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# Therapeutic Targeting of p53-Mediated Apoptosis Pathway in Head and Neck Squamous Cell Carcinomas: Current Progress and Challenges

Solachuddin Jauhari Arief Ichwan<sup>1</sup>, Muhammad Taher Bakhtiar<sup>2</sup>,  
Kiyoshi Ohtani<sup>3</sup> and Masa-Aki Ikeda<sup>4</sup>

<sup>1</sup>*Kulliyah of Dentistry, International Islamic University Malaysia, Kuantan,*

<sup>2</sup>*Kulliyah of Pharmacy, International Islamic University Malaysia, Kuantan,*

<sup>3</sup>*Department of Bioscience, School of Science and Technology,  
Kwansei Gakuin University, Sanda-shi, Hyogo,*

<sup>4</sup>*Section of Molecular Craniofacial Embryology,  
Tokyo Medical and Dental University, Bunkyo-ku, Tokyo,*

<sup>1,2</sup>*Malaysia*

<sup>3,4</sup>*Japan*

## 1. Introduction

Since its discovery three decades ago, p53 has been one of the most intensively and extensively studied tumor suppressor gene, which is accounted more than fifty eight thousand papers have been published to date. The p53 tumor suppressor protein was initially identified as a cellular protein that interacts with a viral oncoprotein, simian virus 40 (SV40) large T antigen. The p53 cDNA isolated from tumor cells (i.e. mutant p53) exhibited oncogenic activity and was therefore initially recognized as an oncogene (Lane & Crawford, 1979). Nevertheless, the identification of wild-type p53 gene and subsequent functional studies in the late 1980's revealed its real action as a tumor suppressor gene (Finlay et al., 1989).

p53 tumor suppressor plays a critical role in the cellular response to genotoxic stress as a major defense against cancer, by maintaining genome integrity to prevent cells from inappropriate growth and division. Mutation of the p53 gene is known as the most common genetic changes in the development of human cancers. p53 regulates a wide variety of target genes responsible for different cellular outcomes related to its function as a tumor suppressor such as cell cycle arrest, apoptotic cell death, senescence, or DNA repair, depending on the cell type and cellular stress. Given the fact that apoptosis is an evolutionary conserved process through which the organisms remove abnormal cells, and thus represents a fundamental roadblock to tumorigenesis (reviewed in Ichwan 2008), it is not surprising that the role in apoptosis has been the focus for most of the scientists working on p53 in cancer treatment research. Loss of p53-dependent apoptosis caused by p53 mutation is believed to be a critical step for carcinogenesis in majority of human malignancies including Head and Neck

Squamous Cell Carcinoma (HNSCC). (Gleich, 2000; Vousden, 2000). Indeed, targeting the p53 pathway of apoptosis to restore the function of p53 gene lost or functionally inactivated in cancer cells has been pursued in recent years.

HNSCC is the most frequently occurring malignant tumor with poor prognosis resulting in major morbidity and mortality. HNSCC is the eighth most common cancer worldwide (Wang et al., 2009; Jemal et al. 2008) and it is increasing in incidence because it is often poorly understood by society in general and frequently ignored in its early stages. The main treatment of HNSCC is either radiotherapy or radical surgery depend on the location and the size of the tumor, which is often combined with adjuvant chemotherapy. However, those conventional therapies in particular radiotherapy and chemotherapy, are non-selective and can cause damage to normal tissue. Modification of the approaches have improved cure rate in only approximately half of the patients (Ichwan & Ikeda, 2008; Thomas & Grandis, 2009). Recently, dramatic improvements in our knowledge of the molecular and genetic basis of HNSCC combined with advances in technology have resulted in novel molecular therapies for the disease by targeting of specific molecule in cancer therapy to selectively destroys cancer cells including targeting the function of p53 tumor suppressor. This chapter attempts to discuss the current state and challenges of the p53-mediated apoptosis pathway as a target in HNSCC therapy.

