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TP53 Gene Signaling Pathways and Protein Interactions with MDM2 and HPV in Oral Cancers – A Review

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Abstract

Oral cancers are heterogeneous group of tumors in topography (they can be localized at on the lips, tongue, upper and lower gums, hard and soft palates, floor of mouth, retromolar region, or inside of cheek), histologic forms (that can be carcinoma, sarcoma, lymphoma, melanoma or cylindroma) and clinical outcomes (good or poor prognosis). However, more than 50% of these cancer phenotypes express a mutation at *TP53* gene while in the other 50% of cases; the *TP53* protein pathway is often partially inactivated. In cancerous tissues, particularly in oral squamous cells, the loss of function at *TP53* gene is associated with three molecular causes: (1) The genotoxic effect of risk factors such as alcohol abuse, tobacco smoking or betel nut chewing, (2) The inhibitory effect of the *TP53* antagonist genes such as *MDM2,* or (3) The action of oncoproteins of *high-risk* human papillomavirus (HPV). This paper attempts firstly to make an exhaustive review of *TP53* gene signalling pathways in normal and stressed cells, and secondly to describe in oral cancers the genetic events that occur at different steps of carcinogenesis after a loss of function in *TP53* encoded protein.

Keywords: *TP53* • Signaling pathways • *MDM2* • HPV • Oral cancers

Introduction

Oral cancers remain a major clinical challenge in oncology and represent the sixth leading cancer worldwide, with an estimated incidence nearly of 300.000 new cases per year and a mortality rate around 50%, according to the 2018 GLOBOCAN report (Global Cancer Incidence, Mortality and Prevalence) [1]. The prognosis of patients suffering from oral cancers is not significantly improved in recent years, despite the strengthening of diagnosis and therapeutic approaches) [2]. This failure is essentially the fact of the clinical heterogeneity of these tumors, resulting from multiple kinds of precancerous lesions, with different biological behaviors and clinical outcomes.

However, despite their clinical and topographic heterogeneities, 50% of oral tumors express a mutation at *TP53* gene, and in the other 50% of cases, the *TP53* protein pathway is often partially inactivated [3]. Indeed, the degradation of the *TP53* gene or the inactivation of its protein is now considered as a full etiological factor in oral carcinogenesis and the main event that precedes and leads to most cancers [4].

Literature Review

To date, *TP53* remains one of the most important and extensively studied tumor suppressor over the past three decades and the new approaches in oral cancers research are focused on its signaling pathway and its protein interactions with MDM2 and *E6-HPV* [5].

In this review, we aimed to summarize the complexities of *TP53* biology by listing in one hand its different ways of signalisation in normal and stressed cells, and in the other hand by studying the effects of its loss of function and mechanisms leading to oral cancers.

Oral Cancers, Epidemiology and Clinical Heterogeneity

Presentation: Oral cancers are a complex disorder that can develop at multiple topographic sites: lips, tongue, upper and lower gums, hard palate, floor of mouth, retromolar region, or inside of cheek; and include mostly squamous cell carcinoma (> 90%) [6,7].

Some authors argue that they are indissociable from cancers of the ORL sphere (oto-rhino-laryngology) and that they fit into the more general framework of head and neck cancers [8].

Epidemiology: Epidemiological data in oral cancers have shown a wide disparity in incidence and mortality around the world, according to the 2018 GLOBOCAN report (Figure 1) [1]. In this report, oral cancers represent the sixth leading cancer worldwide (2-3% of all cancers), with an estimated incidence nearly of 300.000 new cases per year and a mortality rate around 60%, despite the progress noted in medicine and therapeutic research.

Etiopathogenesis: The main risk factors for oral cancer are exposure to genotoxic agents such as tobacco smoking, alcohol consumption, and betel nut chewing [9-11]. These genotoxic agents act by causing genetic alteration in specific genes, particularly those controlling the cell cycle [2,12,13]. Poor oral hygiene, bad set of teeth, inadequate diet and poor nutrition, or immunosuppression can also increase oral cancer risk [14]. The latter can indeed promote chronic infections of the oral mucosa by HPV genotypes with a high carcinogenic potential (genotypes HPV-16 and HPV-18 in particular) [15,16]. The development of oral tumors is described in several stages, from genetic predisposition and exposure to risk factors to the appearance of precancerous lesions in the oral mucosa, eventually followed by the degeneration of these lesions into tumor formations.

Precancerous lesions: Most of oral cancers result from changes to cells of the oral mucosa that make them more likely to develop into cancer. These changes known as precancerous or premalignant lesions correspond to non-neoplastic disorders associated with a significantly higher risk of cancer [17,18]. Oral precancerous lesions are benign and asymptomatic tumors for the most part, beginning as hyperplastic tissue, that can develop (or not) into

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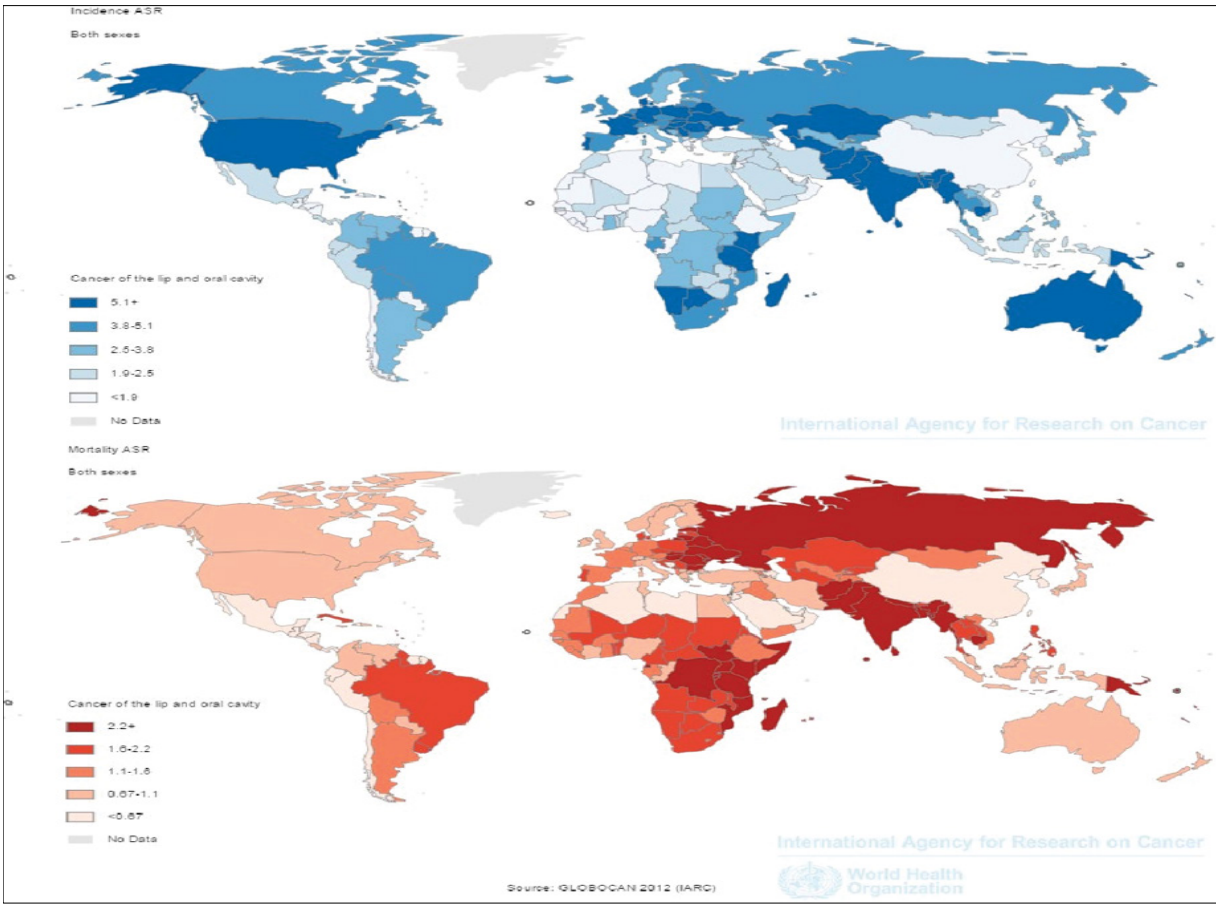

Figure 1. Epidemiological data in oral cancers throughout the word. **a.** Incidence, **b.** Mortality [1].

invasive oral cancer with multiple clinical features [19].

