An Investigation of the Epstein-Barr Virus Genome in Extranodal NK/T-cell Lymphoma (ENKTL)

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Epstein-Barr virus is a Cancer Group 1 carcinogen that has infected 95% of the world’s adult population. However, it is unclear why only a fraction of the population will develop an EBV associated cancer. Furthermore, there is a unique distribution of EBV+ cancers dependent on geographic region. For example, extranodal NK/T-cell lymphoma, the focus of this proposal, accounts for a drastically higher proportion of non-Hodgkin lymphomas in East Asia, Central America and Western South America. This suggests that an inherent genetic predisposition and/or region-specific differences in EBV itself may drive pathogenesis.

Uncovering these disease mechanisms are challenges perfectly met by the comparative analysis of genomes from sequencing data. Indeed, two recent Asian cohorts revealed ENKTL specific EBV variants that resulted in non-synonymous mutations of several genes with known functions in viral replication and immune evasion. However, whether these variants are also present in ENKTL from Central and South America is unknown. Despite several EBV associated cancers occurring at disproportionate levels in Guatemala, representation of these populations in viral and host sequencing studies is extremely limited. Among 627 complete or near complete EBV genomes accessed on NCBI there were no genomes from Central America or Western South America.

Barriers to conducting this work have been the lack of well annotated samples, inadequate collaborative effort between institutions, technical requirements for fresh tissue, and limited funding for international studies. Through an ongoing collaboration we have annotated 168 EBV+ lymphomas from Guatemala including 39 ENKTL and 37 HL with adequate tissue for further analysis. In preliminary experiments we used an oligo-based EBV DNA capture method that can achieve high quality enrichment of the EBV genome from 10-20 um sections of formalin-fixed paraffin embedded (FFPE) tissue and have completed targeted EBV genome sequencing and assembly of 22 ENKTL cases.

In aim 1 of this proposal, we will determine whether established variants from Asia are shared with ENKTL associated EBV genomes from Guatemala. We hypothesize that some EBV genome variants overlap between populations with a high incidence of ENKTL and may uncover targetable pathogenic mechanisms of a disease.

In aim 2 we propose to sequence EBV genomes from a cohort of EBV+ classical Hodgkin lymphoma and healthy EBV carriers from Guatemala. We hypothesize that there are EBV genome variants carried in patients with ENKTL that are significantly different than EBV genome variants carried in classical HL patients or healthy controls from Guatemala.

Taken together we propose that these studies will offer important insights toward developing novel therapeutics to prevent and treat EBV associated malignancies, while expanding our understanding of the global EBV genome.