

REVIEW

Biomarkers for enhancing the radiosensitivity of nasopharyngeal carcinoma

Wei Chen, Guo-Hua Hu

Department of Otorhinolaryngology, the First Affiliated Hospital of Chongqing Medical University, Chongqing 400016, China

ABSTRACT

Nasopharyngeal carcinoma (NPC) is a common head and neck malignancy. The incidence of NPC is higher in Southern China and Southeast Asia compared with Western countries. Given its high radiosensitivity, the standard treatment for NPC is radiotherapy. However, radioresistance remains a serious obstacle to successful treatment. Radioresistance can cause local recurrence and distant metastases in some patients after treatment by radiation. Thus, special emphasis has been given to the discovery of effective radiosensitizers. This review aims to discuss the biomarkers, classified according to the main mechanisms of radiosensitization, which can enhance the sensitivity of NPC cells to ionizing radiation.

KEYWORDS

Nasopharyngeal carcinoma (NPC); radiotherapy; radiosensitization; biomarkers

Introduction

Nasopharyngeal carcinoma (NPC) is a highly metastatic cancer that originates from the epithelial lining of the nasopharynx. NPC occurs mostly in the pharyngeal recess (fossa of Rosenmüller) and the eustachian tube opening in the nasopharynx¹. Compared with other head and neck malignancies, NPC is unique in the aspects of epidemiology, pathology, and clinical manifestation. The etiology involves various factors, including genetic susceptibility, Epstein-Barr virus (EBV) infection, and exposure to chemical carcinogens¹⁻³.

According to the histological classification of World Health Organization, NPC is divided into three types: keratinizing squamous cell carcinoma (type I), non-keratinizing squamous cell carcinoma (type II), and undifferentiated carcinomas (type III)¹. In comparison with the differentiated NPC, undifferentiated NPC is more aggressive, with a higher incidence of distant metastasis⁴.

NPC exhibits a remarkable geographic distribution that the

incidence in southern parts of China and Southeast Asia, usually belonging to types II and III, is higher than that in Western countries. In the West, NPC occurs sporadically and usually belongs to type I¹.

Distinguished by its unique clinical and pathologic characteristics, NPC is highly radiosensitive. Compared with type I, types II and III have a higher response rate to ionizing radiation⁴. Thus, radiotherapy serves as a standard treatment that is effective to control the early tumor with good prognosis, achieving a 5-year overall survival of 90% and 84% for early stage I and IIA disease, respectively⁵. However, along with radiotherapy, radioresistance also exists in many cases. Moreover, radioresistance can cause locoregional recurrence and distant metastasis after radiotherapy in some patients, especially when the tumor is in the advanced stage (stage III or IV)⁶.

Therefore, for the relatively advanced stage, combined radio-chemotherapy may increase survival rate, which is 50%-70% as reported⁶. However, radioresistance still exists in these cases. Along with the damage of radiation to normal tissues, radioresistance remains a serious obstacle to successful treatment. Hence, methods of decreasing NPC radioresistance and enhancing radiosensitivity are urgently needed.

In this context, special emphasis is given to the exploitation of effective radiosensitizers according to the three main categories of radiosensitization mechanisms⁷.

Correspondence to: Guo-Hua Hu

E-mail: hghcq@sina.com

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Biomarkers for enhancing radiosensitivity

Repair inhibition

Cellular radiation repair is a type of ability that is required and vital for cells. Equipped with this ability, cells can correct radiation damage in various ways. First, cellular systems may prevent damage before it occurs. Second, cells may contain molecules that can restore damaged sites chemically. Third, different types of molecules and enzymatic systems can identify and repair damaged substrates through a set of complex and ordered reactions⁷. As follows, some biomarkers, participating in the repair of radiation damage, are related to radiosensitivity of NPC.