The most frequent forms

1. Among the most frequent oral precancerous lesions, we have [19-21]:
2. Leukoplakia: whitish lesions of the oral mucosa resulting in keratotic areas;
3. Erythroplakia: reddish lesions of the oral mucosa characterized by erythematous areas;
4. Oral submucous fibrosis that are chronic progressive disease modifying the fibroelasticity of the oral submucosa;
5. Oral lichen planus, also called lichenoid lesions, which are chronic inflammatory dermatoses, most often papular, pruritic with mucocutaneous localizations;
6. Actinic cheilitis occurring mainly in the lower labial half-mucosa after prolonged exposure to ultraviolet rays; and finally,
7. Keratotic candidiasis that are superficial mucocutaneous and fungal infection caused by *Candida albicans*.

Viro-induced forms

HPV virus mostly induces five kinds of oral premalignancy [22,23]:

1. Squamous cell papilloma that are outgrowths of hilly and pedunculated appearance, with a surface bristling with papillary projections;
2. Oral Florid papillomatosis that are verrucous, keratotic, whitish in appearance, sometimes considered as grade I squamous cell carcinomas;
3. Vulgar verrucas, which are soft eruptions sometimes covered with a keratotic layer;
4. Condyloma acuminata which are inflammatory, proliferative and highly contagious papillomatous lesions classified as sexually transmitted infections;
5. Multifocal epithelial hyperplasia also known as Heck's disease: common in children, these are HPV-induced diseases (HPV 13 and 32 in particular), characterized by the presence of soft layered or rounded papules.

These viro-induced lesions are generally painless, superficial with planar or exophytic topography (rarely endophytic) [23].

Rare forms

Three kinds of hereditary precancerous lesions can lead to oral cancer [19,21]:

1. Congenital dyskeratosis which are rare ectodermal dysplasias that often clinically manifest following the triad nail dysplasia, skin pigmentation abnormalities and oral leukoplakia. They are associated with a high risk of bone marrow failure and cancers;
2. Dystrophic bullous epidermolysis causing by hereditary mucocutaneous fragility manifested by skin that tends to peel off, forming bubbles that are often painful; and,
3. Fanconi anemia, which is a recessive hereditary disease characterized by progressive pancytopenia, bone marrow aplasia, variable congenital malformations and a predisposition to blood diseases and solid tumors.

Some other disorders such as immunodeficiency, or certain forms of hypersensitivity such as *Xeroderma pigmentosum* (extreme sensitivity to ultraviolet rays) have also been associated with an increased risk of cancer in the oral cavity [19,24].

The risk for these different precancerous lesions to evolve towards oral

cancer depends on their size, topography (planar, exophytic or endophytic) and most importantly on the tissue or organ affected. The cytological and histological changes induced by these lesions are called dysplasia.

Oral epithelial dysplasia seems to have a predilection for males. However, the decrease in the male/female ratio observed in recent years suggests that the tendency may be changing [25]. This fact may be related to increased use of tobacco and alcohol among women.

Even though only 5 to 18% of oral epithelial dysplasia becomes malignant, erythroplakia has a much greater probability (91%) of showing signs of dysplasia or malignancy at the time of diagnosis [26]. Thus, oral premalignancy have been classified, according to evolutivity, into three categories: mild (facultative degeneration), moderate (quasi-mandatory degeneration) and severe (mandatory degeneration) (Kuffer classification, 1975) [27].

Although this classification seems intuitive and hard to prove, oral epithelial dysplasia generally progresses to cancer if it is associated with other factors. For example, (1) erythroplakia within a leukoplakia, (2) proliferative verrucous appearance, (3) location at a high-risk anatomic sites such as the tongue or oral floor, (4) presence of multiple lesions, and, paradoxically, (5) precancerosis in an individual with no history of alcohol or tobacco consumption [26].

Histologic and Topographic forms of oral cancers

The characteristics of oral cancers are very diverse (location, size, appearance, prognosis, etc.) and imply a plurality of topographical features such as cancers of gums, tongue, oral floor, palatal vault, retromolar region, the internal surface of the cheeks or the mucous portion of the lips [28,29].

Squamous cell carcinoma, that usually arise from the dysplastic surface epithelium, account for more than 90% of histological forms of tumors located in the oral cavity [6,7]. Various cytological and architectural subtypes of oral squamous cell carcinoma have been described. The most common feature is the conventional invasive squamous cell carcinoma, but there are also numerous cell-forms of squamous cell carcinoma including fusiform, verrucous, papillary, basaloid, cuniculatum, acantholytic or adenosquamous (= adenoid cystic), lymphoepithelial (= lymphoepithelioma), mucoepidermoid and sarcomatoid (also called spindle cell carcinoma, pseudocarcinoma or 'collision tumor') [14,30].

In addition to these squamous cell carcinomas, there are in a much lower prevalence (less than 10%) many other types of oral tumor formation such as sarcoma, chondrosarcoma (=osteosarcoma), lymphoma (Hodgkin's and Non-Hodgkin's lymphoma, Burkitt's lymphoma), cylindroma, basal-cell cancers, odontogenic tumours (teeth), adenocarcinoma (salivary glands) and melanoma (external face of the cheeks) (the last two forms cited are not considered by some authors to be part of oral cancers) [30-33].

The cancerous involvement site can also be multiple, synchronous (concerning many localizations at the same time) or metachronous (shifted in time).

Detection and clinical diagnosis are mostly done by visual inspection, with naked eyes and allows to completely evaluate the oral cavity. It is imperative in this case to be able to clearly differentiate the existing clinical forms. Confirmation of clinical diagnosis is therefore required by means of an anatomopathological examination of a tumour biopsy.

To date, despite the progress noted in medicine and therapeutic research, survival rate after detection at the final stage remains almost unchanged. The main reason for this is probably related to the late diagnosis of these tumors, which are not symptomatic at their early stage.

The phenotypic diversity noted in oral cancers makes necessary to question the expression profile of genetic predisposition markers (polymorphisms at the level of the *TP53* gene in particular), which can be decisive in the prediction and early diagnosis.

The study of the *TP53* gene signalling pathways and its protein interactions with *MDM2* and HPV has now become a classic in therapeutic research against oral cancers.

TP53 signaling and expression in normal cells

The mutation of the *TP53* gene in half of human cancers and the alteration of its protein pathway (p53) in the other half testify to its essential role in tumor suppression [3]. *TP53* acts as the "guardian of the genome" because its target genes are regulators of genome stability and cellular homeostasis [34]. It is also a "tumor suppressor gene" with 20.303 base pairs length and 11 exonic regions, located at the locus 17p13 of chromosome 17 (Figure 2). Its loss of function is described in several cancers including oral cancers [35].

The protein encoded by *TP53* (= p53) consists of 393 amino-acids with 5 main domains: (1) the transactivation domain (amino-acids 1 to 42) in N-terminal responsible for the transcriptional activation as well as the binding to MDM2, (2) the proline-rich domain (amino-acids 40 to 92) containing 5 PXXP motifs (P = Proline and X = any other amino-acid) which has a role in regulating the stabilization and activation of p53, (3) the DNA binding domain (amino-acids 101 to 306) which specifically binds to the promoters of the p53 target genes, (4) the tetramerization domain (amino-acids 307 to 355) that contains a nuclear export site, and (5) the C-terminal domain (amino-acids 370 to 393) that non-specifically binds to DNA and regulates DNA specific binding via the DNA binding domain [36].

