ANALYSIS OF EPSTEIN-BARR VIRUS TRANSCRIPTOME IN ANGIOIMMUNOBLASTIC T CELL LYMPHOMA (AITL) COMPARATIVELY TO OTHER HUMAN LYMPHOMAS

Nader Bayda[1,2], Valentin Tilloy[3], Alain Chaunavel[4], Racha Bahri[1], Adnan Halabi[1], Jean Feuillard[5,2], Arnaud Jaccard[6,2], Sylvie Ranger-Rogez[1,2,7]

[1] Microbiology Department, Faculty of Pharmacy, 2 rue du Dr Marcland, 87025, Limoges, France; [2] UMR CNRS 7276, INSERM U1262; [3] Sequencing Department, CBRS, rue Pr Descottes, 87000, Limoges, France; [4] Pathology Department, CBRS, rue Pr Descottes, 87000, Limoges, France; [5] Biological Hematology Department, CBRS, rue Pr Descottes, 87000, Limoges, France; [6] Clinical Hematology Department, CHU Dupuytren, 2 avenue M. LutherKing, 87042, Limoges, France; [7] Virology Department, CBRS, rue Pr Descottes, 87000, Limoges, France;

nader.bayda@unilim.fr

The Epstein-Barr virus (EBV) is a ubiquitous gamma-herpesvirus that infects the majority of the world's population. The EBV is linked to several malignancies such as carcinomas and B or T lymphomas. EBV, like other herpesviruses, can exist in both lytic and latent phases, with primary lytic infections frequently evolving into lifetime latent infections with sporadic future lytic reactivation. During latency, nine proteins (EBNA-1, -2, -3A, -3B, -3C, -LP and LMP-1, -2A, -2B) as well as two RNAs (EBER, Epstein – Barr virus-encoded small RNAs, and BARTs, Bam-HI A rightward) and miRNAs are expressed and may play a fundamental role in oncogenesis. Angioimmunoblastic T cell lymphoma (AITL), the most common peripheral T-cell lymphoma, is an aggressive lymphoma with a poor prognosis. AITL is more common in Europe than in other regions. AITL is associated with EBV in more than 80% of cases and it is not clear now what role the virus plays in this pathology [1]. This project aimed to identify the EBV transcriptome in AITL biopsies compared to other EBV-positive lymphomas and cell lines by RNA-seq. We studied 14 AITLs and 21 other lymphoma samples and 11 cell lines including B95-8, 4 Burkitt's lymphoma (BL), 2 NK/T lymphoma, and 4 lymphoblastoid cell lines (LCLs). Total RNA was extracted and poly(A) mRNAs were selected *via* oligo(dT) beads. Libraries were prepared after the capture of EBV mRNA by specific probes and finally sequenced on the MiSeq instrument. Reads were aligned against hg19, EBV1, and EBV2, and EBV reads were normalized to transcripts per million (TPM). Results showed that Bam-HI A rightward transcripts (BARTs) comprising BARF0, RPMS1, and A73, were much more strongly and more frequently expressed for AITLs suggesting their participation in this lymphoma with the form of lncRNAs and/or miRNAs. Thus BARTs, which had previously been identified as highly expressed in carcinoma cells, were also shown to be strongly expressed in AITLs, other lymphomas, and LCLs, as opposed to cell lines. We have also shown that AITLs exhibited a latency described until now in carcinomas corresponding to the latency IIc, with the expression of EBNA-1, LMP-2, and BNLF2a, which blocks antigen presentation to cytotoxic T lymphocytes. BCRF1, encoding a homologous protein of human interleukin 10, vIL-10, was in addition present in AITLs. The co-expression of BNLF2a and BCRF1 can contribute to immune escape and survival of infected cells and tumors. In order to understand the behavior of EBV in lymphoma tissues, we compared results obtained for our patients to those obtained for cell lines and we showed that viral behavior was not specific to a type of pathology. These results support the involvement of EBV in this pathology like other lymphomas.

[1] Nader Bayda, Valentin Tilloy, Alain Chaunavel, Racha Bahri, Adnan Halabi, Jean Feuillard, Arnaud Jaccard, Sylvie Ranger-Rogez, 2021, Cancers (Basel), 4, 610.