NFBD1/MDC1

Nuclear factor with BRCA1 C-terminal (BRCT) domain 1/mediator of the DNA damage checkpoint protein 1 (NFBD1/MDC1) is one of the BRCT superfamily members that contains a forkhead-associated domain at the amino-terminus, two BRCT domains at carboxy-terminus, and central Pro-Ser-Thr repeat⁸. Previous studies showed that in response to DNA damage, the ataxia telangiectasia mutated (ATM) kinase catalyzes the phosphorylation of histone variant H2AX to recognize and marks the sites of damaged DNA⁹. NFBD1 then recruits repair factors including MRE11, RAD50, and NBS1 complex to the marked sites to form a nuclear foci, thus contributing to an increase in the fidelity of genomic integrity⁸. Furthermore, Lou *et al.*¹⁰ found that the depletion of endogenous NFBD1 can cause a complete loss of nuclear foci formation and induce genomic instability and DNA repair defects. This finding demonstrates that NFBD1 has a close relationship with the initiation and promotion of DNA repair process. *In vivo*, the generation of MDC1 knockout mice had the characteristics of growth retardation, male infertility, defective class switching, and increased radiation sensitivity¹⁰. The expression level of NFBD1 in NPC cells was absolutely high, and the suppression of NFBD1 could increase the rate of apoptosis of NPC cells and the sensitivity to chemotherapy^{11,12}. Recently, Wang *et al.*¹³ demonstrates that Lentivirus-mediated shRNA targeting NFBD1 can steadily silence the expression of NFBD1 gene and enhance the radiosensitivity of CNE-1 cells. These results may eventually contribute to the clinical investigation of prediction markers and prognostic factors, as well to the development of radiosensitizing molecules for therapeutic use.

Cell cycle redistribution

Radiosensitivity of the cells varies according to their positions

in the cell cycle. Cells in G₂/M are approximately 3-fold more sensitive to radiation than cells in late S-phase/early G₁, but the exact cause of variation is currently not completely known¹⁴. Thus, agents that can block the progression of a cell cycle in a radiosensitive phase may induce significant radiosensitization.

COX-2

Cyclooxygenase or prostaglandin endoperoxidase synthase (COX) is an enzyme that participates in the formation of prostaglandins (PGs) and is also recognized as an important chemical mediator for inflammation. COX has two isoforms: COX-1 and COX-2. COX-2, not usually expressed in most normal tissues, has a close relationship with the synthesis of PGs in inflamed and neoplastic tissues¹⁵. COX-2 overexpression has been reported in most cancers, such as esophageal, gastric, pancreatic, colorectal, lung, and breast cancers¹⁶⁻¹⁸, suggesting that COX-2 overexpression has a close relationship with cancer progression¹⁵. Some preclinical studies have investigated the role of COX-2 in carcinogenesis¹⁹. In these studies, upregulation of COX-2 can regulate angiogenesis, resist apoptosis, and influence cell proliferation successfully through induction of vascular endothelial growth factor (VEGF) and translocation of HIF-1 α protein, increase of the expression of proapoptotic Bcl-2 proteins, inhibition of cytochrome c released from mitochondria, and control of G₁ and S phase cyclins²⁰. Thus, the selective COX-2 inhibitors can be regarded as anticancer agents. Recently, a preclinical study showed that high COX-2 expression was found in more than 70% of NPC, and these tumors had earlier regional lymph node metastasis, distant metastasis, and poor responses to chemotherapy, as well as a lower 5-year survival rate compared with low COX-2 expression or negative tumors²¹. Meanwhile, an *in vitro* study demonstrated that adding the selective COX-2 inhibitor NS-398 in NPC cells could increase the radiation-induced cell death²². Furthermore, Sun *et al.*²³ showed that COX-2 overexpressing proteins in NPC cells have radioprotective effects, and silence of the expression of COX-2 can reduce radiation-induced damage repair, thereby enhancing cellular radiosensitivity; this finding lays a theoretical foundation on new gene-radiation combined therapy for NPC. The underlying mechanism may be attributable to the G₂-M cell phase arrest and enhancement of cell apoptosis²⁴.

GP96 or GDF-15

The 96 kDa glycoprotein (GP96, also known as GPR94) is an endoplasmic reticulum resident protein that belongs to the heat shock protein 90 family. This glycoprotein is involved in the package and transport of membrane-bound oligomeric proteins, such as immunoglobulins, epidermal growth factor receptor

(EGFR), and integrins. It can also induce a variety of immune responses, including antitumor immune responses and the productions of antigen-processing peptides, to collect MHC class I molecules²⁵.

Growth differentiation factor 15 (GDF-15) is a member of the transforming growth factor β superfamily. In response to DNA damage, GDF-15 is also a significant downstream mediator. Moreover, high expression of GDF-15 can induce apoptosis and G₁ cell cycle arrest²⁶. Chang *et al.*²⁷ used siRNA to suppress the expression of *GP96* and *GDF-15* in NPC-radioresistant cells, which demonstrated that silence of these genes could cause cell growth delay, G₂-M cell cycle arrest, and a reduction of clonogenic survival. They also verified that knockdown of the genes could increase the radiosensitivity of NPC cells²⁷. Although further clinical studies are needed, these results may eventually contribute to the development of novel radiosensitizing therapeutics.