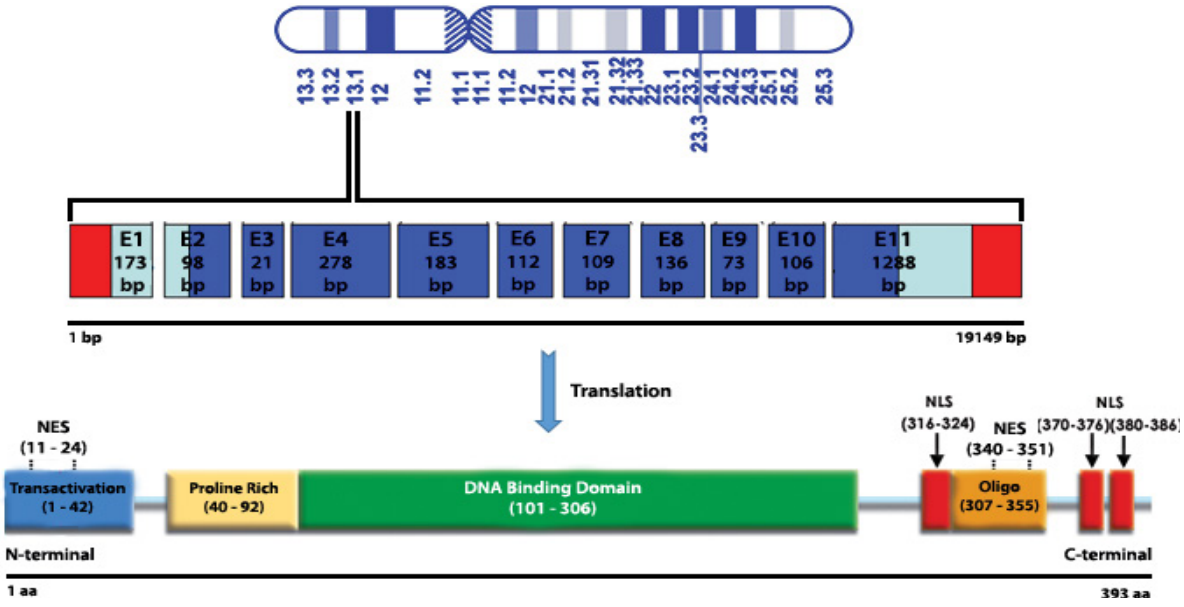

Figure 2. *TP53* locus, gene organization and protein domains [36].

In response to various cellular stresses such as oncogenes activation, hypoxia, depletion of growth factors or the presence of breaks on DNA, p53 has the ability to stabilize and bind DNA in specific sequence to activate or repress hundreds of genes that are involved in multiples biological processes such as cell cycle arrest, DNA damage repair, senescence and apoptosis [37]. The picture below summarizes the different ways of intervention of p53 to regulate the cell cycle (Figure 3).

Know functions of p53

p53, the protein translated by *TP53*, acts like a transcription factor in case of cellular stress by firstly activating genes implicated in cell growth arrest and, depending on scenarios, p53 can lead to the activation of DNA damage repair, (4) programmed cell death (apoptosis) or stoppage of permanent proliferation (senescence) pathways [38,39]. In cancerous cells, p53 can also lead to the inhibition of the angiogenesis (process conducting to tumor growth and metastasis) (Figures 3A-3F) [40].

Concerning its cell growth arrest and DNA damage repair function, p53 acts as a transcription factor to control the cell cycle progression through three target genes: $p21^{WAF1}$ (wild-type p53-activated fragment 1), Gadd45 (Growth Arrest and DNA-Damage-inducible protein) and 14-3-3σ [39]. $p21^{WAF1}$ causes cell cycle arrest in G1 phase and prevents entry into S phase before DNA damage repairing, while Gadd45 and 14-3-3σ control G2/M transition [41,42].

Concerning pro-apoptotic activities of p53, most of them pass through the intrinsic mitochondrial pathway controlled by members of the Bcl-2 family and are dependent on the transcription of several target genes encoding either for cell surface proteins (DR5, CD95 and PERP), for mitochondrial proteins (Bax, Noxa, Puma and p53AIP1), or for cytoplasmic proteins (PIGs and PIDD) [43,44]. At the same time, p53 is able to induce the repression of pro-survival (=anti-apoptotic) factors such as Bcl-2, Bcl-XL and IAPs [45].

Besides inducing cell growth arrest and apoptosis, p53 activation can also modulate cellular senescence and organismal aging. Several p53 isoforms and two p53 homologs, p63 and p73, have been shown to play a role in cellular senescence and/or aging through a process not yet elucidated [46].

p53 also acts against angiogenesis in tumor formations. Angiogenesis is due to the expression in a tumour of the *VEGF* gene (vascular endothelial growth factor) which promotes the formation of new blood vessels in a tumour and metastasis. In the case of prolonged hypoxia (reduction of oxygen delivered to a tissue by blood), a situation frequently observed in tumour formations, p53 indirectly inhibits the expression of *VEGF* via the retinoblastoma pathway [40].

Depending on the cellular activity, two p53 signaling pathways have been described in the literature: a transcriptional activity that takes place at the level of the cell nucleus and concerning the functions such as cell growth arrest, DNA damage repair and senescence and a non-transcriptional activity or cell death pathway that takes place in the cytoplasm and mitochondria.

Transcriptional activity of p53 in cell nucleus: In normal cells, p53 forms a protein complex with MDM2, which complex is able to inhibit p53 transcriptional activity. During a cellular stress, kinases produced by stress phosphorylate p53 at the level of serine and threonine on the transactivation domain (serine15, threonine 18 and serine 20) [47,48]. This phosphorylation induces a relaxation of p53-MDM2 complex, thus freeing p53 which will accumulate and form tetramers in cell nucleus [49]. Tetramerization masks p53 nuclear export sites. p53 then accumulates and remains within the nucleus [50]. Subsequently, phosphorylation of the p53 transactivation domain will promote interaction with histone acetyltransferases (HATs) such as p300 which binds to the proline-rich domain through the PXXP motifs, leading respectively to the acetylation of lysines at the C-terminal domain, the stabilization of p53 and the increasing of its affinity to bind its target genes [51,52]. p300 can also acetylate histones at the promoters of the p53 target genes**,** inducing an opening of their promoters and thus allowing activation of their transcripts [53].

p53 non-transcriptional activity or cell death pathway: In addition to its functions of regulating the transcription of certain genes and inducing DNA damage repair, senescence or apoptosis within the cell nucleus, it has been known for more than 20 years now that p53 can also act at the level of cytoplasm and mitochondria to induce apoptosis through independent mechanisms of transcription [54,55]. This non-transcriptional activity of p53 also known as cell death pathway is controlled by proteins members of the Bcl-2 family (Figure 4) [56].

Bcl-2 proteins family have a general structure that consists of two central predominantly hydrophobic α-helix surrounded by five to seven amphipathic α-helices of varying lengths [57]. Their similarities in amino-acid sequence and function suggest that they have all descended from a common gene [58].

In case of cellular stress requiring intervention of the apoptotic pathway, MDM2 can conjugate a single ubiquitin residue to p53 which induces its transport to cytoplasm [59]. From there, p53 interacts first with Bad (BCL-2 antagonist of cell death) and the formation of p53-Bad protein complex promotes the accumulation of p53 in mitochondrial membrane, which in turn leads to its interaction with pro-apoptotic proteins of the mitochondrial pathway such as Bax (Bcl-2 associated X protein) and/or Bak (Bcl-2 homologous antagonist killer), causing mitochondrial outer membrane permeabilization (MOMP) (Figure 3) [60,61]. The MOMP causes the release of cytochrome c in the cytoplasm, thus promoting apoptosis [62].