## 2. p53: Its structure and role in apoptosis

The structure and sequence of the p53 corresponds to key features of the protein and are well conserved in all vertebrates (Hainaut & Hollstein, 2000). The human *p53* gene is located on the short arm of chromosome 17 at 17p13.1 (Isobe et al, 1986; McBride et al, 1986). The p53 protein consists of four functional domains: N-terminal transactivation domain, central core (DNA-binding domain, DBD), tetramerization domain and C-terminal regulatory domain (Fig. 1A). The DBD displays sequence-specific activity in binding to the consensus motif whereas C-terminal domain binds DNA nonspecifically (Melero et al, 2011). For its role as transcription factor, before they interact and recognizing by recognizing consensus sequences (DNA binding sites) of its target genes, p53 proteins need to form tetramers (Xu et al, 2011; Melero et al, 2011). Therefore, the protein is organized in two stably folded domains, the tetramerization and DNA-binding domains that are linked and flanked by intrinsically disordered segments (Melero et al, 2011) (Fig. 1B). In addition to p53, there are two other members in the unique protein family named p63 and p73 (Irwin & Kaelin, 2001). Structurally and functionally, all of these three proteins are related to each other. However, p53 seems to be evolving in the higher organisms to prevent tumorigenesis. Compared with the other genes in p53 family, p53 structure is the simplest among them.

p53 acts as a transcription factor and mediates its effect by modulating the expression of its downstream target genes (El-Deiry, 1998; Ko & Prives, 1996). A number of p53-target genes have been identified and their function in the p53-pathway has been established. In the most recent genome- wide analyses, of the *p53* binding suggest that hundreds of genes may be up- or down- regulated by *p53* (Smeenk et al., 2008).

In normal conditions, the amount of p53 protein in the cell is maintained at very low levels, which is tightly controlled by its important negative regulator which also an upstream target, MDM2 (also known as HDM2) (Vousden and Lu, 2002). MDM2 and p53 regulate each other through an autoregulatory feedback loop. The MDM2 activity is also modulated by its structural homologue partner protein called MDMX (also known as MDM4, HDM4,

or HDMX). MDM2 forms a heterodimers with MDM2 through C-terminal RING domain interactions (Brown et al, 2009). The MDM2-MDMX complex ubiquitinates p53 and thus targets it for proteasome-mediated degradation. MDM2 also inactivates p53 by both repressing its transcriptional activity (Wiman, 2010; Brown et al, 2009; Vousden & Lane, 2007). Likewise MDM2, MDMX also binds directly to p53 and inhibits its transcriptional activity, however it does not induce p53 degradation. (Bottger 1999 in Shangary 2008). Besides MDM2 and MDM4 complex, ARF tumor suppressor also play a crucial role in preventing p53 from MDM2-induced degradation and stabilizing p53 by interacting with MDM2 (Brown et al, 2009) (Fig. 2).

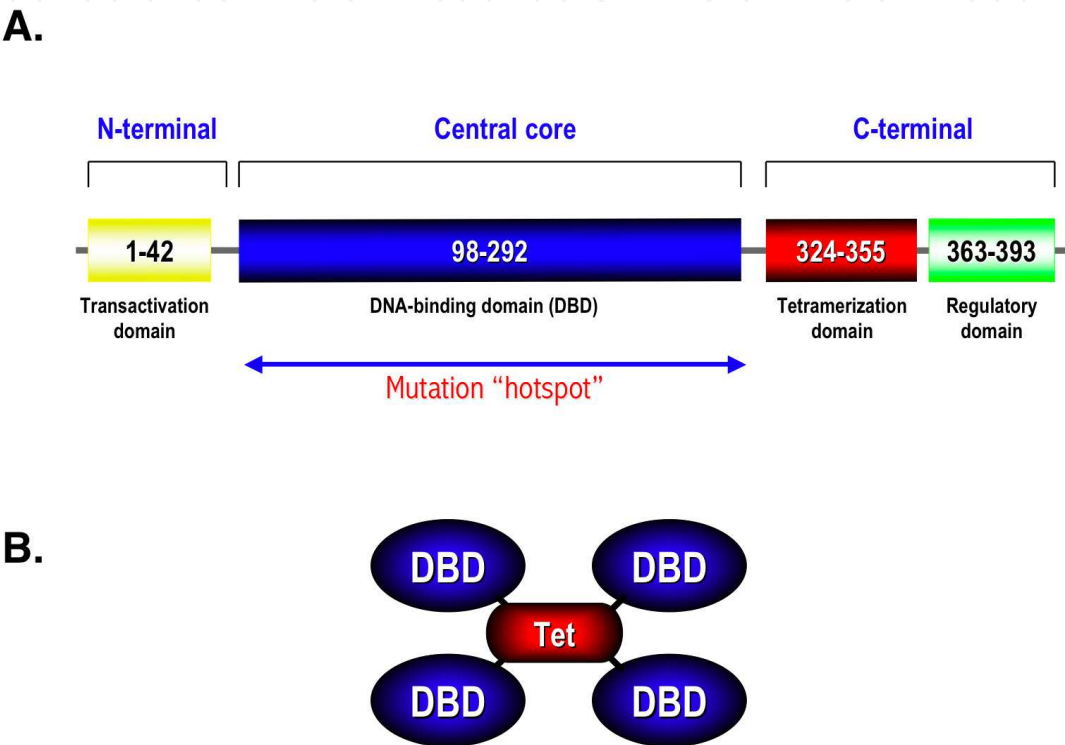


Fig. 1. Schematic representation of: A. Structure of human p53. Note the mutation hotspot is located at DBD. B. Organization of p53 as tetramers.

