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Review Article

Photodynamic Therapy: New Light to the Nasopharyngeal Carcinoma Treatment

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Submitted: 25 October 2016

Accepted: 02 Novemebr 2016

Published: 04 Novemebr 2016

Keywords

- Photodynamic therapy
- Nasopharyngeal carcinoma
- Epstein barr virus
- Drug resistance

Abstract

Development of new treatment strategies is crucial for patients with Nasopharyngeal Carcinoma (NPC). NPC is one of the top ten cancers highly prevalent in Hong Kong with more than 800 new cases reported annually. The epidemiologic evidence implies that Epstein-Barr virus (EBV) infection, environmental factors and genetic factors play roles in the tumorigenesis of NPC. Conventional treatment of NPC is mainly based on chemo-radiotherapy. However, the treatment outcomes in patients with advanced stage of NPC are unsatisfactory. Photodynamic therapy (PDT) is an FDA approved cancer regime in the USA, European Union, Japan and China and could be one of novel strategies in PDT development for NPC patients. It employs a combination of light-activated photosensitiser visible light and molecular oxygen to selectively destroy the biological targets. In-depth investigation for selected PSs mediated PDT on NPC cells is still underway.

OVERVIEW OF NASOPHARYNGEAL CARCINOMA (NPC)

Nasopharyngeal carcinoma (NPC) is endemic in Asia. It is one of the top ten cancers highly prevalent in Hong Kong with more than 800 new cases reported annually (Hong Kong Cancer Registry 2013) [1,2]. The overall incidence is 6.5/100,000 person-years in southeastern Asia. However, in some cities such as Sihui city in the Guangdong and Hong Kong, the incidence rate sharply increase to 30.94/100,000 person-years and 12.2/100,000 person-years, respectively [3,4].

Nasopharyngeal Carcinoma Cells (NPC) encompasses any squamous cell carcinoma arising in the epithelial lining of the nasopharynx, a tubular space situated at the base of the skull. It is characterized by poor or undifferentiated carcinoma with increased radio- and chemosensitivity, and a greater tendency for distance metastasis [5,6].

Aetiology

The aetiology of NPC is complex. The epidemiologic evidence implies that Epstein - Barr virus (EBV) infection, environmental factors and genetic factors play roles in the tumorigenesis of NPC. EBV is listed as one of the major carcinogens and is strongly associated with NPC tumorigenesis. People with family history of NPC will have a 4 to 10 fold excess risk of NPC development [7,8]. Medical conditions in the ear, nose or throat have also been proposed as risk factors for NPC [9,10]. Others non-viral environmental risk factors including salted and pickled foods, alcohol consumption, hearable product use and tobacco smoking.

The first report revealed the correlation between salted fish intakes and NPC development was published by Ho at 1972 [11]. A follow-up study with 2041 cases from Hong Kong was carried out by Ho to further illustrate the correlation between salted fish and NPC [12]. The N-nitrosamine contained in salt-preserved fish and vegetable might be the source of carcinogens that act on nasopharynx. Salted fish is a traditional favorite item in the Cantonese diet and that could explain why the incidence rate of NPC is particularly high among Cantonese.

Alcohol consumption is correlated with NPC risk and is in a complex manner. Recent meta-analysis indicated high volume of alcohol intake with significant increase in NPC risk while low volume of alcohol intake will result as beneficial effect [13,14].

Tobacco smoking is well documented as a risk factor for NPC. The pattern of association between tobacco smoking and NPC risk depends on the tobacco dose. The longer and greater cigarette smoking habit people have, the higher the risk n NPC. Current smoker with a history of more than 60 pack-years have the highest risk. People with a lifetime exposure of more than 30 pack-years still have a 2 fold higher chances in NPC risk [15,16].

Herbal product includes herbal medicine, herbal tea and soups containing herbal ingredients. Studies have proposed that the use

of herbal medicine could be associated with NPC development through re-activation of Epstein-Barr virus [17,18]. However, limited evidence was found for the association between herbal tea/soups containing herbal ingredients and NPC development. Report even suggested that slow cooked soups with herbal ingredients and herbal tea could decrease risk in associated with NPC development, although result is not statistically significant [19].