GnT-V

Protein glycosylation, a type of post-translational modification, is vital for the glycoprotein, which can affect cell growth, differentiation, and tumor metastasis²⁸. The glycosyltransferase, located in the Golgi apparatus, plays an important role in protein glycosylation. The glycosyltransferase contains at least six N-acetylglucosaminyltransferases (GnTs), defined as GnT-I-VI. N-glycosyltransferase-V (GnT-V) is recognized as a primary member of the glycosyltransferase family, catalyzing the formation of β 1, 6 GlcNAc branching structures. Many studies have shown that upregulation of the β 1, 6 GlcNAc branched N-glycans structure is related to malignant transformation through various ways, such as inhibiting cell apoptosis and enhancing cell proliferation²⁹. Previous studies have shown that GnT-V plays an important role in malignant tumors. Recently, Wei *et al.*³⁰ demonstrated that downregulation of GnT-V inhibited NPC cell line CNE-2 clonogenic survival after radiation *in vitro*. Another study investigated the role of GnT-V on the radiosensitivity of NPC cells and its underlying mechanisms. These results showed that downregulation of GnT-V in NPC enhanced radiosensitivity *in vitro* and *in vivo*. The underlying mechanisms may be linked to the cell cycle G₂-M arrest and the reduction of Bcl-2/Bax ratio. GnT-V may be a potential target for predicting NPC response to radiotherapy³¹.

Jab1/CSN5

C-Jun activation domain-binding protein-1 (Jab1) is a modulator of intracellular signaling. Through its existence as the fifth component of the constitutive photomorphogenic-9 signalosome (CSN5), Jab1/CSN5 can regulate cellular

proliferation and apoptosis by functionally deactivating some key negative regulatory proteins and tumor suppressors, such as p53 and p27³². In previous studies, overexpression of *Jab1* was found to be correlated with poor prognosis in some tumor types, such as pancreatic adenocarcinomas³³, breast cancers³⁴, and NPC³⁵. Other previous studies had found that Jab1 played an important role in the pathogenesis and radioresistance in NPC³⁶.

Curcumin is a common chemopreventive agent. Although it plays an important role in anticancer activities in tumor cells³⁷, many previous studies showed that curcumin was limited in its application in anticancer therapy because of its poor bioavailability, rapid metabolism, and instability under several physiologic conditions³⁸. Thus, analogues of curcumin, which have increased anticancer activity and similar safety profiles as curcumin, have been developed in recent years^{39,40}. Pan *et al.*⁴¹ used T83 (a new 4-arylidene curcumin analogue) to inhibit the expression of *Jab1* in NPC cells, demonstrating that inhibition of Jab1 could reduce tumor cell growth, induce G₂/M arrest, and increase tumor cell apoptosis, thus enhancing the sensitivities of NPC cells to radiotherapy. This study verified T83 as a potential targeted therapy, which may increase the radiosensitivities of NPC cells, providing a promising and effective treatment for NPC patients.

Increased initial damage

Through production of free radical species and direct ionization of target molecules, ionizing radiation can cause cellular damage. DNA is the standard target of ionizing radiation damage, and radiation induced double-strand DNA breaks are fatal. Although we do not completely know the exact type of radiation-induced damage, we can use the agents that could cause more initial damage to cellular targets to achieve an increasing cytotoxic effect of radiation.

DNA topoisomerase I

DNA topoisomerases, first discovered in 1971, are important enzymes that can regulate the transformation of DNA topological isomer. DNA topoisomerases have two types: DNA topoisomerase I and DNA topoisomerase II⁴². Topoisomerase I (Top I), which is ATP-independent, catalyzes the relaxation of superhelical DNA by cutting off a single chain, allowing the intact chain through the broken chain (Top IA) or leaving the broken chain free to rotate around the intact chain (Top IB). Topoisomerase II (Top II), which is ATP-dependent, mediates the generation of breaks in both chains of the DNA duplex⁴³. Both topoisomerase I and II play important roles in many aspects of DNA metabolism, such as DNA replication

