HERV Regulation in People Living With HIV-1: Analyzing Differential Expression and HIV-1-related Inflammation

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Introduction

- Human endogenous retroviruses (HERVs) are genomic elements similar to retroviruses. HERVs are defective and most cannot replicate.
- Recent research has indicated that in patients with HIV-1, HERVs can be upregulated, theorized to cause inflammation
- HERVs contain LTR regions at the beginning and terminal ends with internal genes in between.

Collecting Sample & Research Objectives

- Sample of 36 people was collected
  - Nine people without HIV older than 50
  - NIne people with HIV older than 50
  - Nine people with HIV younger than 35
  - Nine people without HIV younger than 35
- Significant regulation of genes across HIV status and age status examined
  - Further analysis within young people, old people, those without HIV, and those with HIV
- Expression of genes in a sample of the internal HERV regions was compared against genes in a sample of the total HERV genomes with the LTR regions through RNA sequencing

Methodology

RNA STAR Pipeline

- RNA reads within peripheral mononuclear cells were converted to cDNA when compared against a reference human genome using RNA STAR.
- Counts of genes from peripheral mononuclear cells calculated using FeatureCounts
- DESeq2 used to conduct differential gene expression analysis across sample of 36

HERV Pipeline

- Files of reads from internal HERV regions without LTR regions and complete HERV sequences isolated using Python
- Both files of reads were aligned against the human genome using Bowtie2
- Counts of genes from both alignments calculated using Telescope

- DESeq2 used to conduct differential gene expression analysis for both counts across sample of 36.

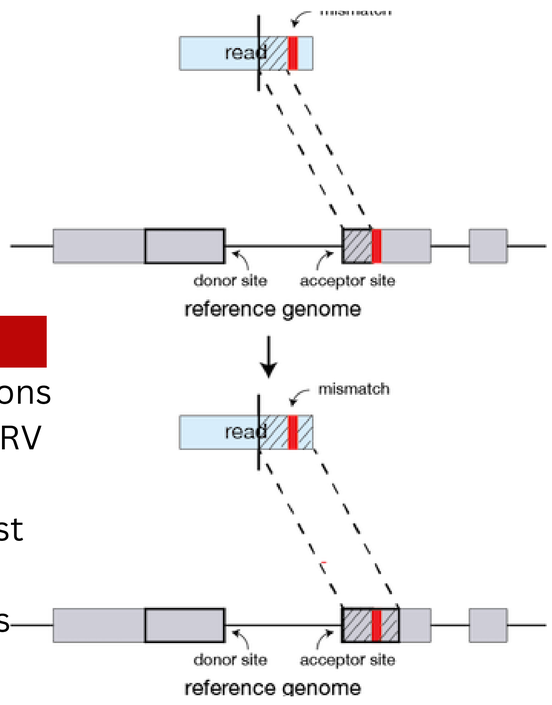

Figure 1: Aligning reads to a reference genome using RNA STAR (Dobin, 2019)

Graphs of Gene Expression for Mononuclear Cells

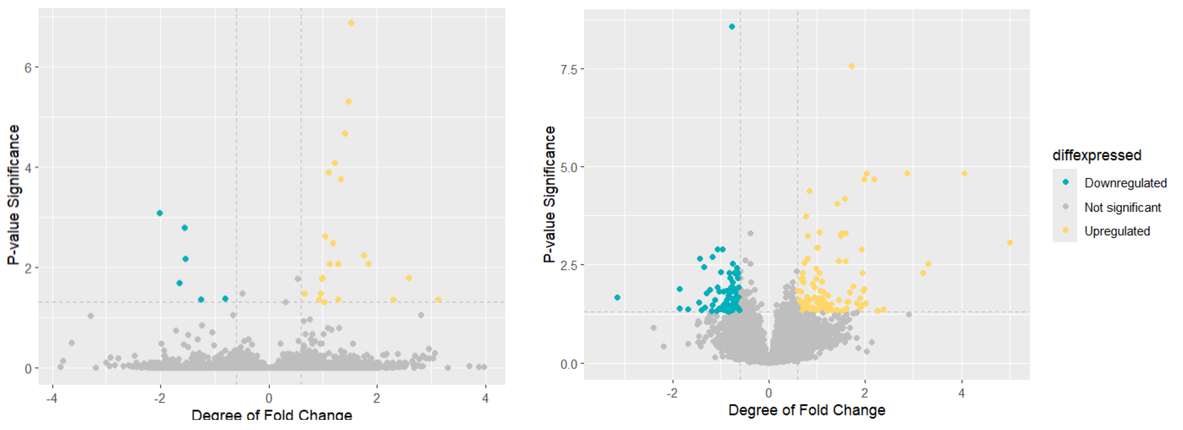

Figure 2: Significant changes in gene expression for peripheral mononuclear cells observed across HIV status for all ages (right) but significant changes not observed for age status across those without HIV and with HIV (left)

