NGS quantification of viral clonal architecture identifies HTLV-1 asymptomatic carriers at high risk of progression to aggressive leukemia

Karpe SD[1,2], Artesi M[2], Durkin K[2], Hahaut V[1,2], Wayet J[2], Uchimaru K[3], Makiyama J[4], Iwanaga M[5], Utsunomiya A[6], Heezen KC[7], Langerak AW[7], Burny A[1], Watanabe T[8], Georges M[2], Van den Broeke A[1,2]

[1] Laboratory of Viral Oncogenesis, Institut Jules Bordet, ULB, Brussels, Belgium
[2] Unit of Animal Genomics, GIGA, ULiège, Liège, Belgium
[3] Laboratory of Tumor Cell Biology, The University of Tokyo, Tokyo, Japan
[4] Department of Hematology, Sasebo City General Hospital, Nagasaki, Japan
[5] Clinical Epidemiology, Nagasaki University Graduate School of Biomedical Sciences, Nagasaki, Japan, [6] Imamura General Hospital, Kagoshima, Japan
[7] Laboratory Medical Immunology, Dept. Immunology, Erasmus MC, Rotterdam, The Netherlands
[8] Graduate School of Medicine, St. Marianna University, Kanagawa, Japan

Background
Human T-cell Leukemia Virus-1-infected asymptomatic carriers are characterized by the presence of multiple T-cell clones, each characterized by a unique proviral integration site (IS) in the host genome. Only ~20% of “high-risk carriers” (identified as having a high PVL, ≥ 4 HTLV-1 copies per 100 PBMCs) will progress to Adult T-cell Leukemia (ATL), a treatment-refractory aggressive disease. There is an urgent need for a molecular tool that can better risk-stratify these patients, thereby avoiding unwarranted fear.

Our group has developed a method for quantifying the clonal distribution of IS (“clonality”) using linker-mediated PCR followed by next generation sequencing (NGS), making it clinically applicable for diagnosis of leukemic patients with monoclonal architecture. We hypothesized that clonality sequencing can be used to identify the premalignant stage of ATL in carriers by detecting the presence of the dominant ATL precursor clone prior to the onset of symptoms.

Methods
We studied a unique cohort of HTLV-1-infected individuals enrolled in the JSPFAD survey initiated in Japan in 2002. We report the analysis of longitudinal samples obtained from high PVL asymptomatic carriers who subsequently developed ATL and compare these with high and low PVL carrier groups followed over an equivalent period and who did not develop malignancy. We explored the potential association between clonality and the patients’ clinical outcome many years later.

Results
i) NGS clonality outperforms PVL as a predictive biomarker of progression towards an aggressive disease, ii) clonality better discriminates asymptomatic carriers from patients with indolent ATL, iii) >30% of progressors harbour multiple integrations within a single predominant T-cell clone as determined

by TCR NGS. Clonality is also powerful in identification of potential progressors with multiple insertions or those with low PVL.

Conclusion

Monitoring clonality signatures in HTLV-1 asymptomatic carriers will allow individuals with increased risk of ATL to be better managed presumptively.

Disclosure of Interest Statement:

There are no disclosures.