Upon cellular stresses such as DNA damage, oncogene activation, hypoxia, oxidative stress, mitotic spindle damage and ribonucleotide depletion, p53 is activated, the ability of MDM2 to interact with the p53 expression is diminished, resulting in the stabilization of p53 protein. On the other hand, MDM2 is degraded by ARF, causing release of p53 from the p53-MDM2 complex in the nucleus (Sherr, 2006). The release of p53 from MDM2-mediated inhibition leads to the stabilization of p53 protein and the activation of its transcription activity, as a consequence of which p53 modulates the expression of its downstream target genes involved in cell cycle arrest, DNA repair, senescence, apoptosis, and inhibition of angiogenesis/metastasis as the final outcomes, Several general factors that influence this decision include p53 expression levels, the type of stress signal, the cell type and the cellular context at the time of exposure to stress (reviewed by Haupt et al., 2003; Balint & Vousden, 2001) (Fig. 2). Nevertheless, the exact criteria and the clear mechanism(s) leading to the choice between these final outcomes still need to be further elucidated.

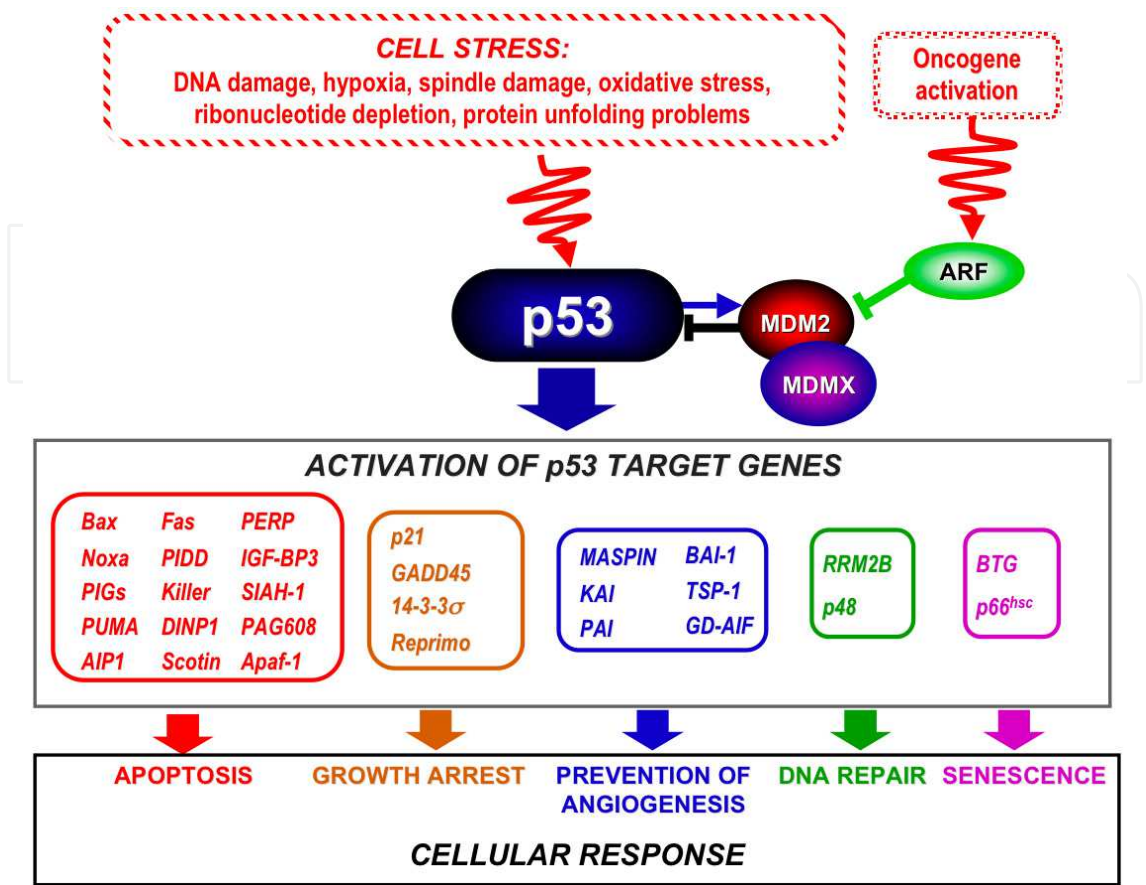


Fig. 2. Cell cycle control by p53. The p53 expression is tightly regulated by MDM2 in a negative feed-back loop manner, whereas MDM2 expression is modulated by MDMX and negatively controlled by ARF. Cellular stresses and/or oncogene activation, disrupts the MDM2-p53 interaction resulting in the stabilization of p53 protein thus modulating the activation of its downstream genes involved in various cellular responses.