Regulation of p53 expression

Because of its growth-limiting and cell cycle-regulating properties,

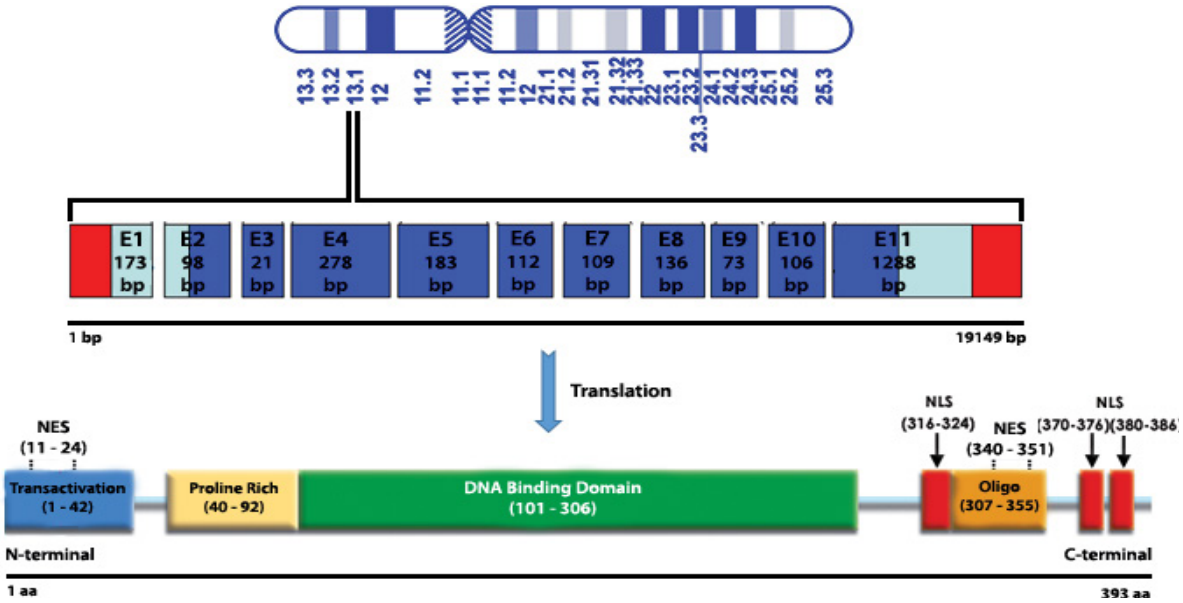

Figure 3. Different signaling pathways of p53. A. Transcription factor, B. Apoptosis, C. Cell growth arrest, D. Senescence,E. Angiogenesis, F. DNA damages repair [38].

p53 expression is finely regulated or inactivated in particular physiological conditions. The p53 wild-type protein has a short half-life (4 to 5 minutes, instead of 6 hours for the mutated form), and remain at a low base level, sometimes undetectable in most tissues, although the p53 mRNA is constitutively expressed [13,63]. The level of its expression is mainly controlled by specific inhibitor such as MDM2 and MDM4 (also called MDMx and hDMX) in different but complementary ways: MDM2 regulates p53 stability, while MDM4 regulates p53 activity (Figures 5A and 5B) [64].

MDM2 is a transcriptional target of p53 and nevertheless represents its main inhibitor [65,66]. The fact that the high mortality in MDM2 deficient mice is suppressed by rendering them deficient in p53 revealed the fundamental role of this protein in the regulation of p53 [61]. MDM2 acts in two ways: firstly by blocking the p53 N-terminal transactivation domain thus preventing it from recruiting co-activators such as p300 and p21, and secondly through its ubiquitin ligase activity on the p53 C-terminal RING domain, by mono-ubiquitylation to promote p53 nuclear export to cytoplasm, or poly-ubiquitylation to induce p53 degradation by the 26S proteasome [66]. This ability of MDM2 to lead to the degradation of p53 makes it an E3 ubiquitin-ligase protein [67]. In response to oncogenic stress, the $p14^{ARF}$ tumor suppressor protein will inhibit MDM2 to release p53 [68].

MDM4 is another specific inhibitor of p53. Unlike MDM2, it does not control the stability of p53 but its transcriptional activity. MDM4 is therefore not a transcriptional target of p53, as its expression does not depend on p53. MDM4 regulates p53 expression at three key levels: (1) by binding to wild-type p53 and inhibiting its transcriptional activity in normal cells, (2) by promoting MDM2 E3 ubiquitin-ligase activity, or (3) by promoting p53 translation from *TP53* in response to cellular stress [69]. Other p53 regulators (= inhibitors) have been found in recent years, such as COP1, Pirh2, PACT, Daxx and CARPs (CARP1 and CARP2) [70-72].

Genetic events in TP53 leading to oral cancers

Most of oral cancers histologic and topographic forms result from multistep accumulation of genetic alterations in *TP53* gene, resulting in clonal outgrowth of transformed cell [2]. Any alteration or inactivation in *TP53* gene is thus described to genetically predisposing to cancers [12,13]. In oral cancers, *TP53* tumor suppressor activity is annihilated either by the genotoxic effect of etiological factors (mainly alcohol and tobacco), or by the oncotic actions of inhibitor proteins such as MDM2 and E6-HPV which act on its expression [9,11,15,16].

Causes of a loss of functions in TP53

Mutations in *TP53*: Mutations in *TP53* lead to loss of function in gene and may result in conformational or functional modifications of the protein. Most

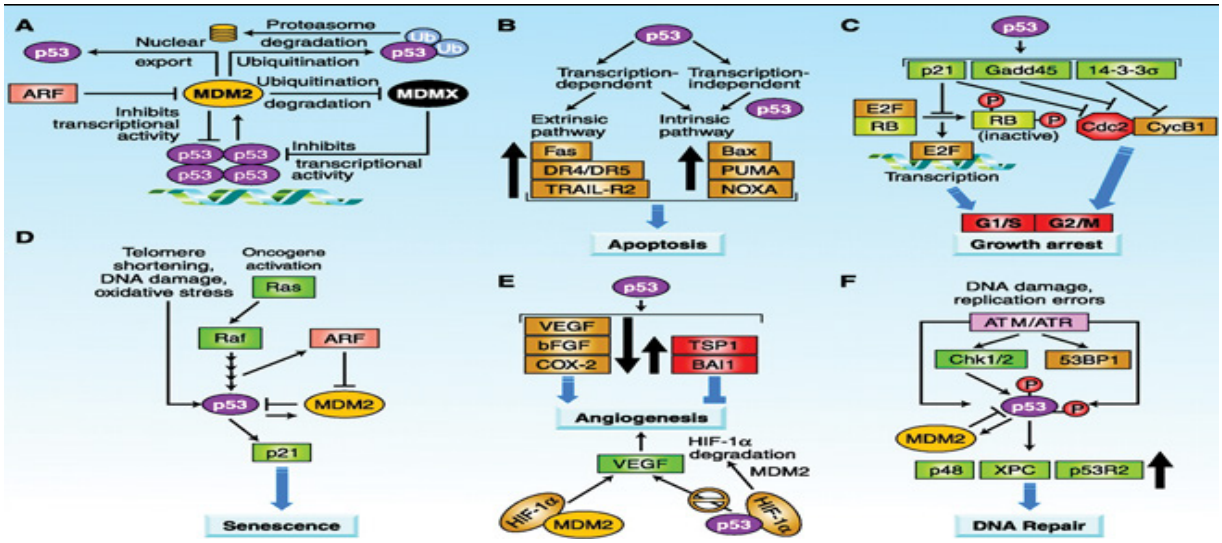

Figure 4. Pro-apoptotic Bcl-2 proteins family [63].

