Genomic landscape of peripheral T-cell lymphomas

Keisuke Kataoka

National Cancer Center Research Institute, Japan

Peripheral T-cell lymphoma (PTCL) is a heterogeneous group of mature T-cell neoplasm. Among PTCLs, the most common in Western countries is PTCL, not otherwise specified (NOS), accounting for approximately 30% of all PTCLs. Combining whole-exome and deep targeted-capture sequencing of more than 130 cases, we delineated the entire picture of genetic alterations in PTCL, NOS. Of note is the identification of a previously undescribed molecular subtype characterized by *TP53* and/or *CDKN2A* mutations and deletions in PTCL, NOS without showing a T follicular helper cell phenotype. This subtype exhibited different prognosis and unique genetic features, including extensive chromosomal instability, which preferentially affected molecules involved in immune escape and transcriptional regulation.

Among PTCLs, the most common entity in Japan is adult T-cell leukemia/lymphoma (ATL), which is an aggressive peripheral T-cell lymphoma associated with human T-cell leukemia virus type-1 (HTLV-1) infection. We previously performed an integrated molecular study, in which whole-exome, transcriptome, and targeted resequencing, as well as array-based copy number analysis were performed. We found recurrent genetic alterations in T-cell receptor/NF-κB signaling, T-cell trafficking, and other T-cell-related pathways as well as immunosurveillance. Although our previous study discovered many driver mutations and copy number alterations, the whole-genome landscape of ATL still remains elusive. To address this issue, we have recently performed high-depth whole-genome sequencing (WGS) of 150 ATL samples. WGS presented a substantially different overview of driver alterations compared with WES. Particularly, we identified novel alterations, such as long-isoform specific mutations of *CIC* and C-terminal truncation of *REL*. In vitro and in vivo analyses also revealed a functional role of these alterations in T-cell lymphomagenesis. Therefore, our WGS analysis not only identifies novel somatic alterations, but also extends the overview of ATL genome, which can lead to future improvement of patient management.

Taken together, our findings provide novel insights into genetic and molecular heterogeneity in PTCLs, which should help to devise a novel molecular classification and to exploit a new therapeutic strategy for these malignancies