p53 triggers apoptosis when cells suffer severe, irreparable damage, whereas it causes cell-cycle arrest when the damage is mild, thereby enabling the cell to fix the damage (Haupt et al., 2003). Depending on the strength of DNA damage, p53 preferentially modulate transcription of either pro-arrest or pro-apoptotic target genes. Upon severe DNA damage, p53 activates expression of multiple target genes whose products execute apoptosis, although evidence indicates that p53 also induces apoptosis in a transcription-independent manner(Gottlieb & Oren, 1998). p53 serves as a regulator of the apoptotic process that can modulate key control points in both the extrinsic (consists of cell surface receptors such as Fas, KILLER) and intrinsic pathways (centers on the mitochondria such as Bax, PUMA, Noxa, p53AIP1, PERP, PIDD) (Fridman & Lowe, 2003). Therefore, p53 apoptotic target genes are enlisted according to their functions in death receptor pathways, mitochondrial machinery and others that play distinct roles in p53-mediated apoptosis (Fridman & Lowe, 2003).

Numerous studies have demonstrated that the stabilization and activation of p53 protein is not only regulated by its interactions with other proteins but also highly governed via complex networks of posttranslational modifications including phosphorylation, ubiquitylation, acetylation, sumoylation, neddylation, ADP-ribosylation, and cytoplasmic sequestration (Vogelstein et al., 2000). The N- and C-terminal regions of p53 is identified



where most of these modifications taken place (Bai and Zhu, 2006). Phosphorylation and acetylation have been thought as the major modifications enhancing the transcription activating ability of p53 because these modifications generally result in p53 stabilization and accumulation in the nucleus, where p53 interacts with sequence-specific sites of its target genes (Xu, 2003; Appella et al., 2001). p53 is phosphorylated on a number of serine residues in the N- and C-terminal domains (Bode & Dong, 2003). Phosphorylation of Ser46 following severe DNA-damage has been shown to be critical for inducing p53-mediated apoptosis (Oda et al., 2000). Severe, irreparable DNA damage induces phosphorylation at Ser46, and Ser46 phosphorylated p53 selectively transactivates pro-apoptotic genes, including *p53AIP1* that is critical for p53-mediated apoptotic induction. Ser46 phosphorylation would change the affinity of p53 to its target gene promoters, shifting from pro-arrest genes to pro-apoptotic genes (reviewed in Ichwan & Ikeda, 2008) (Fig. 3). The most recent study using analysis of genome-wide binding profiles of phosphorylated p53 has demonstrated that the extent of Ser46 phosphorylation of p53 bound to DNA is higher than Ser15 phosphorylation in cells directed towards apoptosis and the amount of chromatin-associated p53 phosphorylated at Ser46 is higher on certain apoptosis related target genes (Smeenk et al., 2011).

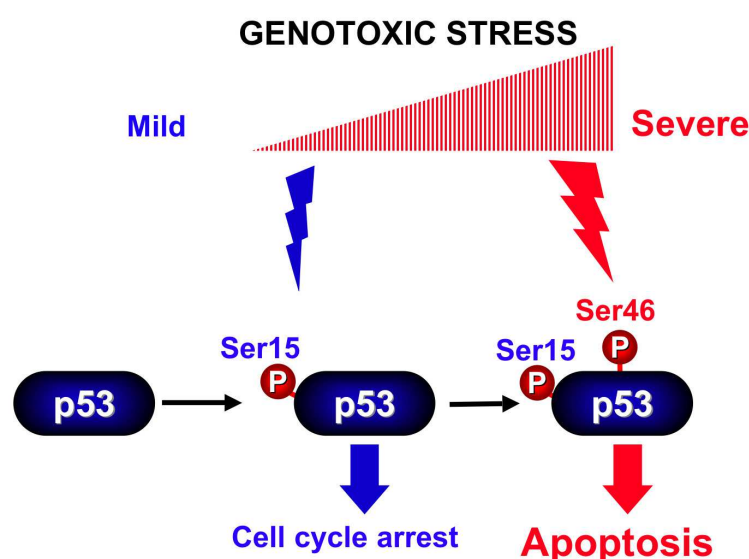


Fig. 3. Phosphorylation of p53 at either Ser15 or Ser46 residue is selectively induced depend on the degree of genotoxic stress (Adopted with modification from Ichwan & Ikeda, 2008).

