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Epstein-Barr virus manipulation of host responses

Epstein-Barr virus (EBV) is a common herpesvirus that is a causative factor in several types of lymphoma as well as gastric and nasopharyngeal carcinomas. In EBV latent infection, cells are immortalized as a result of expression of a small subset of proteins that always includes EBNA1. In addition to maintaining the EBV genomes, EBNA1 alters cells to promote survival and proliferation in part by inducing the degradation of promyelocytic leukemia (PML) tumour suppressor proteins. PML proteins and the nuclear bodies that they form have antiviral properties and are important for several cellular processes including apoptosis. We have shown that PML degradation by EBNA1 involves direct interactions of EBNA1 with CK2 kinase and the PML IV isoform, triggering PML phosphorylation and degradation, which promotes the survival of gastric and nasopharyngeal carcinoma cells. EBV can also switch to a lytic infectious cycle which involves the expression of ~80 proteins, and accumulating data suggests that lytic protein expression contributes to EBV-induced cancers. However, the functions of many of the lytic EBV proteins are poorly characterized or completely unknown. To gain insight into EBV lytic proteins that manipulate cellular pathways, we have screened a library of EBV proteins for those that affect a variety of cellular processes including the DNA damage response (DDR). Herpesviruses typically inhibit some aspects of the DDR to limit downstream consequences, including apoptosis. Our screen identified an uncharacterized EBV tegument protein as an inhibitor of the DDR. Further studies determined that the block in the DDR was at the step of histone ubiquitylation and that the EBV protein bound directly to histones. Furthermore, analysis of transcriptome data from EBV-positive gastric carcinomas showed that this EBV protein is expressed in these tumours. Together our results suggest mechanisms by which both EBV latent and lytic proteins contribute to oncogenesis.

Speaker Biography

Lori Frappier is a Professor of Molecular Genetics at the University of Toronto and a Tier 1 Canada Research Chair in Molecular Virology. Her lab is known for their work on understanding the structure, function and mechanisms of action of Epstein-Barr virus proteins, including EBNA1, as well as of cellular targets of EBNA1, including USP7. Their use of unbiased proteomics approaches has led to several discoveries of viral-host interactions, novel functions for viral and cellular proteins and new mechanisms of regulation of cellular pathways.

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