Appendix

Supplementary Materials

Ethics statement. These studies were performed with the approval of the Tulane University's Institutional Animal Care and Use Committee. Animals were housed at the Tulane Primate Research Center (TNPRC) according to the standards of the American Association for Accreditation of Laboratory Animal Care and Tulane IACUC protocol #3497. Treatment of animals was in accordance with the Guide for the Care and Use of Laboratory Animals of the Institute of Laboratory Animal Resources.

Materials and Methods. Infection and disease pathology of macaques has been described previously(Strickland et al., 2012). Briefly, two matched macaques were infected successfully and quickly displayed similarly elevated viral copy numbers in the plasma, with a first peak (acute infection) between 14-21 days post infection (dpi). One macaque was sacrificed at 21 dpi; the other was followed until the development of multiple AIDS-associated disorders and was diagnosed with SIVE at necropsy (75 dpi) by histopathology of brain tissues. Identical weights of brain tissue samples from each of the macaques' temporal lobes were taken at necropsy. The samples were frozen in Tissue-Tek* CRYO-OCT Compound (Sakura Finetek) at -80°C. Total RNA was extracted with the use of a *mir*Vana miRNA isolation kit (Ambion) according to the manufacturer's instructions. Briefly, the samples were homogenized in lysis buffer and samples were subjected to Acid-Phenol:Chloroform extraction. The sample RNA was eluted with a low ionic-strength solution. Total RNA was quantified on a Nanodrop 2000 (Thermo Scientific).LC Sciences used the TruSeq Small RNA Sample Prep Kit (Illumina) was used to construct small RNA libraries. Total RNA was size-fractionated on a 15% TBE-Urea polyacrylamide gel. RNAs of 15-50 nucleotides were isolated, extracted, quantified, and ethanol precipitated. SRA 5' and 3' adaptors were ligated to the RNA fragments using T4 RNA ligase

(Promega) then size fractionated and purified. The ligated RNA fragments were reverse transcribed to single-stranded cDNAs using M-MLV (Invitrogen). cDNAs were amplified with *pfx* DNA polymerase (Invitrogen) in 20 cycles of PCR using Illumina's small RNA primers set. PCR products were purified on a 12% TBE polyacrylamide gel and ~80-115 bps was excised. The products were quantified on TB5-380 mini-fluorometer (Turner Biosystems) using Picogreen (Invitrogen). Approximately 10nM and 10µl were used in sequencing reactions. The purified cDNA library was sequenced on the Illumina GAIIx following manufacturer's protocols. The raw sequencing reads were obtained using Illumina's Pipeline v1.5 software. MiR sequences are available from the authors upon request.

Illumina data was trimmed for primer sequences and poly-A additions and duplicate miRs were identified. All miRs were then clustered using an alignment-based approach on the seed region following methods described in Hinton et al. (2014). Briefly, pairwise alignment made use of the following criteria: 1) exact identity of the seed regions (nucleotides 2-7) between the two sequences being aligned, 2) >80% sequence identity within nucleotides 8-18 (inclusive), 3) >65% identity for any remaining nucleotides outside of these regions, 4) when a read aligned to two or more known stem-loop sequences, the read was assigned to the stem-loop(s) with the highest sequence similarity, 5) the following parameters were used for the alignments: match for non-N nucleotides = +5, mismatch for non-N nucleotides = -4, match for any nucleotide with N = -1, gap open penalty = -16, gap extension = -4. Overall 2.0 million sequencing reads for the 21 dpi tissue and 3.5 million sequencing reads for the 75 dpi tissue were generated; however, after trimming and clustering the number of reads for each tissue was quite similar, with both samples containing ~200,000 unique putative miRs. The samples were normalized by dividing by the total number of reads from each tissue and expressed as reads per million (RPM). Known human neurodegenerative miRs (ND-miRs) and macaque miRs (mml-MiRs) derived

from various lymphoid macaque tissues were retrieved from miRBase (Release 18). BLAST (Altschul et al. 1990) was used to identify homologs between ND-miRs and mml-miRs. Tarbase v.5c (*diana.cslab.ece.ntua.gr/tarbase/),* was used to identify gene interactions of miRs that have been validated in the literature.

Supplemental References:

1. "Hinton A, Hunter S, Afrikanova I, Jones GE, Lopez AD, Fogel GB, Hayek A, King CC (2014) "sRNA-seq Analysis of Human Embryonic Stem Cells and Definitive Endoderm Reveal Differentially Expressed MicroRNAs and Novel isomiRs with Distinct Targets," *Stem Cells*, in press.
2. Altschul, S.F., Gish, W., Miller, W., Myers, E.W. & Lipman, D.J. (1990) "Basic local alignment search tool." J. Mol. Biol. 215:403-410.