Role of epstein – barr virus (EBV) in NPC tumorigenesis

It is widely accepted that EBV infection plays a major role in the tumorigenesis of NPC. Epstein–Barr virus (EBV) is a herpes virus that infects over 90% of adult population. It is a successful virus which establishes a life-long persistent relationship with human B-cell and remains asymptomatic [20]. However, EBV is also known as the most potent transforming agent for human cells and is associated with a number of malignancies, including: Burkitt's lymphoma, nasopharyngeal carcinoma, T cell lymphomas, Lung carcinoma and Gastric carcinoma [21-23]. The EBV has an envelope with viral glycoproteins and carries an approximately 172 kb double stranded DNA genome. The viral genome enters the infected cell nucleus and forms a circular episome. It is rare to observe viral replication in EBV-infected cells. On the other hand, EBV establishes a latent infection with a restricted set of latent gene being expressed, including two EBV-encoded nuclear RNAs (EBER1, EBER2), six EBV-encoded nuclear antigens (EBNA1, EBNA2, EBNA3A, EBNA3B, EBNA3C, EBNA-LP), and three latent membrane proteins (LMP1, LMP2A, LMP2B). It is now identified at least three different latent viral gene expression patterns in EBV associated tumors, which is known as latency I, II and III. In latency I, only the EBERs and ENBA1 are expressed. In latency II, the EBERs, EBNA1, LMP1 and LMP2 are expressed. And in latency III, all latent genes are expressed [21,24-28].

The association between EBV and NPC was first discovered from serological studies. EBV is consistently detected in NPC patients [29]. There are lines of evidences showing that EBV implicated in the molecular abnormalities leading to pathogenesis of NPC. In NPC, EBV replicates and hides in cells followed by type II latency infection cycle, with expression of a limited number of viral protein. The tumorigenic potential of EBV mainly related to a unique set of latent genes product, including the latent membrane proteins (LMP1, LMP2A and LMP2B) and EBV-determined nuclear antigens (EBNA1 and EBNA2). Among these, LMP1 is the principal oncogene involves in the process of EBV-associated oncogenesis of NPC (Figure 1) [30-33]. The tumorigenic potential of EBV has been proven both *in vitro* and *in vivo*. *In vitro*, EBV immortalizes primary primate B lymphocytes and epithelial cells [34], while *in vivo*, it induces B-cell lymphomas and enhances epithelial tumor cell growth in nude mice [35]. In human epithelial cells, LMP-1 alters many functional properties that are involved in tumor progression and invasions [26,33,36].

LMP1 is a 66kDa integral membrane protein consists of a 6 transmembrane domains and a carboxyl-terminus containing 3 signaling domains called C-terminal activating regions 1, 2 and 3 (CTAR 1, CTAR 2 and CTAR 3). The short cytoplasmic N-terminal segment is responsible for membrane attachment and orientates LMP1 protein to the plasma membrane while

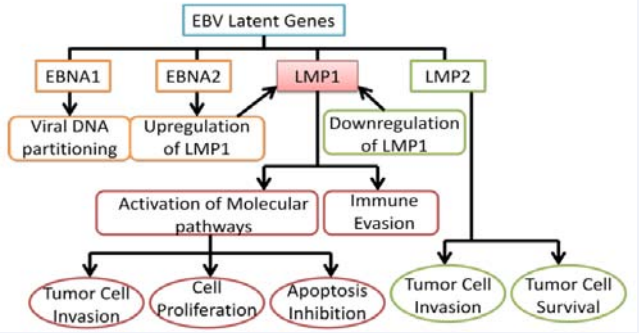

Figure 1 Mechanisms of Epstein-Barr virus (EBV) latent proteins in nasopharyngeal carcinoma (NPC) development.→Stimulatory effect.

the six transmembrane loops are involved in self aggregation and oligomerization. The three CTAR domains provide docking sites for signaling adaptor proteins. Among these, CTAR 1 and CTAR 2 are two of the distinct functional domains responsible for the possess of most of the LMP1 signaling activity via directly activate a number of signaling pathways including nuclear factor kappa B (NF-kB), mitogen-activated protein kinases (MAPK) and Janus Kinase/Signal Transducer and Activator of Transcription (JAK/STAT) pathway [33]. LMP1 induced signal pathways can be attributed to the inhibition of apoptosis; induction of cell immortality; promotion of cell proliferation and influence the cell invasion and metastasis (Figure 2) [25,37,38].

