REVIEW ARTICLE

The Role of Caspase Activity and Apoptosis in Nasopharyngeal Carcinoma

Mohd Aminudin Mustapha[1,2], Sai-Peng Sim[2]

ABSTRACT

Objective: **To determine roles of caspase activity and apoptosis in nasopharyngeal carcinoma development.**

Method: **Review the article related to caspase activity, apoptosis, and nasopharyngeal carcinoma.**

Results: **Caspase activity and apoptosis suggested to be one of the mechanisms underlying the chromosomal rearrangements in nasopharyngeal carcinoma.**

Conclusion: **Caspase activity and apoptosis may be led to nasopharyngeal carcinoma development.**

KEY WORDS

caspase activity, apoptosis, nasopharyngeal carcinoma

INTRODUCTION

Nasopharyngeal carcinoma (NPC) is an epithelial malignancy with highly variable incidence rates around the world. About 84,400 incident cases of NPC and 51,600 deaths occurred in 2008 with the highest incidence in South-Eastern Asia, relative to the Americas, Europe, Africa, and Central and Eastern Asia[1]. NPC is an aggressive human malignancy that originates from the epithelial cells of the retro nasal cavity. It is rare in most populations around the world with an incidence of below 1 per 100 000 persons per year in Europe and the United State of America; however, in southern China and Southeast Asia, NPC is endemic, with an incidence rate of 20 0 per 100 000 persons per year[2]. NPC is a unique malignancy that arises from the epithelium of the nasopharynx and has a restricted prevalence in certain regions of the world. The remarkable geographical variations in NPC prevalence are the result of the complex development of this carcinoma[3].

Apoptosis is a naturally occurring cell death process that is important in various biological systems[4]. It is characterised by a series of typical morphological features, such as shrinkage of the cell, fragmentation into membrane-bound apoptotic bodies and rapid phagocytosis by neighbouring cells. Most of these morphological changes result from the activity of a class of cysteine proteases, called caspases[5]. A number of caspases have been identified, where about two-thirds of them function in apoptosis[6]. Caspases normally exist as inactive pro-enzymes. When apoptosis is triggered, caspases are converted into active enzyme to cleave a subset of proteins[7], either inactivating or activating the target proteins[5].

During apoptosis, while the caspases are activated, the genomic DNA is fragmented into high molecular- weight (HMW) DNA as well as the smaller fragments known as the internucleosomal DNA ladder[8]. These HMW DNA fragments of 50-300 kb corresponds to the DNA-loop structures[9], which interact with the nuclear matrix via the matrix-attachment region or scaffold-associated region (MAR/SAR) sequence[10]. Thus, the HMW DNA formation during apoptosis appears to be DNA loop excision at the MAR/SAR sequence at the base of DNA loop[11]. One of the key enzymes in apoptosis is caspase-activated DNase (CAD)[12]. Normally CAD exists as an inactive complex with its inhibitor, the Inhibitor of CAD (ICAD). During apoptosis induction, ICAD is cleaved by caspase-3, thus releasing the activated CAD, allowing it to cleave the genomic DNA into HMW DNA as well as internucleosomal DNA ladder[13].

APOPTOSIS AND ITS HALLMARK

Caspase-activated DNase (CAD) seems to be playing multiple roles. On one hand it is the apoptotic nuclease, one the other hand, it was also found to play a role in chromosome rearrangement commonly found in leukaemia[14]. In addition, CAD was also shown to promote cell differentiation by inducing DNA strand breaks[15]. Caspase-activated DNase is one of the enzymes involved in apoptosis and play an important role in chromosome rearrangement mostly found in leukaemia[16]. The finding also suggested that CAD may play an important role in chromosomal cleavages mediated by oxidative stress-induced apoptosis. Thus, a potential model for oxidative stress-induced apoptosis mediating chromosomal rearrangements in NPC was proposed[17].

Apoptotic DNA fragmentation can be induced by a range of stimuli including virus infection and oxidative stress[18,19]. Oxidative stress induces apoptotic DNA fragmentation in endothelial cells under an ATP rich environment as well as in skeletal muscle myoblasts[20,21]. It was also found to induce the formation of High Molecular Weight (HMW) DNA fragmentation in leukemic cells[22]. Reactive oxygen species (e.g., H_2O_2, hydroxyl radical and superoxide), cause injuries on various cellular macromolecules. These damages have been proposed to contribute to the development of cancer[23,24]. Oxidatively damaged DNA are repaired by the Base Excision Repair pathway (BER)[25] which involves the function of hOGG1 and XRCC1[26]. Polymorphism of these two genes was shown to be associated with elevated risk of NPC[27], supporting the role of oxidative stress in NPC development.

