EBNA-LP Co-**A**ctivates **OXPHOS T**ranscription **F**actors to **P**romote **M**etabolic **C**hanges in **EBV I**nfected **B C**ells

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Epstein-Barr Virus (EBV) is associated with malignancies including lymphomas and transforms primary human B cells into immortalized lymphoblastoid cell lines (LCLs) *in vitro*. EBV induces metabolic changes upon infection of B cells to overcome cell intrinsic barriers to transformation [1]. Latency proteins including EBV Nuclear Antigens (EBNAs) have been shown to regulate metabolic genes [2]. Our lab and others have found that EBV upregulates oxidative phosphorylation (OXPHOS) related genes early after B-cell infection, although the mechanism by which OXPHOS is regulated is not known [1]. Naïve B cells also require increased OXPHOS upon antigen activation in order to undergo germinal center remodeling and produce memory B cells [4]. EBNA-Leader Protein is one of the first viral proteins expressed and is also essential in naïve, but not memory, B-cell transformation - although the mechanistic role of EBNA-LP in naïve B-cell infection is not well characterized [4]. We hypothesized that EBNA-LP contributes to OXPHOS regulation in infected B cells. Indeed, stable expression of EBNA-LP in an EBV-negative lymphoma cell line elevates oxygen consumption and increases expression of OXPHOS-related genes. By analyzing publicly available ChIP-Seq data in LCLs we observed a large overlap between peaks from EBNA-LP and peaks from several host transcription factors that regulate OXPHOS-genes including NRF1, ERRα, and YY1 [5]. We confirmed co-association between EBNA-LP and these transcription factors by endogenous co-immunoprecipitation. These transcription factors are all regulated by a family of proteins called the PGC transcriptional co-activators, which engage transcription factors through leucine-rich motifs []. By sequence, EBNA-LP contains a leucine-rich motif in the repeated W domain, and in the constant Y domain that are structurally similar to those in PGC proteins and may therefore use this same motif to associate with OXPHOS regulating transcription factors. Our findings suggest EBNA-LP may be essential in upregulation of OXPHOS during EBV infection through mimicking PGC proteins to co-activation transcription factors that regulate OXPHOS and promote naïve B-cell outgrowth.

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