EBV associated intracellular signaling pathways

Modulation of intracellular signaling pathways by EBV LMP1 is one of the elemental factors controlling the biological behaviors of NPC. These signaling pathways are critical for various cell functions, including cell survival, cell growth, cell differentiation and metastasis [39]. Research on molecular signaling pathways reveal the role of different signaling proteins to tumorigenesis of NPC and could provide opportunity in the development of novel diagnostic, prognostic and therapeutic markers. Alternation of signaling proteins by EBV in NPC includes the mitogen-activated protein kinase (MAPK) pathway and the epidermal growth factor receptors (EGFRs) pathway [40-42].

MAPK signaling pathways induced in the cell death mechanism

The MAPK pathway is a chain of proteins in cells which communicates a signal from cell surface receptor to the nucleus by phosphorylation and has been proved to be very important in cancer development. The signals are transmitted by a cascade of kinases, including the extracellular signal-related kinase (ERK), p38 and c-Jun N-terminal kinase (JNK) and they plays an important role in regulating cellular responses to a multitude of environmental stimuli. JNKs are known as the stress-activated protein kinases and their normal function is in response to growth stimuli, cellular transformation and tumor metastasis [43,44]. Interestingly, JNK activity is consistently up-regulated in NPC via LMP1-dependent route [38,45]. LMP1 inducted JNK activity may be regarded asa growth advantage to NPC due to the versatile nature of this important signaling pathway. Constitutive activation of JNK in NPC increased p53 phosphorylation via

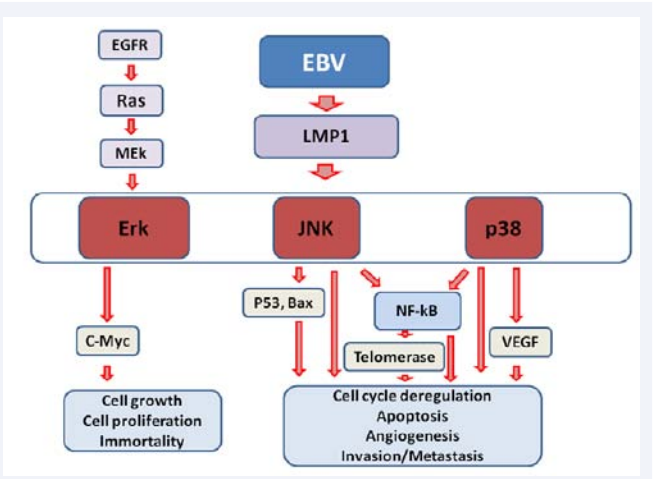

Figure 2 Signal transduction pathways regulated by the viral protein LMP1 [46].

phosphorylation of methyl transferase, result as reduction in E-cadherin gene expression and leading to cell cycle deregulation [38,45,46]. Another possibility of JNK activation is that the pro-apoptotic effect of prolonged JNK activation is overwhelmed by other proliferative signals present in NPC. p38 are known as stress activated protein kinases. Evidences indicate that p38 activity is essential for normal immune and inflammatory responses. However, they could also be strongly activated *in vivo* by environmental stresses. In response to stimuli, p38 protein has been shown to regulate a wide range of cellular functions, including the self-sufficiency of growth signals, unlimited replication of proteins, angiogenesis, tissue invasion and metastasis, regulation of the cell cycle, and protection against apoptosis [47]. Recent study reported that hypericin mediated PDT could induce p38 expression, which counteracting the hypericin mediated PDT in HK-1/NPC cells [48]. It is not surprise that EBV induced ERK has been demonstrated in various carcinomas, such as hepatocellular carcinoma, renal cell carcinoma and NPC. ERKs activation could be triggered via LMP1-dependent route [49,50]. ERKs are constitutively expressed MAP kinases which regulate a diverse range of cellular functions, including cell growth and development. Phosphorylation of ERK is via the Ras/Mek/ERK cascade includes the activation of transcription factors, such as NF-kB. The normal function of ERK activation is in control of cell growth and differentiation via regulation of cellular levels of cyclin D1 and c-myc [51-55]. LMP1 induced ERK activation could also promotes cell motility and invasion by coordinating actin filament dynamics and focal adhesion turnover. Activated ERK proteins regulate the production and secretion of matrix metalloproteinase, resulting in extracellular matrix remodulation [56,57]. Studies also reported that the over-expression of the epidermal growth factor receptors (EGFRs) is associated with ERKs signal pathways activation [58,59].

