

## **HTLV-1 infection promotes excessive T cell activation and transformation into adult T cell leukemia / lymphoma**

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### **Background:**

Human T cell leukemia virus type 1 (HTLV-1) mainly infects CD4<sup>+</sup> T cells and induces an asymptomatic but chronic, persistent infection in infected individuals. However, some asymptomatic carriers' progress to develop an aggressive T cell malignancy known as adult T cell leukemia/lymphoma (ATL). HTLV-1 alters cellular differentiation, activation, and survival; however, it is unknown whether and how these changes contribute to the malignant transformation of infected cells.

### **Methods:**

In this study, we obtained peripheral blood mononuclear cells (PBMCs) from 12 HTLV-1-infected and 3 uninfected individuals and performed single-cell RNA-sequencing and T cell receptor-sequencing to investigate the differentiation and HTLV-1-mediated transformation of T cells.

### **Results:**

In total, we analyzed 87,742 PBMCs from 15 individuals. Using multiple independent bioinformatics methods, we demonstrated the seamless transition of naive T cells into activated T cells, whereby HTLV-1-infected cells in an activated state further

transformed into ATL cells, which are characterized as clonally expanded, highly activated T cells. Notably, the greater the activation state of ATL cells, the more they acquire signatures of regulatory T cells. Intriguingly, infected cells uniquely upregulate HLA class II genes which is further induced in ATL cells. Ex vivo cultivation of HTLV-1-infected cells showed that this upregulation occurred concurrently with the expression of viral protein Tax. Functional assays revealed that by upregulating HLA class II molecules, HTLV-1-infected cells can act as antigen-presenting cells. However, as these cells lack the necessary co-stimulatory molecules, they could induce anergy of antigen-specific T cells.

**Conclusion:**

In conclusion, our study revealed at the single cell level how HTLV-1 exploits physiological T-cell activation mechanisms and may act as tolerogenic antigen-presenting cells for leukemic transformation and immune evasion in vivo.

**Disclosure of Interest Statement:**

Nothing to disclose.