Tan *et al. Cell Biosci (2016) 6:35*
DOI 10.1186/s13578-016-0103-9

Cell & Bioscience

RESEARCH Open Access

Potential role of oxidative stress-induced apoptosis in mediating chromosomal rearrangements in nasopharyngeal carcinoma

Sang-Nee Tan[1], Sai-Peng Sim[1*] and Alan S. B. Khoo[2]

Abstract

Background: Genetic aberrations have been identified in nasopharyngeal carcinoma (NPC), however, the underlying mechanism remains elusive. There are increasing evidences that the apoptotic nuclease caspase-activated deoxyribonuclease (CAD) is one of the players leading to translocation in leukemia. Oxidative stress, which has been strongly implicated in carcinogenesis, is a potent apoptotic inducer. Most of the NPC etiological factors are known to induce oxidative stress. Although apoptosis is a cell death process, cells possess the potential to survive apoptosis upon DNA repair. Eventually, the surviving cells may carry rearranged chromosomes. We hypothesized that oxidative stress-induced apoptosis may cause chromosomal breaks mediated by CAD. Upon erroneous DNA repair, cells that survive apoptosis may harbor chromosomal rearrangements contributing to NPC pathogenesis. This study focused on the *AF9* gene at 9p22, a common deletion region in NPC. We aimed to propose a possible model for molecular mechanism underlying the chromosomal rearrangements in NPC.

Results: In the present study, we showed that hydrogen peroxide (H_2O_2) induced apoptosis in NPC (HK1) and normal nasopharyngeal epithelial (NP69) cells, as evaluated by flow cytometric analyses. Activity of caspases 3/7 was detected in H_2O_2-treated cells. This activity was inhibited by caspase inhibitor (CI). By nested inverse polymerase chain reaction (IPCR), we demonstrated that oxidative stress-induced apoptosis in HK1 and NP69 cells resulted in cleavages within the breakpoint cluster region (BCR) of the *AF9* gene. The gene cleavage frequency detected in the H_2O_2-treated cells was found to be significantly higher than untreated control. We further found that treatment with CI, which indirectly inhibits CAD, significantly reduced the chromosomal breaks in H_2O_2-cotreated cells. Intriguingly, a few breakpoints were mapped within the *AF9* region that was previously reported to translocate with the mixed lineage leukemia (*MLL*) gene in acute lymphoblastic leukemia (ALL) patient.

Conclusions: In conclusion, our findings suggested that oxidative stress-induced apoptosis could be one of the mechanisms underlying the chromosomal rearrangements in NPC. CAD may play an important role in chromosomal cleavages mediated by oxidative stress-induced apoptosis. A potential model for oxidative stress-induced apoptosis mediating chromosomal rearrangements in NPC is proposed.

Keywords: *NPC*, *Oxidative stress*, *H_2O_2*, *Apoptosis*, *AF9 gene*, *CAD*

Background

Nasopharyngeal carcinoma (NPC) is a solid malignancy which demonstrates a unique ethnic and geographic distribution. In most parts of the world, its incidence rates are below one per 100,000 persons per year. However, it has a notable exception in Southern China and South-East Asia [1, 2]. The highest rates were reported among Southern Chinese living in central Guangdong province, the annual incidence rates for males and females are 23.3/100,000 and 8.9/100,000, respectively [3]. More recently, high incidence of NPC (23.1/100,000/year) has also been observed among the native Bidayuh people in

*Correspondence: spsim@unimas.my
[1] Faculty of Medicine and Health Sciences, Department of Paraclinical Sciences, Universiti Malaysia Sarawak, Sarawak, Malaysia
Full list of author information is available at the end of the article