The epidermal growth factor receptors (EGFRs) pathway

Over-expression of EGFRs in NPC is quite frequent and reports indicated that as high as 80% of NPC primary biopsies had the problem of EGFRs over-expression [60-62]. Interestingly, LMP-1 promotes growth and proliferation via the up-regulation of epidermal growth factor receptor (EGFR) expression and increase the phosphorylation of EGFR [24]. Studies indicated that LMP1 would stimulate the endocytosis of EGFR and translocation into the nucleus. Intra-nuclear EGFR serves as a transcription factor to promote the expression of cellular proliferation components while cytoplasmic EGFR binds to cyclin D1 and cyclin E proteins to accelerate G1/S transition [63-65]. Therefore, the signal pathway mediated by EGFR plays a vital role in the carcinogenesis of NPC and causes uncontrolled cell proliferation [62,66].

Conventional treatment of NPC

Treatment selected for NPC patients were based on the AJCC classification system. The conventional treatment for NPC is chemoradiotherapy because of high radio- and chemo sensitivity with a 5-years overall survival of 70-80% for stage I and II NPC. However, the treatment outcomes in patients with stage II NPC become less favor that with stage I NPC because of the distance recurrence. The treatment outcomes for loco regionally advanced NPC even worse, with a significant drop of 5-years overall survival to from 80% to ~ 55% and 30% respectively for stage III and IV NPC. Local recurrence, distant recurrence and development of multi-drug resistance properties are the most common cause of treatment failure [40,67,68]. The distance control was unsatisfactory with a 2-year distant metastasis rates ranged from 10 to 15% and a 4-years distant metastasis rates up to 32%. Complications always resulted after chemo radiotherapy, such as hearing impairment, endocrinological dysfunctions, temporal lobe necrosis, cranial neuropathy, haemorrhage, and bone necrosis. Complications developed are depending on the tumor volume, local treatment and radiotherapy fractionation schedule. Besides, survivors of NPC always have impaired quality of life (QOL), which is increasingly emphasized in selecting appropriate therapeutic approaches, for NPC patients [69,70]. Unfortunately majority of NPC patients were diagnosed with locally advanced stages as it is difficult to detect early because of its complex anatomical location [39,64].Thus development of new treatment strategies is crucial for patients with NPC.

Drug resistance mechanisms in NPC

Multidrug resistance is the major obstacle to chemotherapy in tumor patients. The term multidrug resistance (MDR) refers to the ability of cancer cells being developed to cross resists with a range of antitumor drugs which are structurally and functionally unrelated. Development of MDR may be intrinsically prior to treatment or acquired during treatment [71]. The phenomenon of MDR could be achieved by the following mechanisms, including increase drug efflux from the cells via the adenosine triphosphate (ATP) binding cassette transporters (ABC), inactivation of drugs via detoxifying enzymes, and defective apoptotic pathways [72,73]. Recent studies illustrated the importance of ABC membrane transporters as one of the leading mechanisms of MDR in tumor cells [74,75]. The advances studies in molecular basis elucidating the phenomenon of MDR with cell lines indicate the expression of plasma membrane glycoproteins, including P-glycoprotein (P-gp/ABCB1), multidrug resistance associated protein 1 (MRP-1/ABCC1) and breast cancer resistance protein (BCRP/ABCG2). Among these, P-gp is the best studied mechanisms of MDR phenotype [76,77].

OVERVIEW OF PHOTODYNAMIC THERAPY (PDT)

Development of novel treatment strategies is crucial for patients with Nasopharyngeal Carcinoma in view of the drug resistance properties and complications developed after conventional treatment.

Photodynamic therapy (PDT) is an evolving cancer treatment regimen with approved for use in USA, EU, Canada, Russia and Japan [78-80]. PDT uses a combination of photosensitising agents (PS), visible light and molecular oxygen to selectively destroy the biological target. None of these is individually toxic, but together they initiate photo-destruction to biological target.

