miRNeasy kit (Qiagen).

2.3. Microarray analysis

We used our published microarray data deposited in the Gene Expression Omnibus public database under Accession Number GSE107005 for the identification of putative viral miRNA target transcripts [6]. Array data were in compliance with Minimum Information About a Microarray Experiment (MIAME) guidelines.

2.4. V-miR target prediction of differentially downregulated genes

To identify miR-H1 and miR-K12-3 gene targets with high confidence, we first selected downregulated genes. The 3′UTR of these genes were extracted using BioMart tool on Ensembl (http://www.ensembl.org/biomart/martview/aa867419c3c6fd64f94af6d4a6549d3c). Briefly, we selected Ensembl Genes 87 database and Human Genes dataset (GRCh38.p7). Next, the "Filters" were selected to match the input genes list. In the "Gene" tab set the "ID list limit" filter to "HGNC symbol(s)". Finally, to procure the 3'UTR sequences “Attributes” were set. In the "Attributes", select "Sequences" and then select 3′UTR start and 3'UTR end, click "Ensembl Gene ID" and "Associated Gene Name". The results were exported to by selecting "File", "FASTA" and "Unique results only”. This was done separately for miR-H1 and miR-K12-3 datasets.

Table 2
Predicted miR-K12-3 binding sites on the downregulated host genes. Sequence alignment of selected potential miR-K12-3 binding sites on the predicted targets is shown. Only the binding sites with mfe < –20 kcal/mol are listed.

v-miRNA	Target gene	vmiR and target gene sequence alignment
kshv-miR-K12-3	CBX5	Position 8806 Target 5′ U AUC G U 3′ UC UUGUU U UUGGAAUGUGA AG GACGG G AGUCUUACACU miRNA 3′ CCA G 5′
kshv-miR-K12-3	GOLGA3	Position 3592 Target 5′ G AGU GA A 3′ GC GU UUCU UAGGAUGUGA CG CG AGGA GUCUUACACU miRNA 3′ AG AGC 5′
kshv-miR-K12-3	UIMM21	Position 55 Target 5′ AU 3′ GCUGCC UUC CAGAAUGUG CGACGG AGG GUCUUACAC miRNA 3′ AG C AU 5′
kshv-miR-K12-3	UBL1X	Position 2516 Target 5′ GU A G U A 3′ GCU U GUCUU A GAAUGUGA CGA G CAGGA U CUUACACU miRNA 3′ AG C G G5′
kshv-miR-K12-3	FKBP14	Position 1178 Target 5′ AAA AG U U 3′ CUG GUU C GGGUGUGG GAC CAG G CUUACACU miRNA 3′ AGC GG GA U 5′
kshv-miR-K12-3	DSUN	Position 659 Target 5′ A A GAG A C 3′ UC UUGU UGUCUUC G GAAUGUG AG GACG GCAGGAG U CUUACAC miRNA 3′ CU 5′
kshv-miR-K12-3	ORC2	Position 372 Target 5′ G GU A 3′ UGU UUGUUC CAGAGUGUGG GCG GGCAGG GUCUUACACU miRNA 3′ A AC A5′
kshv-miR-K12-3	COPA	Position 33 Target 5′ A CC AG U 3′ UGUU CC CC AGAAUGUG GCGA GG GG UCUUACAC miRNA 3′ A CCA AG U 5′
kshv-miR-K12-3	POLR3B	Position 228 Target 5′ G UAU A AG U C 3′ GCUGC UG UC C A GGAUGUGA CGACG GC AG G U CUUACACU miRNA 3′ AG AG 5′
kshv-miR-K12-3	RAB3D	Position 260 Target 5′ C UU 3′ UUGCUGCU UCC AGGGUGUG AGCGACGG AGG UCUUACAC miRNA 3′ CAG U 5′
kshv-miR-K12-3	SLC1A4	Position 2435 Target 5′ G G GC 3′ G UGCU UCC AGAGUGUG C ACGG AGG UCUUACAC miRNA 3′ AG G CAG U 5′
kshv-miR-K12-3	CCND2	Position 1742 Target 5′ AAA CA C 3′ GCUGU UGUUU CAGAGUGUG CGACG GCAGG GUCUUACAC miRNA 3′ AG AU 5′

Table 2 (*continued*)

v-miRNA	Target gene	vmiR and target gene sequence alignment
kshv-miR-K12-3	CD101	Position 48 Target 5′ A GAA A 3′ UUG GCU CC AGGGUGUGA AGC CGG GG UCUUACACU miRNA 3′ GA CA AG 5′
kshv-miR-K12-3	RAB40B	Position 98 Target 5′ G AA GC U 3′ CG UGCUG CUU GAAUGUG GC ACGGC GGA CUUACAC miRNA 3′ A G AGU U 5′
kshv-miR-K12-3	PIUPNM3	Position 2628 Target 5′ A GG GU U 3′ GUUG CG U U GAGUGUG CGAC GC G A CUUACAC miRNA 3′ AG GA G GU U 5′

v-miR-target 3'UTR interaction was assessed by target prediction tool RNAHyrbid software (https://bibiserv2.cebitec.uni-bielefeld.de/rnahybrid?id=rnahybrid_view_submission). The procured 3′UTR sequences and miR-H1 and miR-K12-3 sequences (extracted from miRbase v.21) were provided as input for RNA Hybrid analysis. The stringency parameters were set-up for individual sequences and we opted for three hits per target to highlight any probable v-miR binding sequence present on the target.

We considered the following parameters to select putative v-miR regulated genes. (i) There should be high sequence complementarity in the seed region (positions 2–8 nt from 5′ of miRNA), with only 1 mismatch allowed. (ii) For stringency, we picked v-miR-target interactions where more than 11 nts of the v-miR sequence are involved in the interaction. (iii) If there is any mismatch in the seed regions, this should be compensated by strong binding beyond the seed region. (iv) The bulge in the interaction region should not involve more than 3 nucleotides. (v) Entropy of the v-miR-target interaction was set at stringent level with cut-off < 22 kcal/mol.

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Transparency document. Supporting information

Transparency data associated with this article can be found in the online version at https://doi.org/10.1016/j.dib.2018.05.020.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at https://doi.org/10.1016/j.dib.2018.05.020.

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