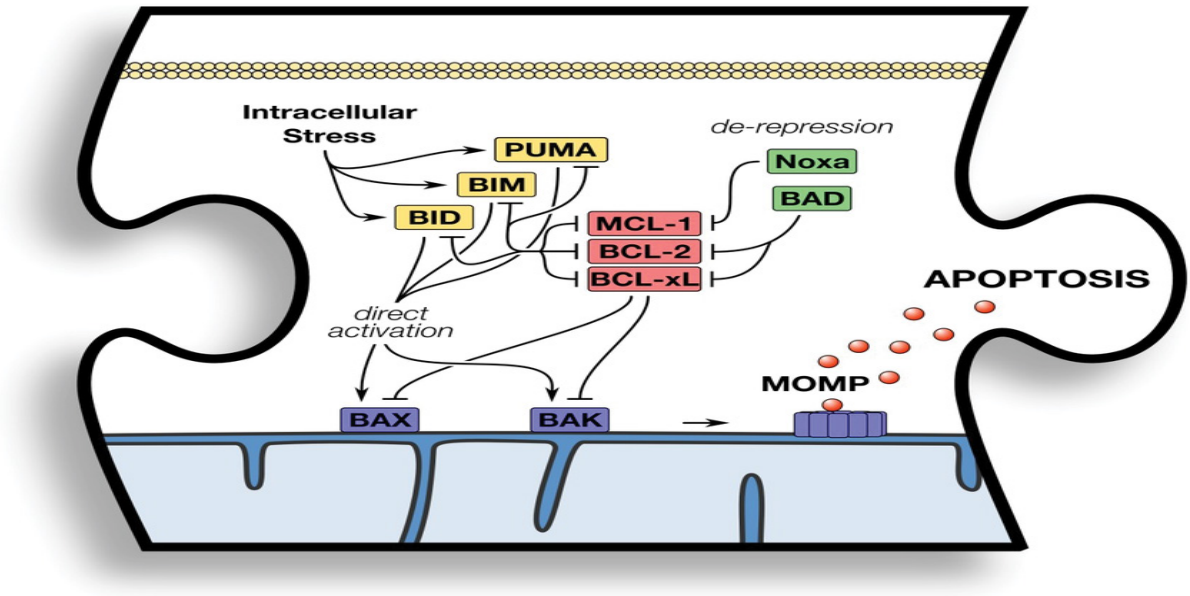

Figure 5A. The MDM2 and MDM4 proteins structure [73].

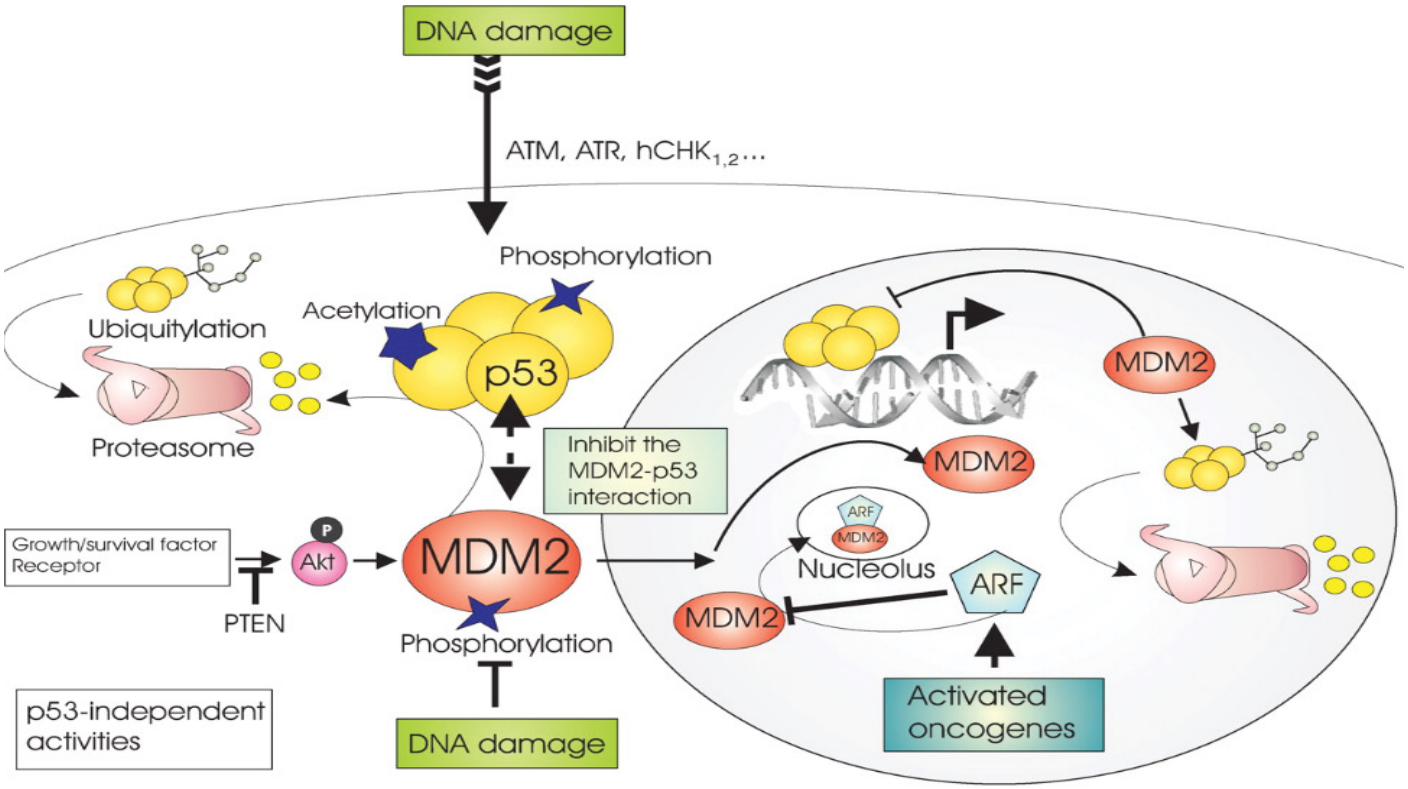

Figure 5B. Mediated regulation of p53expression [73].

TP53 point mutations in oral cancers are caused by the mutagenic effect of genotoxic factors such as alcohol consumption, tobacco smoking or betel nut chewing, and occur preferentially at sites encoding the DNA binding domain of the p53 protein, which may conduct to an inability of the protein to bind and transcribe its target genes [73,74].

Several sequence variations in *TP53* are described as potential risk factors for the development of oral malignancies (29 in non-coding regions and 19 exonic polymorphisms, according to the IARC (International Agency for Research on Cancer) *TP53* mutation database) [75]. Most of these variations have no cancer related consequences. Among the 19 exonic polymorphisms, there are only sufficient molecular evidences for two polymorphisms (Pro47Ser and Arg72Pro) that are formally associated to oral cancer predisposition [10]. Nevertheless, it's important to mention that the functional role of these two polymorphisms of p53 in oral cancer risk remains uncertain and extensively discussed.

The codon 47 polymorphism (Pro47Ser, rs1800371), resulting in Proline (P) to Serine (S) substitution is rare whereas Arginine (R) to Proline (P) substitution in codon 72 (Arg72Pro, rs1042522) is common [76]. These non-conservative amino acid changes are associated with altered electrophoretic mobility of variants, affecting the structure of p53 protein and its biochemical activities such as cell cycle regulation, apoptosis and senescence [77].

In addition, $TP53^{Mut}$ tumors (tumors that express a mutation in *TP53*) are more chemoresistant, and some of these tumors also appear to be more invasive and more likely to metastasize due to the *TP53* non-specifically binding to DNA and the supposed transactivation of genes such as *MDR1*, *MYC* and *VEGF* or inactivation of other members of the p53 family by heterodimerization, which promote tumor growth, angiogenesis, metastasis and chemoresistance [78-80].

Effects of the p53 inhibitor protein MDM2

The inactivation of p53 may be the consequence of overexpression of its inhibitors, particularly MDM2 in oral cancers through the $p14^{ARF}$-MDM2-p53 pathway. MDM2 acts on p53 as ubiquitin ligase protein: its activity may lead to poly-ubiquitination then degradation of p53 via the proteasomal complex 26S [81]. In oral cancers, overexpression of MDM2 is parallel to the inactivation of $p14^{ARF}$ with which it forms an inactive complex [82]. The dissociation of MDM2-$p14^{ARF}$ complex follows a mutation in *CDKN2A* gene and release of MDM2 which becomes overexpressed. $p14^{ARF}$ is an alternative reading frame protein product of the *CDKN2A* gene of which it is one of the transcripts, as well as $p16^{INK4A}$. The first one is involved in the $p14^{ARF}$-MDM2-p53 pathway, and the second is a regulator the p53-pRb-HPV pathway to prevent retinoblastoma [68].