PDT function depends on the tumor localizing photosensitizer, which absorbs photon to produce photo-toxin such as singlet oxygen ($^1O_2$) and reactive oxygen species (ROS). Photosensitizers could be localized in varies cellular organelles including cell membrane, mitochondria, endoplasmic reticulum and Golgi apparatus, nucleus and lysosome [81,82]. ROS can then oxidize many biological molecules, such as protein, lipids and nucleic acids and lead to *in vivo* and *in vitro* tumor cell disruption through apoptosis, necrosis and autophagy [83,84]. The antitumor effects of PDT derive from 3 mechanisms; including direct cytotoxicity effects on tumor cells, destruction of tumor associated vasculature, and induction of inflammatory reaction against tumor cells [78,81,85-89].

The FDA approved therapeutic modality for several malignant diseases, including skin cancer, bladder cancer and head and neck cancer [81]. It is clinically used when the patients unable or failed to chemotherapy and radiotherapy. A number of components contribute to the efficiency of PDT, including type and dose of PSs used, drug incubation time, light dose and tumor oxygen concentration. Since PDT has limited damage to normal human cells, optimization of these components becomes one of the major goals of clinical settings to establish maximum efficacy for PDT application [78,90,91].

Antitumor mechanisms of PDT

The treatment of PDT consists of the three basic factors: i) Photosensitizers, ii) illumination, iii) presents of molecular oxygen. PSs that is administered topically, locally or systemically will be localized and accumulated into tumour cells. The localization of PSs in various organelles depends on types of PSs and they should have some selectivity for tumour cells. The selectivity could also be achieved through directed light delivery with specific system such as laser with optical fibres [92]. After an incubation period, allowing the tissue to absorb the PSs, equilibrium will be reached in order to obtain the maximum drug uptake different between normal cells and tumor cells. The lesion is then exposed to light of appropriate wavelength (usually red visible light with 620 – 690nm), causing photoactivation of photosensitizer and, resulting in formation of ROS in the presence of oxygen [93]. Among these, the processes of light absorption by the photosensitizers and energy transfer are the two most important factors. The mechanism of photosensitizer activation to induce cell death is illustrated in Figure (3) [82, 94].

Fluorescent photon will emits when photosensitizer decay from excited singlet state to ground state. Excited singled-state

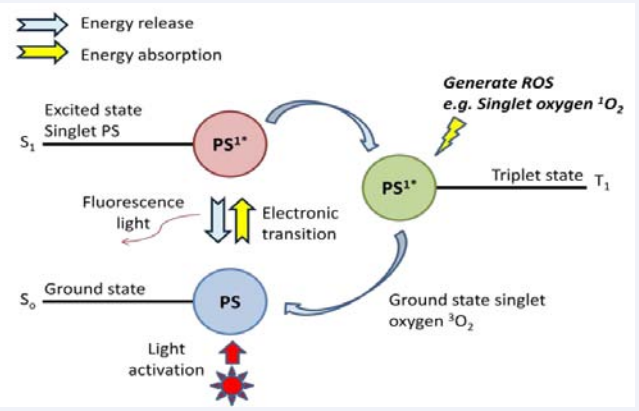

Figure 3 Energy level diagram for photosensitizer activation, Figure showing the singled ground state (So), excited singled state (S_1), and excited tripled state (T_1).

oxygen ($^1O_2$) will be produced when the energy exchange from the photosensitizer triple state to ground state oxygen ($^3O_2$) [82].