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ORCHID ID:
Mohd Aminudin Mustapha: 0000-0002-7457-554X

1) Centre for Pre-University Studies, Universiti Malaysia Sarawak
94300 Kota Samarahan, Malaysia

2) Department of Paraclinical Science, Faculty of Medicine and Health Sciences, Universiti Malaysia Sarawak
94300 Kota Samarahan, Malaysia

Correspondence to: Mohd Aminudin Mustapha
(e-mail: mmaminudin@unimas.my)

CASPASE ACTIVITY AND APOPTOSIS

Caspase-activated DNase (CAD) seems to be playing multiple roles. CAD is the apoptotic nuclease that found to play a role in chromosome rearrangement commonly found in leukaemia[14]. In addition, CAD was also shown to promote cell differentiation by inducing DNA strand breaks[15]. CAD is one of the enzymes involved in apoptosis and play an important role in chromosome rearrangement mostly found in leukaemia[16] as well as in nasopharyngeal carcinoma[28]. The finding also suggested that, CAD may play an important role in chromosomal cleavages mediated by oxidative stress-induced apoptosis as well as bile-acid induced apoptosis[28-30]. The apoptotic nuclease, caspase activated DNase (CAD) was suggested to play a direct role in mediating chromosome translocation in leukaemia[16,31].

CAD is activated by caspase-dependent signal transduction, a proteolytic signalling cascade that alters the activity of numerous substrate proteins[32]. The CAD is associated with an inhibitor of CAD (ICAD) and possibly, the ICAD serves as a chaperone during the synthesis of CAD[12]. To promote DNA fragmentation, Caspase 3 activates CAD by proteolytic inactivation of the inhibitor of CAD[32]. While, Caspase 3 inactivates ICAD by cleaving at two aspartic acid residues, D117 and D224, destabilizing its interaction with CAD and allowing CAD dimerization and subsequent DNA fragmentation[13]. In a study of mouse ICAD and human CAD, expression of ICAD was reported to enhance the expression of endogenous and exogenous CAD[28]. In the study also reported that, ICAD expression induced endogenous CAD expression, it has also extensively reduced H_2O_2-induced *MLL* gene cleavage.

APOPTOSIS IN NASOPHARYNGEAL CARCINOMA (NPC)

Apoptosis was found to be triggered by oxidative stress resulted from excessive production of reactive oxygen species (ROS) such as H_2O_2, hydroxyl radical and superoxide[33]. Oxidative stress was found to induce apoptosis in endothelial cells under an ATP rich environment[20]. It was also found to induce the formation of High Molecular Weight DNA fragmentation (an early step of apoptosis) in leukemic cells (Lelli *et al*., 1998). Data indicated that NPC cells under stress undergo apoptosis-induced chromosome breaks[20]. Although apoptosis is a cell death process, it has also been implicated in chromosome rearrangement. Chemotherapeutic drug-induced apoptosis has been implicated in the introduction of chromosome break within the Mixed Lineage Leukaemia (MLL) gene, a gene frequently involved in chromosome translocations[16].

Although chromosomal abnormalities are commonly found in NPC, the detail molecular mechanisms leading to these abnormalities remain elusive. However, there are increasing evidence that the apoptotic nuclease is responsible for the initial event of chromosome translocation in leukemic cells, that is the breakage of the chromosome[16,34]. Similar mechanism has been proposed for chromosomes rearrangement in NPC. Recently, the apoptotic nuclease was also suggested to play a role in mediating chromosome breaks in NPC cells during oxidative stress, whereby these breaks could serve as the initial event leading to chromosome rearrangement[28]. Based on the study conducted by Tan et al. 2016, oxidative stress-induced apoptosis was suggested to be one of the mechanisms underlying the chromosomal rearrangements in NPC[17].

Oxidative stress plays an important role as it can stimulate the expansion of mutant cell clones by temporary modulation of genes involved in cell proliferation or cell death[35]. Tumour cells can adopt several ways to resist cell apoptosis and ensure their survival[36]. In the process of EBV infection, EBV encodes several anti-apoptotic products such as BHRF1, BARF1, EBNA1, ERERs and miR-BARTs, which usually play important roles in gaining resistance to apoptosis.

CONCLUSION

Previous report has shown that oxidative stress, DNA damage, and mitochondrial membrane depolarisation may all induce cells to undergo apoptosis[37]. Oxidative stress-induced apoptosis could be one of the mechanisms underlying the chromosomal rearrangements in NPC[17]. CAD may play an important role in chromosomal cleavages mediated by oxidative stress-induced apoptosis. Thus, caspase activity and apoptosis may lead to nasopharyngeal carcinoma.

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