Human *MDM2* gene, located at the locus 12q13-14 and its protein (491 amino acids long), interacts through its N-terminal domain with an α-helix present in the transactivation domain of p53 [83]. The *MDM2* gene is a cellular proto-oncogene overexpressed in 25% to 40% of all human cancers, with an even higher proportion in oral cancers (40% to 80%) [2].

One SNP (single nucleotide polymorphism) in *MDM2* is particularly studied as a potential risk factor for the development of malignancies: it is polymorphism T309G (rs2279744) in the first intron of MDM2 (containing p53-responsive elements), that increase the level of expression of MDM2 [81,84,85]. This functional T to G polymorphism in the promoter region of the *MDM2* gene has thus been reported to profoundly accelerate tumor formation, suggesting that it may also represent a powerful cancer predisposition marker [86].

The p53-MDM2 complex forms an autoregulatory feedback loop (Figure 6). MDM2 is able to inhibit p53 transcriptional activity by three different ways: (i) through binding to its transactivation domain, (ii) through mono-ubiquitination and export from nucleus to cytoplasm, (iii) poly-ubiquitination and mediated degradation via proteasome [87]. These interactions between p53 and MDM2 can also be summarized in three situations:

In normal and unstressed cells, p53 is present in small amounts, but sufficient to enable transactivation of the *MDM2* gene [81]. Oncoprotein MDM2 induces in turn inactivation of p53 by masking its transactivation domain, and the p53-mdm2 complex formed is then poly-ubiquitinated and transported from the nucleus to the cytoplasm to be degraded by the proteasome 26S [81]. That's why in normal cells, the half-life of p53 is quite short, only a few minutes (4 to 5 minutes, instead of 6 hours in cancers) [13].

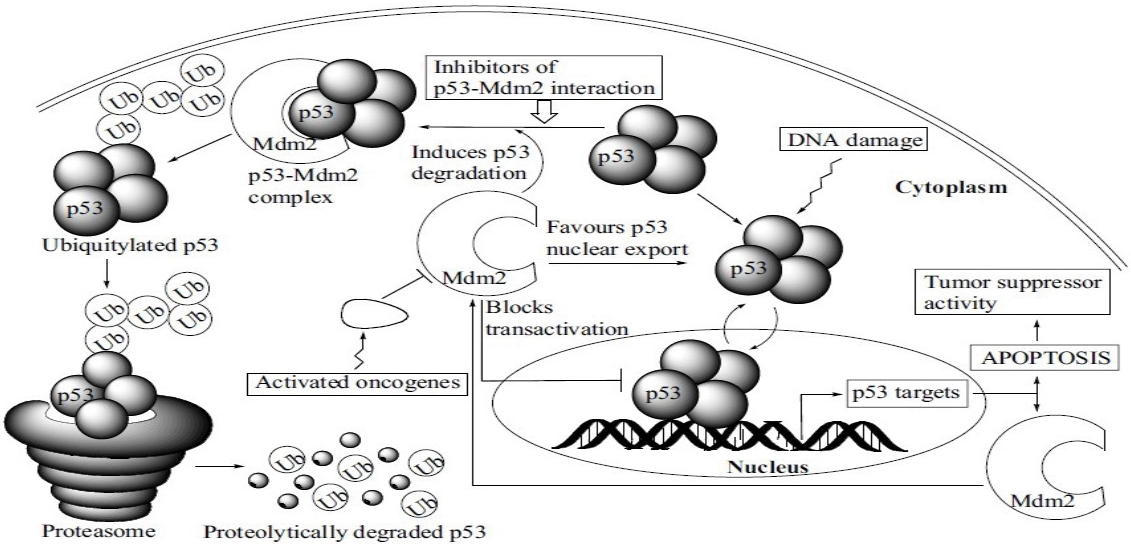

Figure 6. The MDM2 mediated-degradation of p53 [87].

During genotoxic stress, the amino-terminal region of p53 is phosphorylated at specific sites [47,48]. This modification leads to the dissociation of the p53-mdm2 complex and therefore to the accumulation of a stable p53 which form tetramers to enable transactivation of the target genes controlling the cell cycle regulation [49]. Also, in case of cellular stress requiring intervention of the apoptotic pathway, MDM2 can conjugate a single ubiquitin residue to p53 which, instead of leading to its degradation as in the case of poly-ubiquitylation, induces its transport to cytoplasm and then the activation of death pathway via pro-apoptotic proteins of mitochondria [59,81].

In tumor cells however, p53 protein is often completely inactive and would no longer be able to induce the synthesis of MDM2 protein to ensure its degradation [73]. To date, numerous studies have shown that the accumulation of inactive p53 in nucleus, observable by immunohistochemistry would be a prognosticator of poor outcome in Oncology [88].

Oncoproteins of HPV-HR

Exogenous factors such as viral infection (Epstein-Barr virus in cavum cancer or human papillomavirus in cervical and oral cancers) may contribute to the functional inactivation of p53 and the development of many tumours in humans, by inducing cell transformation. According to the latest IARC (International Agency for Research on Cancer) classification (2007), HPV genotypes 16 and 18, and possibly 26, 31, 33 and 35, are considered high-risk for the oral mucosa and infection of keratinocytes in the basal layers of stratified epithelia may lead to oral epithelial dysplasia, which is a precursor to squamous carcinoma [89,90].

In vitro and *in vivo* studies have demonstrated that the immortalizing and transforming power of high-risk HPV genotypes (HPV-HR) are due to their E6 and E7 oncoproteins, early proteins expressed in significant quantities, after integration of the viral genome into the host cell DNA [91]. In HPV-induced carcinogenesis of oral cavity, the latency time between HPV-HR infection and cancer can take many years, showing progression through several stages, leading to an overexpression of the E6 and E7 oncoproteins and immortalization of the infected cells (Figures 7A and 7B) [92]. The oncoprotein E7 initiates carcinogenesis [93].

Oncoprotein E7

E7 preferably associates with the so-called “pocket proteins” pRb, p107 and p130 that have a central role in controlling the cell cycle by negatively regulating the activity of several transcription factors, including members of E2F family [94]. During the G1 phase of the cell cycle, these pocket proteins act as transcription repressor by forming complex with E2F [93].

In healthy cells, the release of E2F is induced by cyclin-dependent kinases (cdk 4 or 6, and cdk2) and leads to a phosphorylation of pRb in G1

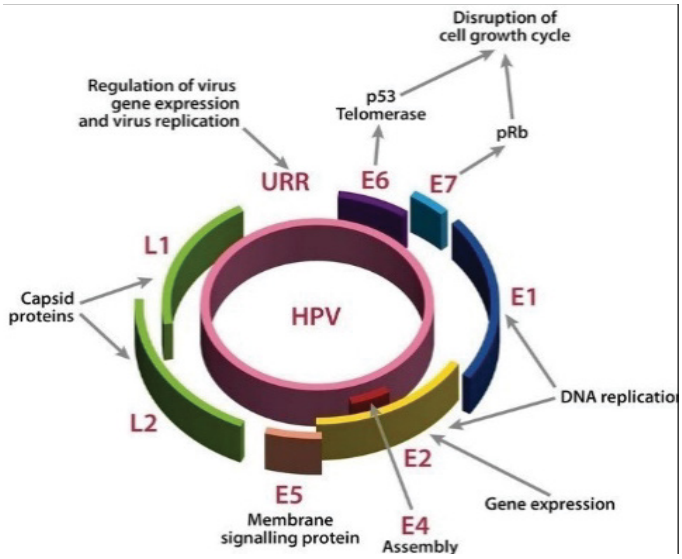

Figure 7A. HPV genome structure [104].

