Abstract

Thesis Title: Cell Proliferation, Differentiation and Mitochondrial Dynamics

Epstein Barr Virus (EBV) is a gammaherpesvirus associated with both epithelial and lymphoid malignancies. In all of these malignancies the virus exhibits one of the three latent phases where the expression of viral genes is restricted to six EBV Nuclear Antigens (EBNAs), three Latent Membrane Proteins (LMPs), two EBV Non-coding RNAs (EBERs) and BamH1 rightward framed transcripts (BamH1W). Our study focuses on EBV associated Gastric Cancer and Breast Cancer cells. Both these cancers expresses EBV latency I proteins that include LMP2A and EBERs. EBERs, the abundantly expressed viral transcripts in latently EBV infected cells are transcribed by RNA Polymerase III into non-coding RNAs of 167 and 172bps respectively. EBERs have been reported to be cause proliferation, anti-apoptosis, cell growth and cytoskeleton organization especially in Burkitt Lymphoma cells. Unlike LMP2A, we found a specific role of EBERs in chemo-resistance to Cisplatin in gastric cancer cells (Virology (2013) 443 pp 294–305). Another Latency I gene commonly detected in gastric cancer cells is LMP2A. We found LMP2A to increase cell proliferation in gastric cancer cells. Mitochondria are essential organelles that determine cell fate by undergoing continuous dynamic fission and fusion cycles. A delicate balance between these two processes is important for many physiological outcomes and dysfunctional dynamics have been associated with important pathological conditions including cancer. We have found mitochondrial dynamics to play an important role in LMP2A induced cell migration as well as epithelial mesenchymal transition in gastric cancer and breast cancer cells. However, EBERs alone could not alter mitochondrial dynamics. Our data indicate that LMP2A causes an elevated mitochondrial fission in gastric and breast cancer cells manifested by elevated Drp1. Furthermore, LMP2A mediated Notch pathway is responsible for this enhanced fission since inhibitors of the pathway decreases the expression of Drp1. Our results further highlights the PI3K/Akt, another signaling pathway commonly altered during cellular migration in epithelial cells to also alter the mitochondrial dynamics via increased Drp1 in our cellular models. Akt lies downstream of the Notch pathway and because there exists a crosstalk between the Notch and the PI3K pathway. EBV LMP2A therefore utilizes common cell signaling pathways such as Notch and PI3K to alter mitochondrial dynamics and manifest its tumorigenic effects (Carcinogenesis (2014) 35(7) pp 1592-601).