**Targeting Epstein-Barr virus (EBV) in EBV-associated malignancies**

***Alan KS Chiang*** [1, 2], ***KF Hui*** [1, 2]

[1]Department of Paediatrics and Adolescent Medicine; [2]Center for Nasopharyngeal Carcinoma Research, The University of Hong Kong, Hong Kong SAR, China

Epstein-Barr virus (EBV) persists in tightly latent forms in every tumour cell in EBV-associated malignancies. Reactivation of lytic cycle or suppression of anti-apoptotic function of EBV may result in therapeutic effects on these malignancies.

We tested a class of chemical compounds known as histone deacetylase (HDAC) inhibitors in activating the EBV lytic cycle. Two clinically relevant compounds, suberoylanilide hydroxamic acid (SAHA) and romidepsin, strongly induced the lytic cycle in EBV-positive nasopharyngeal and gastric carcinoma cells. Induction of the early phase of lytic cycle without the need for full viral lytic production resulted in apoptosis of the cancer cells. Furthermore, romidepsin, a specific inhibitor of class I HDACs (HDAC1-3), could induce EBV lytic cycle at picomolar to low nanomolar concentrations through activation of protein kinase C-delta pathway.

In contrast, EBV-positive Burkitt lymphoma (BL) and lymphoblastoid cells (LCL) were found to be resistant to induction of EBV lytic cycle by HDAC inhibitors. However, adding a proteasome inhibitor, bortezomib, to either SAHA or romidepsin could overcome the resistance and result in synergistic killing of LCL and a subset of BL which expressed the EBNA3 proteins. By testing BL lines harboring EBNA-3A, 3B or -3C knockout EBV genome and its respective revertant, we found that the drug combination counteracted EBNA-3C's anti-apoptotic and cell cycle regulatory function to potently induce apoptosis of the lymphoma cells.

In conclusion, we have shown novel therapeutic strategies against EBV-associated epithelial and lymphoid malignancies by activating viral lytic cycle and antagonizing anti-apoptotic function of latent viral protein, respectively.

*The work is funded by NPC Area of Excellence (AoE/M 06/08 Center for Nasopharyngeal Carcinoma Research) and EBV research (#200004525) grants of AKSC.*