and DNA transcription, especially the topoisomerase I, which is very essential for the maintenance of the genomic stability⁴². Furthermore, drugs that interfere with topoisomerase I-mediated cleavage rejoining of DNA chains can be widely used in the treatment of cancer⁴⁴. These drugs have also been regarded as effective radiosensitizers when used before radiotherapy, including derivatives of camptothecin⁴⁵. Topotecan (TPT) is a derivative of camptothecin, which can inhibit topoisomerase I in S phase cells. TPT has been suggested to be effective in the radiotherapy of NPC. Zhang *et al.*⁴⁶ established a xenografted human NPC model in nude mice and investigated the synergistic effect of TPT and chronoradiotherapy. The results showed that TPT has a radiosensitizing effect on xenografted human NPC. More importantly, TPT has a circadian dependence, thus contributing to further optimization of therapeutic schedules for NPC. Moreover, the potential mechanism of chronomodulated radiosensitization of TPT may be related to the circadian rhythm of tumor hypoxia and the radiation reluctance of cells in S phase, causing G₂/M phase arrest.

Nitric oxide synthases

NO is a gaseous molecule that has two types: enzyme-dependent NO and enzyme-independent NO. In human cells, NO is enzyme-dependent and comes from L-arginine catalyzed by NO synthases (NOS). NO plays a very important role in cell signaling pathway through cell-mediated immune responses, cytotoxicity, formation of guanylate cyclase, and cyclic guanosine monophosphate⁴⁷. Previous studies showed that NO is a hypoxic cell radiosensitizer when combined with radiotherapy⁴⁸. Recent evidence showed that NO is an initiator of apoptotic signals due to its ability to form peroxynitrite, which can activate oxidative stress-induced apoptosis⁴⁹. Stimulated by cytokines, inducible NOS (iNOS) can produce much NO. Thus, increased iNOS is associated with increased apoptosis. To explore the function of iNOS in NPC, Jayasurya *et al.*⁵⁰ demonstrated that low iNOS expression comes with high incidence of tumor local recurrence and metastasis, probably because of decreased apoptosis. In addition, NPC cells with high iNOS expressions may be more sensitive to radiotherapy.

Others

The mechanisms of the following biomarkers do not belong to the three main categories or are not completely known right now.

EGFR and IGF-1R

EGFR and insulin-like growth factor-1 receptor (IGF-1R) are key members of the tyrosine kinase receptor family, whose ligands

are respectively epidermal growth factor and insulin-like growth factor-1 (IGF-1). The combinations of both receptor and ligand are involved in the development of malignant tumor through modulation of tumor cell cycles, apoptosis, and interactions with the surrounding environment⁵¹. Moreover, IGF-1R plays a crucial role in the generation of drug resistance during anticancer therapy and also in the proliferation and transformation of tumor cells. Meanwhile, EGFR significantly contributes to promotion of cell proliferation⁵². Early experiments showed that combining short hairpin RNA segments to *IGF-1* and *EGFRs* via plasmid or virus transfection could significantly inhibit NPC cell growth, induce apoptosis, and increase chemotherapy sensitivity *in vitro*⁵³. Meanwhile, another study found that overexpression of *EGFR* and *IGF-1R* in advanced and recurrent NPC tissues affected the radiosensitivity of NPC cells⁵⁴. Recently, Liu *et al.*⁵⁵ verified that the dual-silencing of *IGF-1R* and *EGFR*, which are capable to decrease the expression of NPC cyclins and to block cell cycles, may promote the radiosensitivities and apoptosis of NPC cells.

VEGF

VEGF, earlier known as vascular permeability factor, is a specific heparin-binding growth factor of vascular endothelial cells that can induce angiogenesis to support the growth of both normal and tumor tissues *in vivo*. As it is very essential for the progressive enlargement of malignant tumor, the function of VEGF in cancer treatment has been widely studied. Some studies found that VEGF made a great contribution to radioresistance in cancer radiotherapy both *in vitro* and *in vivo*. Those results suggested that targeting VEGF may inhibit cancer cell growth, decrease radioresistance, and prevent metastasis⁵⁶.

