

## **Dominant clones in high-risk HTLV-1 carriers have a genetic and transcriptomic profile closely resembling ATL clones**

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### **Background**

Flow-cytometric analysis of T-cell receptor V $\beta$  (TCRV $\beta$ ) subunits identifies HTLV-1 carriers who have a high risk of developing ATL and oligoclonal HTLV-1-infected CD4+CCR4+CD26-T-cell clones circulating in peripheral blood. We compared the exomes and transcriptomes of expanded clones with polyclonal HTLV-1-infected T cells to learn more about the processes driving transformation to ATL.

### **Methods**

Peripheral blood mononuclear cells from high-risk HTLV-1 carriers were flow-sorted into three subsets: (1) HTLV-1 infected dominant clones, (2) high PVL polyclonal CD4+ cells and (3) other (low PVL) CD4+ cells, on the basis of CD4, CCR4, CD26 and TCRV $\beta$  expression. RNA was extracted from each subset and subjected to RNA-Seq. For each subset, somatic variants were called using Mutect2, comparing RNA to the germline sequence (CD33+/19+ cells) and differential gene expression was analysed using DeSeq2.

### **Results**

Clones (8/9 carriers) had  $\geq 1$  mutation(s) in genes which are frequently mutated in ATL, including CSNK2B (n=2), PRKCB (n=2) and CIC (n=2). In three subjects who subsequently transformed to ATL, dominant clones all had  $\geq 1$  mutation(s) in a gene in the T-cell receptor/NF $\kappa$ B pathway. Transcriptomic analysis of the dominant clone revealed similarities to but also significant differences from the transcriptomes of polyclonal HTLV-1 infected cells and ATL cells, consistent with an intermediate transcriptomic profile between ATL and non-malignant HTLV-1 infection. Gene set enrichment analysis of differentially expressed genes in clones vs infected polyclonal cells showed enrichment of ATL-associated pathways as well as suppression of pathways involved in lymphocyte differentiation and immune receptor activity.

### **Conclusion**

In high-risk HTLV-1 carriers, HTLV-1 infected clones identified by flow-cytometry resemble ATL genetically and transcriptomically, even in subjects who have no clinical evidence of ATL. Mutations in the TCR/NF $\kappa$ B pathway may be stronger drivers of the transformation process. DEGs identified in clones may offer potential targets for preventative therapy.

**Disclosure of Interest:** None