p53 is also posttranslationally modified through acetylation at Lys370, Lys372, Lys373, Lys381, and Lys382 by p300/CBP and at Lys320 by PCAF (p300/CBP-associated factor). Acetylation augments p53 DNA binding, and to stimulate p53-mediated transactivation of its downstream target genes through the recruitment of coactivators (Ozaki & Nakagawara, 2011). Additionally, acetylation has been suggested to regulate the stability of p53 by inhibiting its ubiquitylation by MDM2. In vivo, acetylation at Lys320, Lys373, and Lys382 is induced by many genotoxic agents such as UV-or Ionizing radiation, hypoxia, oxidative stress, and even depletion of ribonucleotide pools (Bai & Zhu, 2006). p53 can also be deacetylated by HDAC1 (Histone Deacetylase-1) and SIRT1 (Silent mating type information regulation 2 homolog 1). Intrinsic deacetylase activity of human SIRT1 attenuates p53-dependent cell cycle arrest and apoptosis through down-regulation of the p21WAF1 and Bax (Brown et al., 2009).

### 3. Dysfunctions of p53-mediated apoptotic pathway in HNSCC

Dysfunction of p53 by mutation and/or attenuated expression of the wild-type p53 by oncogenic proteins account in majority of tumor development have been well documented in HNSCC. Loss of heterozygosity 17p and mutations of the p53 have been detected in approximately half of all primary and most of recurrent cases of HNSCC (Nemunaitis et al., 2009; Gasco & Crook, 2003; Osman et al., 2002; Taylor et al., 1999). Studies of HNSCC and cell lines suggested that after mutation of one *TP53* allele, the remaining wild-type allele is deleted and accordingly the mutant phenotype expressed (Nylander et al., 2000 as cited in Yin et al., 1999). Mutations in *p53* gene consist of high proportion of missense mutations, which lead to expression of mutated protein at high levels (reviewed in Goldstein et al., 2011 and Nylander et al., 2000). More than ninety percent of the mutations are found in “hot spots” DBD (Fig 1), which highlighted several residues, such as R175, R282, R273 and the mostly occurred, R248. In HNSCC the main part is found within exons 5–8, but the pattern has been shown to vary between countries and races (Nylander et al., 2000). These mutations involved either in making direct contacts with DNA or support the structure of DNA binding surface. The examples of mutant proteins categorized as “contact” are R248 and R273, while “structural” are R175 and R282 (Joerger & Ferscht, 2010). Structural mutants cause deformation that created internal cavities or surface crevices in the protein scaffold, thus inducing conformational changes in the DNA binding surface (Olivier et al., 2009). Intriguingly, it has also been suggested that instead of the p53 loss-of-function, there are also “gain-of-function” mutants with oncogenic properties; they possess dominant negative activity due to their abilities to prevent wild-type p53 from binding to the promoter of its target genes through formation of a heterotetramer complex (Fig. 4) (Ichwan & Ikeda, 2008). Unfortunately, such mutants are usually has a prolonged half-life (Nylander 2000; Prives & Hall, 1999) and may neutralize the apoptotic activity of exogenous wild-type p53. Defect in Ser46 phosphorylation is also responsible for the acquisition of p53 resistance to p53 gene transfer on HNSCC (Ichwan et al., 2006). Furthermore, specific polymorphic forms at codon 72 “gain-of-function” p53 mutants which encode polymorphic alleles encode either proline (72P) or arginine (72R) have been shown to exhibit significant differences in the biochemical properties of the p53 protein (Murphy, 2006). In HNSCC cells, mutant p53 proteins with 72R are commonly found than 72P (Marin et al., 2000; Brooks et al., 2000). The mutants that harbors 72R allele have also been shown to physically interact with a member of p53 family, p73 and repress its apoptotic activity in cancer cells (Marin et al., 2000).

Accumulating evidences have shown that roughly half of all HNSCC cases still retain normal (wild-type) p53, supporting the idea that HNSCC is not characterized by a single molecular change. In this circumstance, the expression of the wild-type p53 may be inactivated by amplification or overexpression of oncogenic protein including MDM2, MDMX and HPV-E6 (Fig. 4).