Angiotensin II (Ang II) is an important part of the renin-angiotensin-aldosterone system, which can regulate the expression of vasoconstriction, vasopressin, and aldosterone; induce angiogenesis by upregulating VEGF; and promote cell proliferation. In the circulatory system, almost all the physiological functions of Ang II are generated by stimulating the angiotensin II type 1 receptors (AT1R)⁵⁷. Valsartan is a type of AT1R antagonist that can cut off the binding of Ang II to AT1R to reduce the production of VEGF. Previous studies reported that NPC cells could produce VEGF⁵⁸, and its expression had a close relationship with the clinical stage⁵⁹ and the prognosis of NPC⁶⁰. In exploring whether valsartan plays a role in the treatment of NPC, Wang *et al.*⁶¹ revealed that the expression of AT1R was very high in NPC cells, and AT1R blocker valsartan could suppress the secretion of VEGF in NPC cells, thus inhibiting cancer cell growth. All these results implied that AT1R blocker valsartan could increase the radiosensitivity of NPC cells. Meanwhile, Zhou *et al.*⁶² used RNA interference

(RNAi) technology to block *VEGF* expression of NPC cells, thus suppressing the proliferation and migration of NPC cells, inducing tumor apoptosis, and increasing the therapeutic efficacy of ionizing radiation. Therefore, methods to decrease VEGF in NPC cells may have great potential as novel therapeutic strategies against NPC.

LMP-1

EBV, a prototype gamma herpes virus that infects the great majority of the population worldwide, has been implicated in the pathogenesis of several human malignancies including lymphoproliferative malignancies, such as Burkitt's and Hodgkin's lymphomas, as well as epithelial tumors, such as NPC and gastric carcinoma. EBV infection in NPC is classified as latency type II, which is characterized by the expression of a limited series of latent genes, including EBV nuclear antigen-1, latent membrane protein-1 (LMP1), LMP2, and EBV early RNA⁶³. Considering its oncogenic potential, LMP1 is speculated to be an essential factor in the tumorigenesis of NPC⁶⁴. The LMP1 protein is an integral membrane protein and can be subdivided into three domains: a short intracellular N terminus, which orientates the LMP1 protein to the plasma membrane; six hydrophobic transmembrane domains, which are involved in self-aggregation and oligomerization⁶⁵; and an intracellular carboxyl-terminal activating region, which activates most of LMP1's signaling activities⁶⁶ and induces a variety of downstream pathological changes in cell proliferation, anti-apoptosis, and metastasis^{67,68}. Therefore, Yang *et al.*⁶⁹ successfully obtained a phosphorothioate-modified "10-23" DNAzyme, named DZ1, which could downregulate the expression of *LMP1* in NPC cells, to explore the potential use of DNAzymes for the new treatment of NPC. All results demonstrated that low expression of *LMP1* in NPC cells could inhibit cell proliferation and metastasis, promote apoptosis, and enhance radiosensitivity of NPC. In addition, the potential mechanism is through the interferences of signal pathways, which are launched by LMP1 including NF- κ B, AP-1, and STAT3 signal pathways⁶⁹. Recently, Ma *et al.*⁷⁰ confirmed that LMP1 could regulate the expression of *ATM* via the NF- κ B pathways, thus resulting in the change of radiosensitivity in NPC cells. Moreover, Xiao *et al.*⁷¹ used a metabolomics approach to investigate EBV-modulated metabolic changes, indicating that there is a close relationship between EBV and glycolysis in NPC. Significantly, LMP1 plays a key role in the reprogramming of EBV-mediated glycolysis in NPC cells, and anti-glycolytic therapy can effectively enhance the sensitivity of *LMP1*-overexpressing NPC cells to radiation. Thus, anti-glycolytic therapy may be a novel therapeutic strategy for NPC patients⁷¹.

Protein kinase CK2

Protein kinase CK2 (formerly known as casein kinase 2 or II) is a common serine/threonine protein kinase that is localized in the cytoplasmic and nuclear compartments of the cell. Protein kinase CK2 contains two regulatory (28-kDa β) subunits and two catalytic (42-kDa α and 38-kDa α') subunits, forming the heterotetrameric configurations $\alpha 2\beta 2$, $\alpha\alpha'\beta 2$, and $\alpha'2\beta 2$. The role of CK2, which is multifunctional, in normal and abnormal cell growth, proliferation, and apoptosis has been recognized for a long time. CK2 exerts its anti-apoptotic effects through the phosphorylation of a series factors, and inhibition of CK2 can induce apoptosis and promote tumor cell proliferation⁷². Furthermore, Liu *et al.*⁷³ used RNAi technique to downregulate the *protein kinase CK2a* expression in NPC cells and demonstrated that *CK2a* knockdown significantly decreased the clonogenic activity and increased the radiosensitivity of the NPC cells. Hence, suppression of the expression of CK2 may be a potential therapeutic approach to NPC.