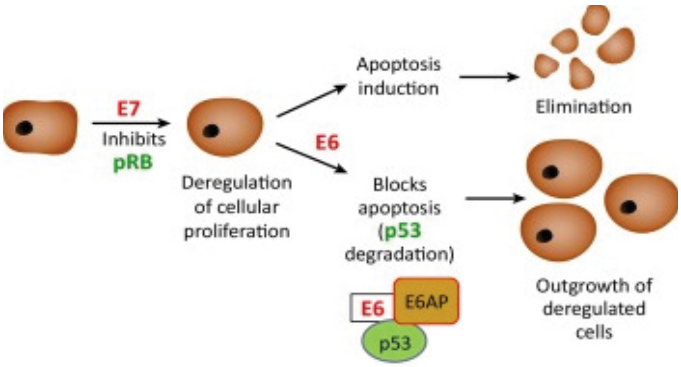

Figure 7B. Role of oncogenes E6 and E7 in HPV-induced cancers [104].

and inactivation of its growth-inhibitory function [95]. However, in HPV-induced cancers, it is found that E7 competes with E2F to bind to pRb. E2F is then released and causes p53 activation, which normally leads to G1 cell cycle arrest and apoptosis [93]. To thwart the apoptosis response, E6 oncoprotein starts the 2nd step of the HPV-mediated carcinogenesis.

Oncoprotein E6

The most important activity of HPV-HR oncoproteins E6 is their abilities to

promote cell proliferation by stimulating degradation of the tumor suppressor protein p53 [96]. On its own, E6 cannot target p53 for proteasomal degradation. Rather, it first forms a protein complex with a cellular E3 ubiquitin ligase E6AP (E6-associated protein), and the stable E6/E6AP complex formed then labels p53 for degradation in a proteasome-dependent manner [97].

As well, E6 has the ability to inhibit the activity of the protein p53, according to 4 mechanisms:

1. Induction of post-translational modifications of p53 which lead to conformational and functional changes in the protein [98];
2. Sequestration of p53 within the cytoplasm and loss of any transactivation function on its target genes [99];
3. Stop of the p53 induced transactivation by interaction with p300, a histone acetyltransferase promoting stabilization of p53. In HPV infection, the E6 oncoproteins bind p300 which therefore inhibit p53 acetylation. All E6 proteins are able to bind p300, but only those of high-risk HPV genotypes seem to bind it with more affinity [100];
4. Inhibition of p53 activation by interacting with hADA3, a component of histone acetyltransferase, which may allow E6 to perturb numerous cellular pathways during HPV oncogenesis [101].

Another characteristic of the HPV-HR E6 protein is its ability to inhibit the differentiation of epithelial cells normally leading to their keratinization and death [102]. As a result, viro-induced cancers of the oral cavity are histologically undifferentiated from the epithelium.

Also, to counter telomere erosion causing death of tumor cells, E6 stimulates the transcription of hTERT (human telomerase reverse transcriptase), which conduct to cellular immortalization, malignant transformation by stabilizing telomere length and erasing the senescence barrier, so unlimited and aberrant cellular proliferation [103].

TP53 gain of functions and oncogenic effects associated

In most cancers, there are large amounts of non-functional p53 accumulated in the cytoplasm and are no longer undergoing degradation by MDM2 [104,105]. Moreover, according to the oncogenic "gain-of-functions" theory, mutated *TP53* (*TP53*^{Mut}) acquires a potential for malignant transformation, which is why, in oncology; mutations in *TP53* are readily associated with a poor prognosis [106].

In fact, the mutant p53 protein released into the cytoplasm has been shown to inhibit autophagy defined as the sequestration and digestion of a portion of the cytoplasm allowing the cell to be cleansed of its damaged and potentially toxic cytoplasmic organelles, in order to maintain genome stability [107]. The fact that p53, which should guarantee the stability of the genome, inhibits this function may therefore seem paradoxical.

In the case where the mutation at *TP53* only concerns its DNA binding domain, p53 is no longer able to activate the MDM2 pathway leading to its ubiquitin-degradation. However, the autophagy-inhibition function is not affected. This is how p53 accumulates in the cytoplasm and that accumulation may partly explain its associated oncogenic effects.

Conclusion

TP53 influences a multitude and highly diverse cellular processes, and represents one of the most important and extensively studied tumor suppressor gene. The inactivation of this gene is particularly described in oral cancers, which pathology is particularly known for its great histological and topographical diversity. Today, our understanding of *TP53* signaling pathways and its molecular implications in carcinogenesis, documented in several publications, has motivated pharmaceutical research and drug development to reactivate the p53 protein functions in most tumors. However, many questions remain to be answered and the molecules discovered until now have still not made it possible to eradicate this pathology that is cancer.

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Conflicts of Interest

No potential conflicts of interest were disclosed.

References

1. Bray F (2018) "Global Cancer Statistics 2018: GLOBOCAN Estimates of Incidence and Mortality Worldwide For 36 Cancers in 185 Countries". CA Cancer J Clin 68: 394-424.
2. Denaro, N, C Lo Nigro, G Natoli and EG Russi, et al. "The Role of P53 and MDM2 in Head and Neck Cancer." *Int Scholarly Res Notices* 2011(2011).
3. Cheok, Chit Fang, Chandra S Verma, José Baselga and David P Lane. "Translating P53 into the Clinic." *Nat Rev Clin Oncol* 8(2011): 25-37.
4. Zushi, Yusuke, Mako Narisawa-Saito, Kazuma Noguchi and Yuki Yoshimatsu, et al. "An *in vitro* Multistep Carcinogenesis Model for Both HPV-Positive and-Negative Human Oral Squamous Cell Carcinomas." *Am J Cancer Res* 1(2011): 869.
5. Stegh, Alexander H. "Targeting the P53 Signaling Pathway in Cancer Therapy–The Promises, Challenges and Perils." *Exp Opinion Therap Targets* 16(2012): 67-83.
6. Rivera, Cesar and Bernardo Venegas. "Histological and Molecular Aspects of Oral Squamous Cell Carcinoma." *Oncol Letters* 8(2014): 7-11.
7. Montero, Pablo H and Snehal G Patel. "Cancer of the Oral Cavity." *Surg Oncol Clin* 24(2015): 491-508.
8. Amana, Bathokedeou, Winga Foma, Essobozou Pegbessou and Haréfétéguéna Bissa, et al. "Cancers Primitifs Oto-Rhino-Laryngologiques Et Cervico-Maxillo-Faciaux: Aspects Épidémiologiques Et Histopathologiques." *Pan African Med J* 25(2016): 177.
9. Freier, Christoph P, Annika Stiasny, Christina Kuhn and Doris Mayr, et al. "Immunohistochemical Evaluation of the Role of P53 Mutation in Cervical Cancer: Ser-20 P53-Mutant Correlates with Better Prognosis." *Anticancer Res* 36(2016): 3131-3137.
10. Patel, KR, BN Vajaria, RD Singh and R Begum, et al. "Clinical Implications of P53 Alterations in Oral Cancer Progression: A Review from India." *Exp Oncol*(2018): 177.
11. Stiasny, Annika, Christoph P Freier, Christina Kuhn and Sandra Schulze, et al. "The Involvement of E6, P53, P16, MDM2 and Gal-3 in the Clinical Outcome of Patients with Cervical Cancer." *Oncol Letters* 14(2017): 4467-4476.
12. Choi, S and JN Myers. "Molecular Pathogenesis of Oral Squamous Cell Carcinoma: Implications for Therapy." *J Dental Res* 87(2008): 14-32.
13. Williams, HK. "Molecular Pathogenesis of Oral Squamous Carcinoma." *Mol Pathol* 53(2000): 165.
14. Singh, J. "Histopathology of Oral Squamous Cell Carcinoma – A Review". TMU J Dent. 1(2014): 4.
15. Entiauspe, Ludmila Gonçalves, Fabiana Kömmling Seixas, Emily Montosa Nunes and Fernanda Martins Rodrigues, et al. "Uncommon Non-Oncogenic HPV Genotypes, TP53 and MDM2 Genes Polymorphisms in HIV-Infected Women in Southern Brazil." *Brazilian J Infect Dis* 18 (2014): 643-650.
16. Gupta, Shilpi, Prabhat Kumar and Bhudev C Das. "HPV: Molecular Pathways and Targets." *Curr Prob Cancer* 42 (2018): 161-174.