Graphs of Gene Expression across HERVs

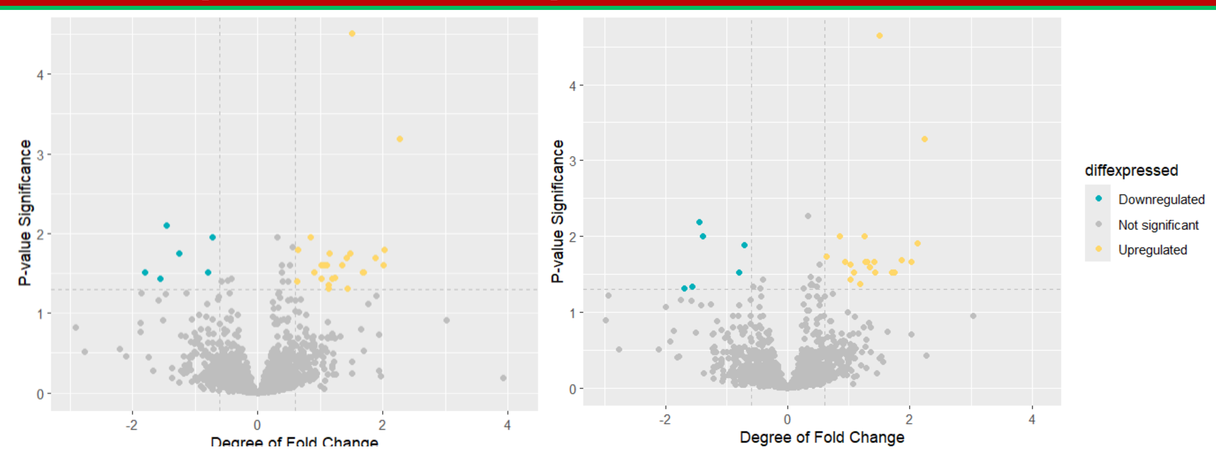

Figure 3: Significant changes in gene expression for both complete HERVs (left) and internal HERV regions (right) observed across HIV status for all ages

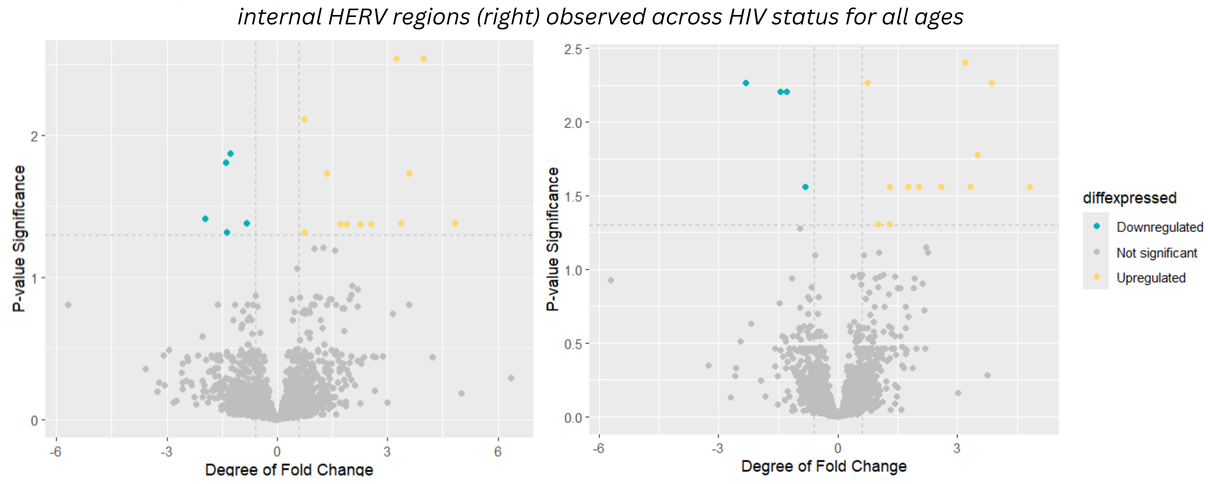

Figure 4: Significant changes in gene expression for both complete HERVs (left) and internal HERV regions (right) observed across HIV status for young people

- As observed for the peripheral mononuclear cell genes, major gene expression differences were not observed across age

Gene Expression for Complete and Internal HERVs

Gene	diffexpressed comp		Type of HERV in which Gene is Expressed?
ERV316A3_8q13.1b	UP	HIV across Ages Broadly	Complete
HERVFH21_8q21.11	UP	HIV across Young People Broadly	Internal
HERVH_22q13.1b	UP	HIV across Young People Broadly	Internal
HERVH_8q24.21a	DOWN	HIV across Young People Broadly	Complete
HERVIP10FH_12p13.2	UP	HIV across Ages Broadly	Complete
HERVL_17q12b	UP	HIV across Ages Broadly	Complete
HML1_2p11.2	UP	HIV across Young People Broadly	Complete
MER34B_19p13.11	DOWN	Ages across People with HIV Broadly	Internal
MER4B_19q13.42b	UP	HIV across Ages Broadly	Complete
PRIMA4_8p22	UP	HIV across Young People Broadly	Complete

Table 1: Table of HERV elements that are differentially expressed in either only complete HERVs or internal HERV regions across one sample group

- Twelve HERV gene expression across sample groups discrepancies were observed out of forty differentially expressed genes.
- ~75% of HERV elements were found to be upregulated during HIV pathogenesis

Conclusions

- Significant gene expression discrepancies found across HIV status (between those without HIV and those with HIV).
- Significant gene expression discrepancies were not found across age status (younger and older people)
- Noteworthy difference in HERV element gene expression found between internal HERV regions without LTRs and complete HERVs
- Most HERV elements largely found to be upregulated

Key References

[1] alexdobin, “alexdobin/STAR,” GitHub, Aug. 2019. https://github.com/alexdobin/STAR

Acknowledgements

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Future Work

Further research should focus on the role of specific genes found to be differentially regulated between complete and internal HERV regions. Specifically, these genes should be assessed as to whether they contribute to HIV-related inflammation. The discrepancies between gene expression across HIV status could also be studied for other retroviruses such as HTLV-1.