Bcl-2

Bcl-2 gene (also known as B-cell lymphoma/leukemia gene-2) is one of the strongest genes that have an anti-apoptotic effect and is recognized as a human longevity gene⁷⁴. *Bcl-2* gene can inhibit many apoptotic signal-induced apoptosis, promote cell survival, and disorder regulatory mechanism of apoptosis *in vivo*; this gene is found expressed in a variety of malignancies, such as NPC, lung cancer, and cervical cancer⁷⁵. Previously, a study found that *Bcl-2* gene played a significant role in the promotion of tumor invasion and metastasis, and its evolution had a close relationship with the progression of NPC⁷⁶. Other studies demonstrated that Bcl-2 and Bcl-2/bax could be used as important indicators of radiation sensitivity in treating NPC cells⁷⁷. Furthermore, Tian *et al.*⁷⁸ successfully suppressed the expression of Bcl-2 protein by using RNAi technology, thus contributing to an increase of the radiosensitivity of NPC cells. All results suggested that *Bcl-2* may be a potential indicator for predicting the responses of NPC cells to radiotherapy.

Notch signaling pathway

Notch gene, first found in 1917 by Morgan⁷⁹, is involved in the Notch signaling pathway, which is essential to determine cell fate, maintain the stability of stem cell, and regulate the pattern formation. In addition, its dysfunction is related to various defects of developments and human pathologies, including tumorigenesis⁸⁰. Notch signaling pathway is found highly expressed in many malignant tumors, such as breast cancer⁸¹, glioma⁸², and NPC⁸³. This pathway can be activated by EBV-coded latent membrane protein 2A, which is also an important

factor to NPC oncogenesis⁸⁴. Thus, Notch signaling pathway plays a vital role in NPC tumorigenesis.

γ -secretase, a type of proteolytic enzyme, is very essential for the Notch signaling pathway, which can release the Notch intracellular domain. Given that Notch signaling pathway contributes to the progression of NPC, γ -secretase inhibitors (GSIs) that block Notch signaling pathway may achieve better effects when combined with radiotherapy⁸⁵. Yu *et al.*⁸⁶ investigated the effect of one GSI (N-[(3,5-difluorophenyl)acetyl]-L-alanyl-2-phenyl]glycine-1,1-dimethylethylester, DAPT) combined with radiotherapy. This study demonstrated that downregulation of Notch signaling pathway could increase the radiosensitivity of NPC cells, thus indicating GSIs as radiosensitizers for NPC treatment⁸⁶.

Conclusion

NPC is a common head and neck cancer. The incidence rate is higher in southern China and Southeast Asia than in Western countries. Given its high radiosensitivity, radiotherapy is considered the primary treatment for NPC. However, radiotherapy is challenging for NPC because of the radiosensitive structures that surround the nasopharynx, including the brain stem, spinal cord,

pituitary-hypothalamic axis, temporal lobes, eyes, ears, and parotid glands⁸⁷. In addition, radiotherapy often brings adverse effects, such as xerostomia and temporal lobe necrosis. Many NPCs are resistant to radiation, which brings difficulties to treatment⁸⁷. To improve the efficacy of radiotherapy, the use of radiosensitizers combined with ionizing radiation is beneficial.

The concept of radiosensitizers was first proposed in 1958. All the chemical and biological methods that can affect the sensitivity to radiation are named radiosensitizers, including chemotherapeutic drugs and molecular targeted agents^{88,89}. Chemotherapeutics, such as 5-fluorouracil, platinum analogs, and DNA topoisomerase I-targeting drugs, are commonly used when combined with radiotherapy and can achieve better local-regional therapeutic effects⁹⁰. Molecular targeted agents that target DNA or not are also helpful to radiation therapy, such as *EGFR* blockers and *COX-2* inhibitors⁸⁹. In this article, we have summarized some of the biomarkers, classified according to the main mechanisms of radiosensitization, to enhance the responsiveness of NPC cells to radiation treatment (**Table 1**).