In general, the photosensitizer molecules will be excited from singlet ground state (S_0) to a higher energy state (S_1) by photon from the light source (such as laser, quartz-halogen lamp or LED light) with specific wavelength. The molecules at the excited state are in nanosecond range and are usually unstable, which may easily decay to a lower energy state (T_1) by internal conversion and vibrational relaxation. Some molecules may further return to the ground state S_0 through fluorescence emission, but some will pass to the triplet excited state. Molecules in the triplet excited state can decay back to S_0 state through the fluorescence emission of phosphorescence by two process known as the electron transfer process (type I reaction) or the energy transfer process with molecular oxygen (type II reaction). At type I mechanism, T_1 stage molecule may generates a free radical species and will further react with environmental oxygen to form oxidized products. At type II mechanism, T_1 stage molecule may generate singled oxygen. It is believed that the singled oxygen is the key agent of cellular damage, result as biological damage of the proteins, lipids and various cellular constituents and thus the type II mechanism is predominant over the type I mechanism [82,85,95]. However, the lifetime of singlet oxygen is very short (in the micro- to millisecond range) that limits its diffusion in cells. Thus the photodynamic damage is closely related with the properties and intracellular location of the photosensitizers [78,96,97].

The antitumor effects of PDT derive from 3 mechanisms; including direct cytotoxicity effects on tumour cells, destruction of tumor associated vasculature, and induction of inflammatory reaction against tumor cells [78,81,85-89]

Direct cytotoxicity effects on tumor cells

The search to define the molecular target of PDT is one of the key questions in PDT mechanistic research. This question is closely related to the intracellular localization of PSs as ROS have a short half-life.ROS will only interacts with intracellular structures close to their site of generation. The type of photodamage triggered by PDT thus depends on the subcellular localization of PS within the

cell. Recent research has elucidated many pathways lead to cells destruction, including apoptosis, necrosis and autophargy [98].

Necrosis

The first type of cell death mechanism is known as necrosis, a quick form of degeneration affecting extensive cell populations. Typical characteristic of necrosis including cell swelling, destruction of organelle and distripution of the plasma membrane, leading to the release of intracellular contents and inflammation. Necrosis has been identified as accidental cell death which caused by physical or chemical damage. Decomposition of cells in necrosis is principally mediated by proteolytic activity [87].

Apoptosis

Different from necrosis, apoptosis is identified in a single cells surrounded by healthy neighours. It has been reffered as programmed cell death and is an ATP-requiring process morphologically characterized by nucleus condensation, fragmentation of DNA, cell shinkage, bledding of the plasma membrane and formation of multiple membrane-enclosed spherical vesicles known as apoptotic bodies. Apoptotic bodies are then scavenged by phagocytes *in vivo* and inflammation is prevented. As reffered as programmed cell death, apoptosis is controlled by transcriptional activation of specific genes, include the activation of endonucleases and caspases, and DNA degradation into fragments [95,99,100]. Caspases consists of a group of enzymes known as the cysteine dependent aspartate-specific proteases. The apoptotic caspases could be activated by two pathways, called extrinsic pathway and intrinsic pathway. Extrinsic pathway is triggered by binding of death ligands to their corresponding receptors while intrinsic pathway is triggered by the mitochondria. The role of the intrinsic pathway in PDT has been documented as mitochondria is one of the molecular target for most of the PSs. Release of cytochrome c followed by destruction of mitochondria after PDT is observed and apoptotic caspase being activated, result as PDT mediated apoptosis [101, 102].

Autophagy

The third type of cell death mechanism is knwon as autophagic cell death. Autophagy is reffered to catabolic process initiated in eukaryotic cells. The purpose of autophagy is to remove damaged organelles by forming autophagosomes and recycling of cytoplasmic components. This is a survival mechanism allowing the maintainacne of cell function. However, constitutive activation of autophagy can promote cell death as a result of excessive self destruction of cellular organelles. Autophagy is characteristized by a series of cellular changes, started as formation of autophagosomes, a double membrane structure which surrounded the cytoplasmic components or organelles. The autophagosomes will eventually fused with the lysosomes. Enzymes stored in lysosomes will digest the cytoplasmic materials and useful materials will be recycled [103]. Recent studies reveal that PDT may induce the formation of autophagy through photogenerated ROS. Formation of autophagy may aim as to remove the oxidatively damaged organelles or due to the accumulation of AMP by destruction of the mitochondria after PDT [83,104].

Antitumor mechanisms

The generation of knowledge concerning cell biology and signal transduction pathways is one of the principal areas of mechanistic research in field of PDT. The alternation of signal transduction proteins induced by PDT includes tyrosine kinase expression, transcritpion factors and cytokines.

