NOVEL EPSTEIN BARR VIRUS STRAINS ISOLATED FROM ENDEMIC BURKITT LYMPHOMA PATIENTS DISPLAY UNUSUAL AND REVERSIBLE SPONTANEOUS LYTIC PHENOTYPES

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Epstein Barr virus (EBV) prototypically exists in either a latent or lytic state and movement between these two states is tightly regulated by the virus. We isolated five patient-derived, EBV-positive endemic Burkitt lymphoma (eBL) cell lines. Three of these new eBL lines constitutively display elevated lytic activity (>20% cells expressing viral glycoprotein gp350). Importantly, when we infected naïve B cells with virus isolated from these eBL cells, the subsequent lymphoblastoid cell lines (LCLs) showed the same lytic activity/ phenotype. Moreover, this lytic phenotype is basally maintained and reversible; when eBL cells are sorted into pure gp350+ or gp350- populations, they quickly revert to the original level of gp350 expression present in the bulk culture. These data suggest that this novel lytic phenotype is not detrimental to cell survival or B cell transformation and is encoded by the viral genome.

EBV strain diversity is categorized into two major genetic types: Type 1 (T1) and Type 2 (T2) [1]. Our novel EBV strains include both T1 and T2 varieties and the constitutive lytic phenotype is present in both genetic types. Previous studies indicate that the Z promoter polymorphism Zp-V3 in T2 strains enhances a similar spontaneous lytic phenotype [2]. However, this spontaneous lytic phenotype has never been described in T1 strains without Zp-V3. This suggests that there is an alternate mechanism for the development of this phenotype in Zp-P T1 strains, which we are investigating.

Our results indicate that the prototypical tightly latent EBV infection of B cells might not be as common as once thought. This notion is supported by another recent study that identified spontaneous lytic EBV strains isolated from transplant patients [3]. Given the connection between lytic activity and oncogenesis, the high level of constitutive lytic replication of these newly described strains may contribute to development of EBV-associated diseases. Moreover, these lytic strains will enable studies of host cell tolerance of productive EBV replication. Thus, these recently established eBL cell lines and the wild-type EBV strains infecting them will be a valuable resource for EBV and virology researchers.

1. Palser, A.L., et al., *Genome diversity of Epstein-Barr virus from multiple tumor types and normal infection.* J Virol, 2015. **89**(10): p. 5222-37.
2. Bristol, J.A., et al., *A cancer-associated Epstein-Barr virus BZLF1 promoter variant enhances lytic infection.* PLoS Pathog, 2018. **14**(7): p. e1007179.
3. Delecluse, S., et al., *Identification and Cloning of a New Western Epstein-Barr Virus Strain That Efficiently Replicates in Primary B Cells.* J Virol, 2020. **94**(10).