REVIEW ARTICLE

The Role of Epstein-Barr virus *LMP1* Gene Expression in Oxidative Stress in Nasopharyngeal Carcinoma

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ABSTRACT

Objective: **To determine roles of Epstein-Barr virus *LMP1* gene expression in oxidative stress in nasopharyngeal carcinoma.**
Method: **Review the article related to Epstein-Barr virus *LMP1*, oxidative stress and nasopharyngeal carcinoma.**
Results: **Epstein-Barr reactivation shows overexpression of *LMP1* significantly increased the level of oxidative stress.**
Conclusion: LMP1 **expression causes cellular oxidative stress accumulation in nasopharyngeal epithelial cells, thus may be led to cancer development.**

KEY WORDS

Epstein-Barr virus, *LMP1*, oxidative stress, nasopharyngeal carcinoma

INTRODUCTION

It has been shown that recurrent chemical reactivation of EBV promotes genome instability and thus enhances tumour progression of NPC cells[1]. In addition, a N-nitroso compound, N-methyl-N'-nitro-N-nitrosoguanidine (MNNG) was found to cooperate with 12-O-tetradecanoylphorbol-1,3-acetate (TPA)/sodium butyrate to enhance EBV reactivation[2]. Interestingly the same treatment increased the levels of reactive oxygen species (ROS), and enhanced genome instability in NPC cells. Furthermore, expression of the EBV latency gene, the latent membrane protein (*LMP1*) gene also promotes genome instability, detected as nonclonal chromosomal aberrations in Burkitt's lymphoma cell line[3].

In addition, spontaneous and bleomycin-induced micronucleus formation was found to be more in *LMP1*-expressing cells[4]. *LMP1*'s role in promoting genome instability was suggested to be attributed to its ability in inhibiting DNA repair, whereby the involvement of oxidative stress was moderate[3]. *LMP1*'s involvement in oxidative and nitrative DNA damage is evident. This was demonstrated by observation that its expression triggers the expression of inducible nitric oxide synthase (iNOS)[5]. Oxidative and nitrative DNA lesions has long been associated with EBV-positive patients[6]. The oncogenic potential of *LMP1* is also associated with its modulation on stress-induced apoptosis. Both etoposide- and cisplatin-triggered apoptosis were enhanced by *LMP1* expression. This potentiation is thought to be at early stage of apoptosis[7].

LMP1 GENE IN NASOPHARYNGEAL CARCINOMA (NPC)

LMP1 gene, which is encoded in EBV, is the most important oncoprotein in EBV-related malignancies. Constitutive expression of *LMP1* contributes to the initiation and progression of NPC. *LMP1* is one of the seven informative genes that can accurately predict the survival of NPC patients[8]. However, the mechanisms by which *LMP1* contributes to the radio resistance of NPC are largely unknown. *LMP1* is a crucial EBV oncogene, which has been shown to transform rodent fibroblasts in vitro and induce tumours in nude mice[9]. The oncogenic potential of *LMP1*, which results in B cell transformation, is suggested by its high functional similarity to the tumour necrosis factor receptor (TNFR) family members, CD40 and TNFR1[10].

LMP1 is critical for EBV-induced B-cell transformation and is also abundantly expressed during the lytic cycle of viral replication. Several studies have indicated that *LMP1* is likely a candidate for inducing ROS. Cerimele et al. used a tetracycline-inducible epithelial cell line to determine whether *LMP1* can induce ROS generation. They found that the addition of tetracycline led to a significant decrease in *LMP1*-expression, as well as ROS production, thus implicating *LMP1* as a major inducer of ROS[11]. The C-terminal activating regions (CTAR) of *LMP1* interact with members of the tumour necrosis factor (TNF) receptor-associated factor (TRAF) families. While activation of ROS has not been associated previously with *LMP1* signalling, TRAF activation by other ligands has been shown to induce reactive oxygen species (ROS) signalling, thereby providing a potential mechanism for LMP mediated ROS induction. On the other hand, Chen *et al*. demonstrated that EBV infection of B lymphocytes could induce the accumulation of ROS, and quenching ROS was associated with selective down-regulation of viral *LMP1*[12].