Tyrosine kinase expression

Signal transduction cascades are important networks for cells to receive external stimuli and response to the stimuli in an appropriate manner. The mitogen activated protein kinase (MAPK) signal pathways paly an important role in eurkaryotic cells and modulate many cellulat events including i) regulation of cell cycle, ii) regulation of embryoic development, iii) cell movement, iv) cell differetiation, and v) apoptosis [105,106]. The MAPK signal pathways consist of ”three kinase modules” including the extracellular signal regulated kinases (ERK1/2), the c-Jun N-terminal kinase (JNK) and the p38 kinases. The role of JNK, ERK1/2 and p38 kinases in cell survival after PDT has been studied. There were studies indicating the decrease in ERK’s expression after PDT treatment and is related with PDT induced cell death. Inhibition of ERK expression has been found after PDT and is in relation to a significantly decrease in cell survival. p38 kinases was found to act as stabilizer for cyclooxygenase 2 enzyme. Decrease in the p38 expression could contributes to tumor growth and sensitizes cancer cells to apoptosis [48,107, 108]. The epidermal growth factor receptor (EGFR) is another tyrosin kinase involved in the initiation and progression of various cancers and is related to cell proliferation, angiogenesis, invasion, and metastasis [109,110]. Many studies found that PDT could induce complete loss of EGFR on different cell models and so induce anti-poliferative response [111-113].

Transcritpion factors

Transcription factors are proteins which bind to the enhancer regions of genes to initate gene expression. Transcription factors which couple with receptor-generated signals act as intracellular messengers to activate various gene expression. Nuclear factor kappa B (NF-kB) is present in the cytoplasm and its activation typically initiate a specific signal trasnduction cascades, which regulates many cellular genes including a number of cytokines and growth factors. Activation of NF-kB upon photosensitization has been shown to either promote or inhibit apoptosis depends on the cell types [114-116]. In general, a number of PDT studies have shown that promotor regions of many genes, such as NF-kB, p53, B-cell lymphoma 2 (Bcl-2) and Interleukin 8 (IL-8) could be activated after PDT treatment and is related to both induction and prevention of apoptosis [117,118].

Historical and clinical applications of photodynamic therapy

Treating disease with photosensitizing drugs is an old idea that the first attempts can dates back to ancient Egypt, India and Greece [119]. However, the term Photodynamic was coined by Jesionek and von Tappeiner in 1904 when they reported experiments on cancer treatment with photo sensitizers. R. L. Lipson and S. Schwartz opened the door to the current research of PDT in 1960. They observed that injection of crude preparations

of hematoporphyrin led to characteristic red fluorescence accumulate in neoplastic lesions during surgery. Afterward, a mixture that Schwartz obtained from treating hematoporphyrin with acetic acid and sulfuric acid was used by Lipson for tumor detection. The mixture is now known as the hematoporphyrin derivative (HpD). The expanding use of PDT in clinical applications is based on the pioneering work of Thomas J. Dougherty (USA) in the 1970s with the derivative of hematoporphyrin (HpD). In 1980's, a purified product of HpD named Photofrin, which has a wide range of proven curative effect, was approved by the US FDA as the first photosensitizer for PDT clinical application in cancers, such as skin, oral, bladder cancer and gynecological cancer. Since then, PDT has gained increasing interest in both therapeutic and diagnostic aspect [86,88,120,121].

Photosensitizers: As one of the critical element for PDT, there are a large number of photo sensitizers being tested *in vivo* and *in vitro* in PDT experiments. The prerequisites of an ideal photosensitizer including: chemical purity, low dark toxicity, high quantum yield of singlet oxygen, selective accumulation in tumor cells, short time interval between drug administration and maximal accumulation within target cells, rapid clearance from the body, and being activated by longer wavelength with better tissue penetration [122]. Hematoporphyrin derivative (HpD) was the first FDA approval photosensitizer for clinical PDT with high response rate and promising result were obtained. It was developed in the 1970s and early 1980s and is now known as the 1st generation photo sensitizers. The major drawback of HpD is the cutaneous photosensitivity and this drives the development of the next generation of photo sensitizers. A number of 2nd generation photo sensitizers of different chemical families were synthesized in the late 1980s to offer potential advantages over the 1st generation photo sensitizers, including higher chemical purity, better tumor selectivity and faster clearance [123,124]. These 2nd generation photo sensitizers include prophyrin precursors (5-aminolevulinic acid), chlorines (chlorine e6); meta-tetrahydroxy-phenyl chlorine (m-THPC), etc.