Amplified expression of either MDM2 and MDMX, in which both are known as p53 inhibitors would severely degrade the protein, resulting in apoptotic blockade. Indeed, MDM2 is overexpressed in a variety of human cancers in HNSCC and has become a prognostic marker (Valentin-Vega et al., 2007; Huang et al., 2001; Ganly et al., 2000; Matsumura et al., 1996). The G-allele single nucleotide polymorphism at 309 of MDM2 (MDM2 SNP309G) has been shown to be associated with significantly higher levels of the

MDM2 expression (reviewed in Vasquez et al., 2008). MDM2 overexpression also induces centrosome hyperamplification and chromosome in cultured HNSCC cells (Caroll et al., 1999). The scenario may become worse when MDMX are excessively co-expressed as reported in a study in which majority of tumors with amplified MDM2 were also positive for MDMX (Valentin-Vega et al., 2007). Since MDMX potentiates MDM2, overexpression of MDMX may accelerate the p53 degradation and subsequently result in abrogation of p53-mediated apoptotic pathway.

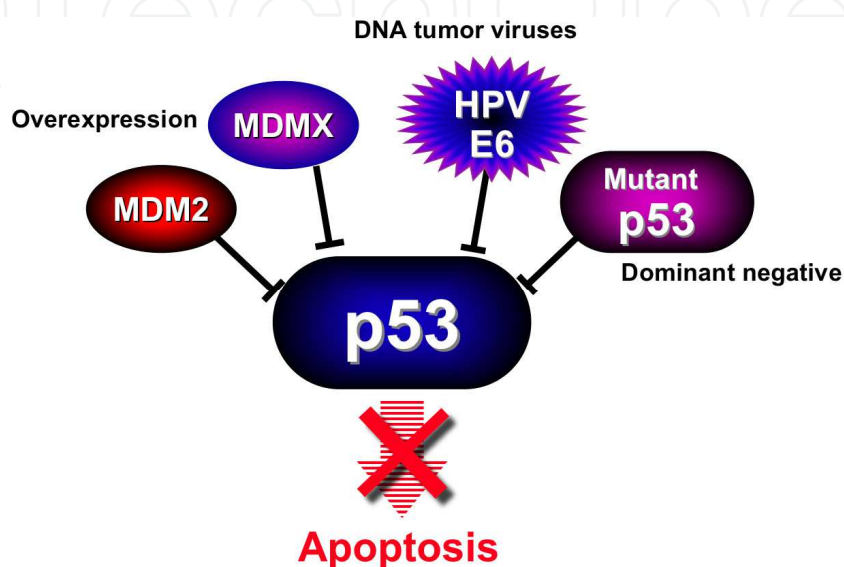


Fig. 4. The pro-apoptotic function of p53 is abrogated in HNSCC by mutation and/or oncogenic proteins MDM2, MDMX, HPV-E6.

HPV-E6 is an oncoprotein encoded by human papillomavirus (HPV), a double-stranded DNA virus that commonly associated with a diverse of human neoplasms such as warts (benign papilloma) as well as malignancy at cervical, vulvar, vaginal, anal, penile, and more recently HNSCC (Chung et al., 2009). More than 100 types of HPV have been identified but the most commonly detected HPV in HNSCC is HPV-16, which has been showed in 90–95% of all HPV positive HNSCC cases, followed by HPV-18, HPV-33, and HPV-33 (reviewed in Perez-Ordóñez et al., 2006). The viral genome also encodes another two oncogenic proteins E5 and E7. However the key players involved in tumorigenesis are attributed to E6 and E7. The oncogenic potential of E6 and E7 are due to their ability to induce degradation of the tumor suppressors p53 and pRB respectively (Werness et al., 1990; Dyson et al., 1989). The HPV-E6 binds to and targets p53 for inactivation and degradation by forming a complex with an E3 ubiquitin ligase, E6-associated protein (E6AP)(Chung et al., 2009).

