KEY EPIGENETIC EVENTS DURING EBV-MEDIATED B CELL TRANSFORMATION

Francesca Manara[1], Grace Akinyi odongo[1], Rita Khoueiry[1], Henri Gruffat[2], Zdenko Herceg[1].

[1] *Epigenomics and Mechanisms Branch*, *International Agency for Research on Cancer, World Health Organization, 69000 Lyon, France*
[2] *CIRI, Centre International de Recherche en Infectiologie, Univ. Lyon, Inserm, U1111, Université Claude Bernard Lyon 1, CNRS, UMR5308, ENS de Lyon, F-69007, Lyon, France*

manaraf@iarc.fr

The epigenome acts as an interface between the genome and the environment, dynamically modulating gene expression according to environmental changes and exposures, like viral infections. Some resulting epigenetic aberrations might lead to cancer initiation and progression. For example, Epstein Barr Virus (EBV)'s ability to hijack B-cell maturation pathways to establish a lifelong persistent infection in B cells derives, in part, from the viral proteins' manipulation of the human epigenetic machinery to regulate both viral and host cells' transcriptional programs. Although many studies have shown that EBV's interaction with several human epigenetic enzymes is crucial for the virus-mediated onco-epigenetic reprogramming of the infected cell, the broad spectrum of EBV-induced epigenetic events during B-cell transformation remains unclear.
Here, we aim to explore EBV-mediated epigenetic events occurring at the early stages of cell immortalization to identify regulatory mechanisms underlying the transformation of EBV-infected B cells. To this end, we will identify epigenetic drivers (”epidrivers”) of B-cell immortalization using a genome-wide CRISPR loss-of-function screen targeting 426 epigenetic regulator genes (ERGs). By analyzing available RNA-seq data, we identified 32 ERGs significantly perturbed transcriptionally upon EBV infection. Those ERGs may be playing a crucial driver role in the epigenome rewiring underlying virus-mediated B-cell immortalization. Among these, we found the histone methyltransferases KMT2 (D, C, A) that often show mutations in the genome sequencing data of non EBV+ lymphomas (available in TCGA data) and that have been described to drive tumorigenesis. This suggests a putative driving role of EBV-induced KMT2D downregulation during EBV+ lymphomagenesis. Our preliminary results confirmed that during EBV-mediated B cell immortalization, KMT2/C/A are progressively silenced and H3K4 methylation is reduced following the activation of NF-KB pathway by the viral protein LMP1.
In parallel, we are characterizing the epigenome and transcriptome rewiring during EBV-induced B cell immortalization by applying a multi-omics integrative approach.
Overall, our study by unravelling epigenetic mechanisms and biomarkers involved in EBV-mediated lymphomagenesis will advance our understanding of EBV-associated cancer aetiology and reveal potential “Achilles' heels” of Burkitt's lymphoma that may be exploited for the development of novel targeted therapeutic approaches.