

# Chronological genome and single-cell epigenome/transcriptome integration characterizes the evolutionary process of adult T cell leukemia-lymphoma

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Subclonal genetic heterogeneity and their diverse gene expression impose serious problems in understanding the behavior of cancers and contemplating therapeutic strategies. We developed and utilized a capture-based sequencing panel, which covers host hotspot genes and the full-length genome of human T-cell leukemia virus type-1 (HTLV-1), to investigate the clonal architecture of adult T-cell leukemia-lymphoma (ATL).

For specimens collected chronologically from patients with ATL or pre-onset individuals, we integrated deep DNA sequencing and single-cell RNA sequencing to detect the somatic mutations and virus directly and characterized the transcriptional readouts in respective subclones. We found that characteristic genomic and transcriptomic patterns were associated with subclonal expansion and switches during the clinical timeline. Multi-step mutations in the T-cell receptor (TCR), STAT3, and NOTCH pathways establish clone-specific transcriptome abnormalities that further accelerate proliferative potential and generate highly malignant clones, leading to disease onset and progression. This new platform links genetic variation and gene expression in individual clones. These new data provide direct evidence that genetic mutations play an important role in the process of natural selection of each clone, and that certain clones evolve into malignant cells by changing the nature of the infected cells (Yamagishi *et al.*, *Nat. Commun*, 2021).

We also implemented an integrative scRNA/scATAC-seq platform to detect host epigenomic heterogeneity, which is significantly affected by HTLV-1. Using high-resolution open chromatin data and corresponding ChIP-seq data, we demonstrated that epigenetic dysregulation, such as accumulation of histone H3K27me3, is involved in early processes and clonal evolution of infected cell populations.

The data suggest that cell populations infected with HTLV-1 acquire multistep abnormalities in the host epigenome and genome during a long latency period, and that infected cells evolve into malignant cells through a complex interplay of these genetic and epigenetic abnormalities.

## Disclosure of Interest Statement:

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