#### 4. Restoration of p53-mediated apoptosis in HNSCC: The challenges and strategies to overcome

Conventional treatment of HNSCC to destroy cancer cells by combination of radiotherapy and chemotherapy is often non-selective because it also destroys normal cells. Moreover, some cancer cells may acquire resistance to chemotherapy (i.e. doxorubicin, cisplatin, etc)



and radiation due to the expression some forms of mutant p53 that enhanced tumorigenic potential (Thomas & Grandis, 2009). For the past few years, several novel anticancer therapeutic strategies for restoration of the p53 pathway have been developed such as gene therapy, DNA vaccine, small-molecule inhibitors, antisense molecules, and tumor vaccines (Bayon et al., 2011). In particular, gene therapy, which represents the use of genetic material for therapeutic purposes, has been regarded as a promising therapeutic approach (Vattemi & Claudio, 2009). Several strategies have been developed for HNSCC gene therapy including targeting the function of p53 tumor suppressor gene. Indeed, HNSCC has become the focus of p53-targeted gene therapy and an ideal model for testing the efficacy of gene therapy strategies in a localized area with minimal systemic exposure to the agent (Thomas & Grandis, 2009). The replacement of the mutated gene with wild-type p53 gene transfer (mostly using recombinant adenovirus Ad-p53) has been explored as a popular approach, either as a single anticancer agent or combined with other agents. Various studies have reported that wild-type p53 gene transfer efficiently induces apoptosis in most of cancer cells including HNSCC (reviewed in Ichwan & Ikeda, 2008). Clinically, this approach is usually carried out through local injection of recombinant Ad-p53 into tumors. Several “brand names” of the recombinant adenoviruses have been introduced (Table 1). China became the first country to approve the use of Ad-p53 as a gene therapy agent (Gendicine) for HNSCC treatment. (Pearson et al., 2004). However, the clinical efficacy relies on the bystander effect in the tumor since not all cells will be injected (Brown et al., 2009), thus it may require multiple rounds of treatment. Moreover, some HNSCC cells are found to be resistant to Ad-p53 gene transfer (Ichwan et al., 2006). Although mechanisms underlying the p53 resistance have not been fully understood, it has been reported that certain dominant negative mutant p53 proteins expressed in p53-resistant tumors may interfere the action of exogenous wild-type p53 and inhibition of the mutant p53 protein using mutant specific small interfering RNA (siRNA) simultaneously restored the p53-mediated apoptosis in p53-resistant HNSCC cells (Ichwan et al., 2006). Defect in phosphorylation of p53 protein at Ser46, which is critical for p53-mediated apoptosis, also plays a role for the acquisition of the resistance to p53 gene transfer in HNSCC cells and this resistance can be overcome by introducing p53S46D mutant that mimicks Ser46 phosphorylation (Ichwan et al., 2006). In regard to the potential use of recombinant adenoviruses in HNSCC treatment, specific oncolytic adenoviruses have been designed on the idea that the virus only replicate in cancer cells that lack p53 function. Examples of these oncolytic viruses are ONYX-015, currently under Phase III development in the United States (Vattemi & Claudio, 2006) and H101 that have been commercially approved in China (Crompton & Kirn, 2007).

Reactivating mutant p53 has been considered as an alternative strategy to treat HNSCC carrying mutated p53. Several small molecules have been discovered (Table 1) and all of them are still under early stage of preclinical trial. So far, there are only two reports regarding the utilization of these molecules to induce p53-dependent apoptosis on HNSCC cells. PRIMA-1 and CP-31398 work by protecting p53 mutants from unfolding (Roh et al., 2011). and induce the expression of p53-dependent pro-apoptotic mediators PUMA, Noxa, and Bax thus restoring p53-dependent transcription (Wang et al., 2007; Ho & Li, 2005). WR1065 has been proven as a radioprotector in a Phase III randomized trial (Brizel et al., 2002).

Agent/Molecule	Stage in HNSCC clinical trial	Mechanism of action	Reference
Gendicine	Approved (in China)	Wild-type p53 restoration using recombinant adenovirus encoding p53	Pearson et al., 2004
Advexin	Phase III		Nemunatitis, 2011
SCH 58500	N/A		Vasquez et al., 2008
CDB3	N/A	Mutant p53 reactivation	Vasquez et al., 2008
CP-31398	Preclinical		Roh et al., 2011
Ellipticine	N/A		Vasquez, et al., 2008
WR1065	Phase III		Brizel et al., 2000
PRIMA-1	Preclinical		Roh et al., 2011
MIRA-1	N/A		Vasquez, et al., 2008
Nutlin3	Preclinical	p53 stabilization via inhibition of MDM2-p53 interaction	Roh et al., 2011
			Vassilev et al., 2004
M219	N/A		Shangary et al., 2008
RITA	Preclinical		Roh et al., 2011
HL198C	N/A	p53 stabilization via inhibition of MDM2-E3 ligase	Atwal et al., 2007
ONYX-015	Phase III	Oncolytic adenoviruses	Vattemi & Claudio, 2006
H101	Approved (in China)		Crompton & Kim, 2007

Table 1. Agents that targeting p53-mediated apoptosis.

