Regulation of the DNA damage response by the large tegument protein of the oncogenic herpesviruses

Soham Gupta1, Teresa Frisan1,2, Maria G Masucci1
1Department of Cell and Molecular Biology, Karolinska Institutet, Sweden
2Department of Molecular Biology, Umeå University, Umeå, Sweden

Introduction

- Epstein-Barr virus (EBV) is a human oncogenic γ-herpesvirus that establishes a lifelong latent infection in the host.
- The N-terminal domain of the large tegument protein of EBV, BPLF1, is a cysteine protease with potent ubiquitin and NEDD8-specific deconjugase activities.
- BPLF1 regulates EBV replication and the early cellular response to infection by interacting and deubiquitinating/deneddylating cellular factors including PCNA, Cullin-ring ligases, Rad6/18 ubiquitin complex, RIG-I signalosome complex and TRAF6.
- However, only few substrates have been identified and the mechanisms of these effects remain largely unknown.

Aim

To find novel interacting partners and substrates of BPLF1 based on co-immunoprecipitation and mass-spectrometry and assess the functional significance of these interactions.

![Diagram showing the interaction network of BPLF1 proteins and their biological processes](image1)

The BPLF1 Interacting proteins identified in MS/MS and their biological process

![Diagram showing the regulation of DNA damage response](image2)

BPLF1 & its homologues KSHV-ORF64 and HCMV-UL48 inhibits the DNA damage response

![Schematic illustration of possible mechanisms of BPLF1 mediated inhibition of the DNA damage response](image3)

Findings

- BPLF1 interacts with several E3-ligases (HUWE1, RNF2, UBR5, CUL-1, CUL-4A) that are known to be involved in the regulation of the DNA damage response machinery at various levels.
- BPLF1 interferes with the DNA damage repair pathways and causes increased cell death upon induction of DNA damage.
- These interactions are conserved among BPLF1 homologues encoded by other herpesviruses (KSHV-ORF64, HCMV-UL48 and HSV-UL36). ORF64 and UL48 inhibits γH2AX foci formation but not UL36.