IMPLICATION OF *LMP1* IN NASOPHARYNGEAL CARCINOMA (NPC) DEVELOPMENT

The role of *LMP1* in the pathogenesis of NPC remains speculative. There is considerable variation in the reported expression of *LMP1* in NPC biopsies and a consensus that approximately 20% 0% of tumours

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express *LMP1* at the protein level[13]. In one study, all 6 early, preinvasive NPC (NPC *in situ*) lesions analysed expressed the *LMP1* protein, arguing for a critical role of *LMP1* in the early pathogenesis of NPC[14]. *LMP1* expression was shown to inhibit the AMPK/LKB1 signalling pathways to promote cellular growth and survival[15].

LMP1 affects EBV lytic reactivation acting by different mechanisms. Emerging reports have demonstrated different roles of *LMP1* in EBV lytic reactivation. The expression of *LMP1* contributes to EBV lytic reactivation. Inducible expression of *LMP1* during the viral lytic cycle plays a vitally important role in virus production because loss of *LMP1* severely impaired virus release into culture supernatant fractions, resulting in poor infection efficiency[16]. EBV utilizes *LMP1* for dual purposes during its life cycle[17]. First, in latently infected B lymphocytes, steady-state expression of *LMP1* is critical for maintaining transformation status. Second, at the onset of the virus production cycle, the strong induction of *LMP1* enables efficient virus release from cells. Therefore, *LMP1* is apparently one of the most important viral proteins required for EBV's life cycle in its survival and transmission from host to host.

The carboxyl terminus of *LMP1* contains consensus tumour necrosis factor receptor associated factor (TRAF) binding domains, which can constitutively activate signal transducers and activators of transcription (STAT), Janus kinase (JNK), and nuclear factor (NF) κB pathways for cell survival and growth[18]. The LMP1 is also considered as a classical viral oncogene which activates multiple cells signalling, including NFκB, MAPK and PI3K, to drive tumorigenesis[18]. As a key effector in EBV-driven B cell transformation and an established "transforming" gene, LMP1 displays oncogenic properties in rodent fibroblasts and induces profound morphological and phenotypic effects in epithelial cells[18].

Analysis of the mechanism by which high levels of ROS support *LMP1* expression revealed a selective inhibition of viral microRNAs that target the *LMP1* transcript[12]. *LMP1* was demonstrated to induce the generation of ROS, and the oxidative stress microenvironment could also affect the expression of LMP1 by targeting viral microRNAs. The researchers found that a potential mechanism occurs through the interference signalling pathways, which are launched by *LMP1*[19].

OXIDATIVE STRESS IN NASOPHARYNGEAL CARCINOMA (NPC)

In the human body, oxygen is used in metabolic processes to produce the necessary energy. One of the stages of cellular respiration is the four-stage electron transport chain in which oxygen is their acceptor. Sometimes, there is so-called "leakage of electrons from the respiratory chain" which results in incomplete full four-electron reduction of oxygen molecule. These disorders lead to formation of reactive oxygen species (ROS)[20]. ROS is free radicals' molecules that containing at least one unpaired electron on the outer electron shell. These molecules strive to pair electrons by taking them away or donating them to other molecules, which results in their high reactivity. Formation of free radicals is strongly influenced by physical factors, such as ionising radiation, ultraviolet radiation, ultrasounds, or elevated temperature. Reactive oxygen species (ROS) are by products of oxygen metabolism and play an important role in cell signalling and homeostasis. Oxidative stress act as neutralization ability of antioxidants in human body counteract the free radicals' harmful effects. Example of free radical is reactive oxygen species (ROS) which is highly reactive with other molecules due to an oxygen pair with one or more unpaired electrons. Normal oxygen is relatively unreactive but some metabolism process in biological system makes it highly reactive oxidant.