Different strategies are applied to restore p53-dependent apoptosis in the HNSCC cells that retain wild-type p53 but are not active because of the expression of negative regulatory proteins MDM2, MDMX and HPV-E6. Therefore, diminishing the expression of those p53 inhibitors would be the ultimate choice. To this end, siRNA and specific small molecule inhibitors have been shown to be feasible. Previous studies have shown that siRNA delivery into HPV-E6 positive cancer cells induces rapid apoptosis and restore p53 response (Jiang & Milner 2002; Butz et al., 2003). On the other hand, introduction of siRNA did not induce apoptosis but markedly sensitized the different HPV-E6 expressing cells to the chemotherapy drugs (Koivusalo et al., 2005). siRNA treatment also seems effective to silence MDM2 and MDMX overexpression in some cancer cell lines (Lane et al., 2010; Brown et al., 2009; Zhang et al. 2005). Despite these promising achievements, the delivery of siRNA into the tumor of a patient is an important burden since siRNA is prone to degradation. To accomplish this, antisense oligonucleotide carried in an adenoviral vector could be used instead of siRNA; nonetheless, the clinical efficacy still needs to be confirmed. Recent advancements in research on the p53 pathway has been lead to the discovery of several non-genotoxic small compounds to activate the p53 response (Table 1) that targeting p53-MDM2 complex. Nutlin3 is the first molecule known to mimic p53 binding by interacting with the hydrophobic pocket of MDM2, discovered by a combination of high-throughput screening and computer modeling (Vassilev et al., 2004).

Subsequently, another MDM2 inhibitor MI-219 was discovered (Shangary et al., 2008). Both have been shown to disrupt p53-MDM2 interaction through binding to MDM2 thereby reactivate p53-dependent apoptosis and are currently under Phase I clinical trial. RITA works by binding to p53 thus protecting it from interacting to MDM2 and was shown more effective in inducing apoptosis than the Nutlin3 (Issaeva et al., 2004). HL198C stabilize p53 by inhibiting MDM2 ubiquitin ligase activity (Atwal et al., 2007). Despite their early-stage (most are still in the preclinical trial) of development, the utilization of above-mentioned molecules may emerge as an attractive approach in the p53-based cancer therapy for HNSCC.

## 5. Conclusion

Dramatic advances in gaining knowledge of the p53 pathway have shift paradigms in cancer therapy. The ability of p53 tumor suppressor gene to induce apoptosis has been targeted as a novel therapeutic strategy for the patients with HNSCC in which aberrant function of p53 is a common event. Several molecular approaches including wild-type p53 gene transfer and non-genotoxic molecules that capable to reactivate the p53-mediated apoptosis pathways in HNSCC have been established. Regardless a number of successful clinical trials, most of the attempts are still in preclinical stage and yet also facing a number of obstacles. Likewise other malignancies, HNSCC is caused by multiple genetic changes therefore p53 novel mechanisms for p53-induced apoptosis will remain challenging. Further intense efforts are still required to achieve a more efficient therapy of HNSCC in the future.

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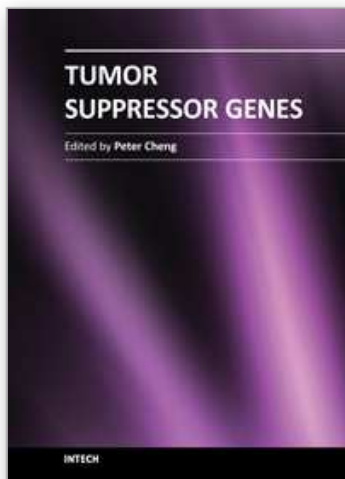


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## **Tumor Suppressor Genes**

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Functional evidence obtained from somatic cell fusion studies indicated that a group of genes from normal cells might replace or correct a defective function of cancer cells. Tumorigenesis that could be initiated by two mutations was established by the analysis of hereditary retinoblastoma, which led to the eventual cloning of RB1 gene. The two-hit hypothesis helped isolate many tumor suppressor genes (TSG) since then. More recently, the roles of haploinsufficiency, epigenetic control, and gene dosage effects in some TSGs, such as P53, P16 and PTEN, have been studied extensively. It is now widely recognized that deregulation of growth control is one of the major hallmarks of cancer biological capabilities, and TSGs play critical roles in many cellular activities through signaling transduction networks. This book is an excellent review of current understanding of TSGs, and indicates that the accumulated TSG knowledge has opened a new frontier for cancer therapies.

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Phone: +86-21-62489820  
Fax: +86-21-62489821



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