EBV-DEFECTIVE GENOMES IN DIFFERENT CELL-TYPES ARE ASSOCIATED WITH EBV-RELATED MALIGNANCIES

Cristina Venturini[1], Ben Carpenter[2], Claire Booth[3], Winnie Ip[3], Austen Worth[3], Judith Breuer [1,3]

[1]Department of Infection, Immunity and Inflammation, UCL Great Ormond Street Institute of Child Health, University College London, London, United Kingdom; [2]University College London Hospitals NHS Foundation Trust, London, United Kingdom; [3]Great Ormond Street Hospital for Children NHS Foundation Trust, London, United Kingdom.

c.venturini@ucl.ac.uk

Chronic active Epstein Barr Virus (CAEBV) disease is a rare life-threatening condition with persistent high level EBV replication following an infectious mononucleosis syndrome. The disease is characterised by infiltration of tissue by EBV-positive T, NK or less frequently B cells and can progress into lymphoproliferative disease. Defective EBV genomes have been found in East Asian patients with CAEBV and other EBV-related malignancies. We previously showed that all genomes, even from healthy individuals, contain small deletions in genes associated with latency. However, only blood samples from CAEBV patients contain a small number of viral genomes with bigger deletions which may affect viral replication. Importantly we have shown that these larger deletions are lost following successful treatment with drugs (rituximab) or bone marrow transplant. Loss of cells carrying these deletions was associated with clinical improvement.
To better understand when and where these deletions occur, we sequenced 18 samples from three additional patients, patient A with EBV-positive diffuse large B cell lymphoma (DLBCL) and patient B and C with CAEBV diagnosis. The samples were taken from whole blood, B, T and NK cells fractions and tumours so we could directly compare different cell types within the same patient.
All patients had the 5' (12 kbp-15 kbp) and 3' (127 kbp-140 kbp) EBV deletions, the latter covering the BART microRNAs and late lytic genes ie. BXLF2. Here we show that the large 3' (127 kbp-140 kbp) EBV deletion is present in different lymphocyte subsets for each patient. Additional deletions encompassing part of the genome from 140-149kbp were also present in two patients. Poor outcome in patient A was associated with increased frequency of the 3' deletion.

These findings may be explained by the fact that the deletions are present in premalignant clones which occur when a particular subset of the patients' blood cells are infected with EBV. Progenitor lymphoid cells have been suggested to be the target cells, however our results showed that deletions might also occur later when progenitor lymphoid cells differentiate into B, T or NK cells. Using the EBV genome data from these and previously published cases, we map the minimal genome loss common to all cases.