The respiratory chain is the source of about 90% of free radicals[21]. The constant presence of ROS in low concentrations in the body helps the organism to properly run many life processes[20]. Reactive oxygen species participate in cellular functions such as intracellular signal transduction, proliferation, cell apoptosis, control over internal homeostasis of calcium Ca^{2+}, regulation of gene expression, as well as protein phosphorylation processes. They may also activated transcription factors such as nuclear factor-kappa B — NF-κB, which causes disorders in the normal functioning of cells[21]. Reactive oxygen species (ROS), mainly comprised of superoxide anion (O^{2-}) and hydrogen peroxide (H^2O^2), are generated in mitochondria or by nicotinamide adenine dinucleotide phosphate (NADPH) oxidase[22]. Superoxide can be converted into H^2O^2 by dismutation. Regarded as a second messenger, H^2O^2 can permeate through cell membranes to act as a mild pro-oxygenic agent. Furthermore, H^2O^2 can be oxidized into derivatives such as hydroxyl radicals and hydrochloric acid (HOCl)[23].

Reactive oxygen species and reactive nitrate species (RNS) have a dual nature, on the one hand, they are necessary for normal cellular functions, but on the other hand, in excess they can damage cells and can lead to cancer development[24]. Free radicals may also damage biomolecules found in the body at the molecular level and cell organelles. Imbalance between the formation of reactive oxygen species and the body's antioxidant capacity are called oxidative stress[21]. Oxidative stress plays a role in many diseases, including inflammation states, diabetes, cardiovascular diseases, or cancer. The role of free radicals and ROS in many cancers has been documented. Intermediate products of oxygen reduction attack DNA and other cellular components, such as lipids, proteins, leaving reactive compounds that in turn can react with DNA bases[24].

The effects of an increased amount of ROS or RNS with a simultaneous reduction of antioxidants are noticed in various cancers, including head and neck cancer[25]. ROS can be produced from endogenous and exogenous substances. Endogenous sources involve mitochondria, cytochrome P450 metabolism, peroxisomes, and activation of inflammatory cells. Exogenous sources include environmental factors, including non-genotoxic carcinogens, xenobiotics, ultrasounds and microwave radiation[25]. Cancer development is a complex, multi-stage process involving initiation, promotion, and progression. Even low levels of oxidative stress can stimulate cell division in promotion stage and therefore promote tumour growth. It may be concluded that ROS production at this stage is the main mechanism for the promotion of ROS-related cancers[25]. Cancer development is a complex, multi-stage process involving initiation, promotion, and progression. Reactive oxygen species take part in all these stages. In certain stages of carcinogenesis, the influence of oxidative stress is directly proportional to the type and reactivity of the radicals present. Cancer development with the involvement of ROS is supported by the occurrence of oxidative DNA modifications in tumour tissues.

Not all ROS are harmful to human body because some of ROS are useful in immune system by killing invading pathogen or microbes. However, when ROS contact directly with molecules such as DNA, protein, or lipid, the electron from that molecule will transfer to ROS to make it stable. Transfer of electron from these molecule to the ROS will cause stabilizes of the cells component molecules that trigger to a large chain of free radical reactions[26]. Although reactive oxygen species are needed in normal cellular processes, they are also involved in various pathological processes in the environment of chronic oxidative stress, including carcinogenesis. Reactive oxygen species contribute to the development of head and neck cancer not only through general mechanisms of DNA damage and protein modulation, but also through many risk factors, such as connection with viruses[25]. Reactive oxygen species are also involved in many benign oral disorders. ROS are clearly key intermediates in the toxicity against tumours induced by radiotherapy. When ROS levels rise beyond a tolerable limit inside tumour cells, apoptosis is initiated and ROS-induced cell death may be either direct or indirect[27]. High levels of ROS cause a cluster of lesions to form within DNA that are difficult to repair and lead directly to cell death.