As described above, certain useful biomarkers can be silenced in NPC radiotherapy to enhance radiosensitivity. Meanwhile, to modify the expression of unwanted molecular biomarkers, short nucleic acid-based cancer therapeutics containing short

Table 1 Biomarkers for enhancing the radiosensitivity of nasopharyngeal carcinoma (NPC)

Biomarkers	Potential mechanism of radiosensitization of NPC	Methods	References
<i>NFBD-1</i>	Induction of a complete loss of nuclear foci formation, DNA repair defects, and genomic instability	Use of Lentivirus-mediated shRNA targeting <i>NFBD 1</i> to silence the expression of <i>NFBD 1</i> gene in CNE-1 cells	11-13
<i>COX-2</i>	Reduction of G ₂ /M phase arrest in order not to be fully repaired after receiving radiation	Use of shRNAmir lentiviral vector to silence the expression of <i>COX-2</i> gene	22-24
<i>GP96 or GDF-15</i>	Elevation of the proportion of the cells in radiosensitive G ₂ -M phase	Use of siRNA to knockdown the <i>gp96</i> and <i>GDF-15</i> in NPC-radioresistant cells	26,27
<i>GnT-V</i>	Arrest of cell cycle G ₂ -M and reduction of Bcl-2/Bax ratio	Use of Lipofectamine 2000 to transfect the plasmid of antisense <i>GnT-V</i> cDNA into CNE-2 cells	30,31
<i>Jab1/CSN5</i>	Arrest of cell cycle G ₂ -M	Use of T83 (a new 4-arylidene curcumin analogue) to inhibit the expression of <i>Jab1</i> in NPC cells	39-41
DNA topoisomerase I	Relationship with the circadian rhythm of tumor hypoxia and G ₂ /M phase arrest	Administration of Topotecan (DNA topoisomerase I-targeted drug) into xenografted human NPC model through peritoneal injection	45,46
Nitric oxide synthases (NOS)	Direct cellular toxicity or interaction with NO reactive species that increase apoptosis	Use of terminal deoxynucleotidyl transferase-mediated dUTP-biotin nick end labeling assay to detect the expression of inducible nitric oxide synthase	50

Table 1 (continued)

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Biomarkers	Potential mechanism of radiosensitization of NPC	Methods	References
<i>EGFR and IGF-1R</i>	Decrease of the expression of NPC cyclins and blocking cell cycles	Use of plasmid or virus transfection to combine short hairpin RNA segments to insulin-like growth factor 1 receptor and to epidermal growth factor receptor	54,55
<i>VEGF</i>	Reduction of tumor angiogenesis that inhibit cancer cell growth, prevent metastasis, and decrease resistance to therapy	Use of valsartan (an AT1R antagonist that can inhibit <i>VEGF</i> expression and secretion in NPC cells)	61,62
<i>LMP-1</i>	Interference of signal pathways, which are abnormally activated by LMP1, including NF- κ B, AP-1, and STAT3 signal pathways	Use of phosphorothioate-modified "10–23" DNAzyme, namely, DZ1, to downregulate the expression of <i>LMP1</i> in NPC cells	70,71
<i>Protein kinase CK2</i>	It exerts its anti-apoptotic effects through the phosphorylation of a series of factors, but the mechanism of radiosensitization is unknown right now	Use of RNAi technique to downregulate the <i>protein kinase CK2α</i> expression in NPC cells	73
<i>Bcl-2</i>	Inhibition of many apoptotic signals induced apoptosis, promotion of cell survival, and disorder of regulatory mechanism of apoptosis <i>in vivo</i>	Use of RNAi technology to reduce the expression of Bcl-2 protein	76-78
Notch signaling pathway	Decrease of the proportion of cancer stem cells and inhibition of tumor growth	Use of γ -secretase inhibitors to inhibit Notch signaling	80,85,86

interfering RNAs, antisense oligonucleotides, DNAzymes, and ribozymes were employed⁹¹. In addition, some agents can be used to silence or inhibit the expression of unwanted biomarkers, including topotecan, valsartan, and analogues of curcumin. Targeting the biomarkers to enhance the radiosensitivity of NPC is very promising and practicable. However, some problems need to be resolved. First, most of the candidate biomarkers are examined only in the molecular level studies and are not yet evaluated in large population clinical trials. Second, the mechanisms of some biomarkers leading to radiosensitization of NPC are not yet completely known. Third, whether some of the biomarkers are specific only to NPC or are common in other cancers is unclear. Hence, large cohort clinical trials are needed to verify the feasibility, availability, and safety of biomarkers to enhance the radiosensitivity of NPC cells.

Conflict of Interest Statement

No potential conflicts of interest are disclosed.

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