Recurrent chemical reactivations of EBV promotes genome instability and enhances tumor progression of nasopharyngeal carcinoma cells.

陳志榮

Fang CY;Lee CH;Wu CC;Chang YT;Yu SL;Chou SP;Huang PT;Chen CL;Hou JW;Chang Y;Tsai CH;Takad

摘要

Abstract

Nasopharyngeal carcinoma (NPC) is an endemic malignancy prevalent in South East Asia. Epidemiological studies have associated this disease closely with Epstein-Barr virus (EBV) infection. Previous studies also showed that EBV reactivation is implicated in the progression of NPC. Thus, we proposed that recurrent reactivations of EBV may be important for its pathogenic role. In this study, NPC cell lines latently infected with EBV, NA and HA, and the corresponding EBV-negative NPC cell lines, NPC-TW01 (TW01) and HONE-1, were treated with 12-O-tetradecanoylphorbol-13-acetate (TPA) and sodium n-butyrate (SB) for lytic cycle induction. A single treatment with TPA/SB revealed that DNA double-strand breaks and formation of micronuclei (a marker for genome instability) were associated with EBV reactivation in NA and HA cells. Examination of EBV early genes had identified several lytic proteins, particularly EBV DNase, as potent activators that induced DNA double-strand breaks and contribute to genome instability. Recurrent reactivations of EBV in NA and HA cells resulted in a marked increase of genome instability. In addition, the degree of chromosomal aberrations, as shown by chromosome structural variants and DNA copy-number alterations, is proportional to the frequency of TPA/SB-induced EBV reactivation. Whereas these DNA abnormalities were limited in EBV-negative TW01 cells with mock or TPA/SB treatment, and were few in mock-treated NA cells. The invasiveness and tumorigenesis assays also revealed a profound increase in both characteristics of the repeatedly reactivated NA cells. These results suggest that recurrent EBV reactivations may result in accumulation of genome instability and promote the tumor progression of NPC.