INDUCTION OF HISTONE MODIFICATION AS TARGET OF ANDROGRAPHOLIDE ON INHIBITION OF EPSTEIN-BARR VIRUS LYTIC PRODUCTION IN EBV POSITIVE CANCER CELL LINES

Praphatson Malat[1,3], Tipaya Ekalaksananan[1,3], Chukkris Heawchaiyaphum[1,3], Supawadee Suebsasana[2,3] and Chamsai Pientong[1,3*]

[a] Department of Microbiology, Faculty of Medicine, Khon Kaen University, Khon Kaen 40002, Thailand; [b] Department of Pharmaceutical Sciences, Faculty of Pharmacy, Thammasat University, Bangkok 10200, Thailand; [c] HPV & EBV and Carcinogenesis Research Group, Khon Kaen University, Khon Kaen 40002, Thailand.

chapie@kku.ac.th

Reactivation of Epstein-Barr virus (EBV) infection from latency to lytic phase is essential for spreading and it was also associated malignancies. Regulation of lytic phase is therefore crucial and is considered to be of great benefit in the treatment of EBV-associated malignancies. Andrographolide, a natural compound, exhibited anti-viral and anti-tumor activities. This study aimed to investigate the effect of andrographolide on the inhibition of EBV lytic reactivation in EBV positive cancer cells. EBV positive cancer cell lines; P3HR1, AGS-EBV and HONE1-EBV cells were treated with andrographolide and induced for lytic phase by sodium butyrate (NaB) for indicated time points. The cytotoxicity of andrographolide on EBV positive cell lines was evaluated by MTT assay. qRT-PCR, qPCR and western blotting were used for determining the effects of andrographolide on inhibition of EBV lytic reactivation and for inhibition of EBV lytic production, EBV genome copy number was quantified by qPCR. The proteomics and bioinformatics approaches were used to elucidate the molecular mechanism of andrographolide to inhibit EBV lytic reactivation. The result showed that andrographolide significantly inhibited the expression of EBV lytic gene, including BZLF1, BRLF1 and BMRF1, but not latent gene, LMP1 in all EBV-positive cell lines. Consistently, Zta protein was also abolished in andrographolide treated cells that was also corresponded with the inhibition of viral production. Our proteomic and bioinformatics analysis suggested that the andrographolide treatment significantly promoted the expression of epigenetic machineries, especially histone modifications, such as histone H3-K9 modification, histone H3-K27 methylation and histone H3-K4 methylation. In conclusion, andrographolide inhibits the lytic reactivation of EBV by suppressing the expression of EBV lytic genes and the production of EBV virion, probably via epigenetic modifications, particularly histone modifications. Therefore, andrographolide might be a promising therapeutic compound against EBV-associated malignancies.