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High cell density and latent membrane protein 1 expression induce cleavage of the mixed lineage leukemia gene at 11q23 in nasopharyngeal carcinoma cell line

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Abstract

Background: Nasopharyngeal carcinoma (NPC) is commonly found in Southern China and South East Asia. Epstein-Barr virus (EBV) infection is well associated with NPC and has been implicated in its pathogenesis. Moreover, various chromosome rearrangements were reported in NPC. However, the underlying mechanism of chromosome rearrangement remains unclear. Furthermore, the relationship between EBV and chromosome rearrangement with respect to the pathogenesis of NPC has not been established. We hypothesize that during virus- or stress-induced apoptosis, chromosomes are initially cleaved at the base of the chromatin loop domain structure. Upon DNA repair, cell may survive with rearranged chromosomes.

Methods: In this study, cells were seeded at various densities to induce apoptosis. Genomic DNA extracted was processed for Southern hybridization. In order to investigate the role of EBV, especially the latent membrane protein 1 (LMP1), *LMP1* gene was overexpressed in NPC cells and chromosome breaks were analyzed by inverse polymerase chain (IPCR) reaction.

Results: Southern analysis revealed that high cell density resulted in cleavage of the mixed lineage leukemia (*MLL*) gene within the breakpoint cluster region (bcr). This high cell density-induced cleavage was significantly reduced by caspase inhibitor, Z-DEVD-FMK. Similarly, IPCR analysis showed that *LMP1* expression enhanced cleavage of the *MLL* bcr. Breakpoint analysis revealed that these breaks occurred within the matrix attachment region/scaffold attachment region (MAR/SAR).

Conclusions: Since *MLL* locates at 11q23, a common deletion site in NPC, our results suggest a possibility of stress- or virus-induced apoptosis in the initiation of chromosome rearrangements at 11q23. The breakpoint analysis results also support the role of chromatin structure in defining the site of chromosome rearrangement.

Background

Nasopharyngeal carcinoma (NPC) is a common cancer in Asia, especially in Southern China and South East Asia [1]. NPC is well associated with chromosome rearrangements. Among them, chromosome gains are commonly found in 12p11.2-p12, 12q14-q21, 2q24-q31, 1q31-qter, 3q13, 1q13.3, 5q21, 6q14-q22, 7q21, 8q11.2-q23 and 18q12-qter. On the other hand, chromosome deletions are commonly found in 3p14-p21, 11q23-qter, 16q21-qter and 14q24-qter [2]. Much effort has been made to identify the candidate tumor suppressor genes and oncogenes, but studies investigating the mechanism(s) leading to the chromosome anomalies are rather lacking.

Epstein-Barr virus (EBV) is strongly associated with NPC [3] although the EBV genome is not required for epithelial to mesenchymal transition of NPC cells [4]. Nevertheless, various EBV antigens had been used in the diagnosis of NPC [5]. The actual mechanism of EBV infection contributing to carcinogenesis in NPC remains

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