Epstein-Barr Virus reactivation as well as expression of the latency genes could play an important role in inducing chromosome rearrangements perhaps via the production of reactive oxygen species (ROS) and the involvement of apoptosis. It is known that ROS induces apoptosis which resulted in chromosome breaks within regions that are commonly rearranged in NPC[28]. Therefore, it is possible that during repeated EBV reactivation and establishment of latency, ROS is produced, and the cells' genomes are subjected to oxidative damage repeatedly, leading to apoptosis. In the effort of DNA repair, erroneous repair occurs resulted in cells bearing rearranged chromosomes survived the apoptosis, continue to replicate, and eventually contribute partly to NPC carcinogenesis. In infected host, the virus tends to establish a lifelong latent infection, during which the virus alternates between latent state and lytic replication. The transition from latent to lytic phase is symbolized by the expression of two viral immediate early genes, namely Zebra (also named as BZLF1, Zta, or Z) and Rta (also named as BRLF1 or R)[29].

ASSOCIATION OF OXIDATIVE STRESS WITH LMP1 EXPRESSION

Notably, reactive oxygen signalling can distinguish EBV-positive

versus EBV negative Burkitt's lymphoma based on the finding that elevated levels of ROS are observed in EBV positive tumours but not in EBV-negative tumours[11]. This demonstrated that EBV infection could cause the generation of ROS, which leads to high levels of oxidative stress in EBV positive cells or tumours. Study of inner relationship and regulatory mechanism among oxidative stress and EBV reactivation that shows overexpression of *LMP1* significantly increased the level of ROS[30]. They also determined the role of *LMP1* on ROS generation on transfected cells with *LMP1*. They demonstrated that, *LMP1* promotes ROS generation both in transient transfection and stable cell lines. The same study also showed *LMP1* significantly induced EBV reactivation. Their data also illustrated that *LMP1* promotes EBV reactivation through the production of ROS. *LMP1*-transformed NP69 cells was reported exhibited significantly increased basal ROS levels (approximately 8- and 10-fold increased)[31]. They suggested that *LMP1* expression causes cellular ROS accumulation in nasopharyngeal epithelial cells. *LMP1* induces excessive ROS generation by upregulating the expression of NADPH Oxidase through the JNK/AP-1 signalling pathway in nasopharyngeal epithelial cells without affecting the antioxidant system[31].

Emerging reports have demonstrated different roles of *LMP1* in EBV lytic reactivation, the expression of *LMP1*contributes to EBV lytic reactivation. Inducible expression of *LMP1* during the viral lytic cycle plays a vitally important role in virus production. It is because loss of *LMP1* severely impaired virus release into culture supernatant fractions, resulting in poor infection efficiency[16]. Generating oxidative stress is a critical mechanism by which host cells defend against infection by pathogenic microorganisms[32]. *LMP1* was reported to contribute to the radio-resistance of NPC by activating several oncogenic signalling axes, including *LMP1*/JNKs/c-Jun/HIF-1/VEGF[33]. Reactivation of EBV by *LMP1*-induced high oxidative stress could lead to radioresistance of NPC cells both in vitro and in vivo, suggesting that EBV reactivation plays an important role in NPC resistance, and *LMP1* is one of the factors that mediated resistance[30].

CONCLUSION

DNA viruses may encode oncogenic genes that are also capable of hijacking host cellular mechanisms to regulate cell survival and propagation. When these oncogenic genes overcome the ability of host cell machinery to control homeostasis, they trigger the tumour microenvironment associated with an elevated level of mutations that cause malignant transformation and ultimately cancer[34]. ROS is also involved in the progression at this stage, the generation of large amounts of ROS may contribute to mutation, increase the amount of matrix metalloproteinases (MMPs) and damage local tissues. Increased levels of DNA modified due to oxidation can contribute to genetic instability and may be crucial in tumour metastases in developed cancer[24,35]. *LMP1* expression causes cellular oxidative stress accumulation in nasopharyngeal epithelial cells, thus may be led to cancer development.

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