Current development of photosensitizer, also known as the 3rd generation of photosensitizers, amis at improve the drug delivery approached, such as biological modifications like antibody conjugate or liposome conjugate [87,92, 125-127].

Advantages and limitations of PDT

The board acceptance of PDT to tumor cells with repeatable administration without cumulative toxic effect makes PDT suitable as alternative cancer treatments. PDT has several advantages for cancer treatments including no life time limited to PSs, treatment can be repeated as often as needed, fast clearance (depends on the types of PSs), side effects are rare, minimize damage to normal tissues, and no known interaction exists between current chemo- and radiotherapy [78,79]. However, some drawbacks limited the application of PDT in clinical practices. The well known disadvantages are the prolonged photosensitivity, which could be fatal. In order to minimize this adverse effect, patients are advise to keep in dark for weeks until the PS is eliminated from the body. Other limitations includes limited choices of light sources (clinical window is between 600 to 800nm), variation of therapeutic effect according to PSs selected and tumor cell types, and the limitation in systemic treatment for widespread metastasis [91,127].

New perspectives of PDT in tumor therapy: There is increasing interest and research effort focused on developing new photo sensitizers, exploring PDT mechanisms at molecular level, and enhancing PDT efficacy with new drug delivery system. The Novel strategies in PDT including Two-Photon PDT, PDT molecular Beacons, Liposomes package and nanotechnology in PDT. Two-Photon PDT, different from the standard method, is to activate the photo sensitizers by short laser pulse with very high peak power instead of using continuous light. Because the photosensitizer is activated by two photons, each of the photon only contributes one half of the excitation energy and thus near-infrared light can be used to achieve deeper tissue penetration [128,129]. PDT molecular Beacons apply the concept of molecular beacons, which inactive photosensitizer by linking it to a quenching molecule. The photosensitizer will be activated until the linker is cleaved by a target specific enzyme. Alternatively, the linker may be an oligonucleotide and is opened by hybridization to complementary gene sequence, such as complementary mRNA [130,131]. To improve the cellular uptake of water soluble photosensitizer, liposomes with different modification and nanoparticles are applied. The advantage of liposomal photosensitizers and nanoparticles is good membrane penetration and can coat with multiple targeting molecules such as antibodies or peptides [126,132-137].

PDT for nasopharyngeal carcinoma: Alternative treatment is advisable to NPC as it is often inoperable because of its complex anatomical location [39, 64]. The development of improved therapeutic strategies, such as PDT and immunotherapy, shed light on the development of NPC treatment [48,100,138-141]. Yow's group also demonstrated promising outcomes from a number of *in vitro* studies concerning the PDT effect using several PSs including hypericin, mTHPC, merocyanine 540, 5-ALA and hexyl-ALA on NPC/HK1, NPC/CNE1 and NPC/CNE2 cells [100,142-147]. Lai and his colleagues showed that PDT has an immuno-enhancing effect in NPC patients by increasing natural killer cells and interleukin-2 (148). Another group from Hong Kong has illustrated similar outcomes by using other PSs curcumin and Zn-BC-AMon NPC/CNE2 cells and NPC/HK1 cells respectively [149-151]. Preliminary clinical studies using hematoporphyrin and temoporfin for the treatment of the local and recurrence of NPC after curative radiotherapy found encouraging result for residual or recurrent NPC restricted locally to the nasopharynx [152,153].

To conclude, PDT could induces apoptosis in NPC via alternation of mitogen-activated protein kinase, alternation of Epidermal growth factor receptor (EGFR) pathways, or alternation of Bcl-2 protein expression level [144,150,151, 154] . PDT could also modulate the inflammatory cytokine production and angiogenic factors production [155,156]. All these findings suggested that PDT should be one of the best choices over the conventional cancer therapies for NPC.

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Cite this article

Ricky WWK, Ellie CSM, Christine YMN (2016) Photodynamic Therapy: New Light to the Nasopharyngeal Carcinoma Treatment. JSM Head Neck Cancer Cases Rev 1(1): 1005.