17. World Health Organization. "*WHO Guidelines for Screening and Treatment of Precancerous Lesions for Cervical Cancer Prevention*". World Health Organization, 2013.

18. Loeb, I, and L Evrard. "Precancerous and Cancerous Lesions of the Oral Cavity." *Revue Medicale De Bruxelles* 29(2008): 267-272.

19. Yardimci, Gurkan, Zekayi Kutlubay, Burhan Engin and Yalcin Tuzun. "Precancerous Lesions of Oral Mucosa." *World J Clin Cases* 2(2014): 866.

20. Liu, Zi-Hui, Ming-Hui Wang, Hong-Jiu Ren and Wei Qu, et al. "Interleukin 7 Signaling Prevents Apoptosis by Regulating Bcl-2 And Bax via the P53 Pathway in Human Non-Small Cell Lung Cancer Cells." *Int J Clin Exp Pathol* 7(2014): 870.

21. Steele, Toby O and Arlen Meyers. "Early Detection of Premalignant Lesions and Oral Cancer." *Otolaryngologic Clin North America* 44(2011): 221-9.

22. Foulquier, Etienne. "Approche Clinique Et Anatomopathologique Des Lésions Papillomateuses De La Cavité Buccale." Phd Diss, Université Toulouse Lll-Paul Sabatier, 2016.

23. Van Heerden, Willem Francois Petrus, EJ Raubenheimer and Belinda Kathleen Bunn. "Human Papillomavirus Infection of the Oral Cavity: What the Dentist Should Know." *South African Dental J* 72(2017): 52-55.

24. Van Der Waal, Isaäc. "Potentially Malignant Disorders of the Oral and Oropharyngeal Mucosa; Present Concepts of Management." *Oral Oncol* 46(2010): 423-425.

25. Kaugars, George E, James C Burns and John C Gunsolley. "Epithelial Dysplasia of the Oral Cavity and Lips." *Cancer* 62(1988): 2166-2170.

26. https://Oralcancerfoundation.Org/Cdc/Premalignant-Lesions/

27. Neid, M and A Tannapfel. "Squamous Intraepithelial Neoplasia (WHO 2005). Precancerous Lesions of the Head and Neck Region." *HNO* 57(2009): 181-187.

28. De Camargo Cancela, Marianna. "Les Cancers De La Cavité Buccale Et De L'oropharynx Dans Le Monde: Incidence Internationale Et Classification TNM Dans Les Registres Du Cancer." Université Claude Bernard-Lyon I, 2010.

29. De Camargo Cancela, M, Les Cancers De La Cavité Buccale Et De L'oropharynx Dans Le Monde: Incidence Internationale Et Classification TNM Dans Les Registres Du Cancer. 2017, Université Claude Bernard De Lyon: France.

30. Touil, A, Les Cancers De La Cavité Buccale: À Propos De 145 Cas À L'institut Joliot Curie De Dakar. In: Médecine. 2012, Université Cheikh Anta Diop De Dakar, Senegal.

31. Auriel, MM and Y Le Charpentier. Anatomie Pathologique Des Lésions Tumorales De La Cavité Buccale, Des Glandes Salivaires Et Maxillaires. EMC Stomatologie 2(2007): S10.

32. Magremanne, M and C Vervaet. "Melanoma of the Oral Mucosa." *Revue De Stomatologie ET De Chirurgie Maxillo-Faciale* 109(2008): 175-177.

33. Kanté, F (2005) Les Cancers De La Cavité Buccale : Point Sur Le Rôle De L'odontologiste Dans La Prise En Charge, In Département Odontologie, FMPOS. Université Cheikh Anta Diop De Dakar, Senegal.

34. Mantovani, Fiamma, Licio Collavin and Giannino Del Sal. "Mutant P53 as a Guardian of the Cancer Cell." *Cell Death Different* 26(2019): 199-212.

35. Zedan, Walid, Mohamed I Mourad, Sherin M Abd El-Aziz and Nagla M Salamaa, et al. "Cytogenetic Significance of Chromosome 17 Aberrations and P53 Gene Mutations as Prognostic Markers in Oral Squamous Cell Carcinoma." *Diag Pathol* 10(2015): 1-9.

36. Pessôa, Igor Andrade, Fabio P Estumano Da Silva, Nilson Praia Anselmo and Edivaldo Herculano C De Oliveira. "Alterations in TP53 Gene–Implications in Tumorigenesis. Process and Prognosis in Central Nervous System Cancer." *Tum Cent Nervous Sys Prim Second 2*(2014): 127-174.

37. Hafner, Antonina, Martha L. Bulyk, Ashwini Jambhekar and Galit Lahav. "The Multiple Mechanisms that Regulate P53 Activity and Cell Fate." *Nature Rev Mol Cell Biol* 20(2019): 199-210.

38. Shangary, Sanjeev and Shaomeng Wang. "Targeting the MDM2-P53 Interaction for Cancer Therapy." *Clin Cancer Res* 14(2008): 5318-5324.

39. Chen, Jiandong. "The Cell-Cycle Arrest and Apoptotic Functions of P53 in Tumor Initiation and Progression." *Cold Spring Harbor Perspect Med* 6(2016): A026104.

40. Ghahremani, M Farhang, Steven Goossens, David Nittner and Xavier Bisteau, et al. "P53 Promotes VEGF Expression and Angiogenesis in the Absence of an Intact P21-Rb Pathway." *Cell Death Different* 20(2013): 888-897.

41Rother, K, R Kirschner, K Sänger and L Böhlig, J, et al. "P53 Downregulates Expression of the G 1/S Cell Cycle Phosphatase Cdc25A." *Oncogene* 26(2007): 1949-1953.

42. Wang, Xin Wei, Qimin Zhan, Jill D Coursen and Mohammed A Khan, et al. "GADD45 Induction of a G2/M Cell Cycle Checkpoint." *Proceed National Acad Sci* 96(1999): 3706-3711.

43. Gibson, Christopher J and Matthew S Davids. "BCL-2 Antagonism to Target the Intrinsic Mitochondrial Pathway of Apoptosis." *Clin Cancer Res* 21(2015): 5021-5029.

44. Erster, Susan, Motohiro Mihara, Roger H Kim and Oleksi Petrenko, et al. "*In vivo* Mitochondrial P53 Translocation Triggers a Rapid First Wave of Cell Death in Response to DNA Damage that Can Precede P53 Target Gene Activation." *Mol Cellular Biol* 24(2004): 6728-6741.

45. Leibowitz, Brian and Jian Yu. "Mitochondrial Signaling in Cell Death via the BCL-2 Family." *Cancer Biol Therap* 9(2010): 417-422.

46. Qian, Yingjuan, And Xinbin Chen. "Senescence Regulation by The P53 Protein Family." *Cell Senescence* (2013): 37-61.

47. Lavin, MF and AN Gueven. "The Complexity of P53 Stabilization and Activation." *Cell Death Different* 13(2006): 941-950.

48. Maclaine, Nicola J and Ted R Hupp. "The Regulation of P53 by Phosphorylation: A Model for How Distinct Signals Integrate into the P53 Pathway." *Aging* 1(2009): 490.

49. He, Fan, Wade Borcherds, Tanjing Song and Xi Wei, et al. "Interaction between P53 N Terminus and Core Domain Regulates Specific and Nonspecific DNA Binding." *Proc National Acad Sci* 116(2019): 8859-8868.

50. Beckerman, Rachel, Kathryn Yoh, Melissa Mattia-Sansobrino and Andrew Zupnick, et al. "Lysines in the Tetramerization Domain of P53 Selectively Modulate G1 Arrest." *Cell Cycle* 15(2016): 1425-1438.

51. Jenkins, Lisa M Miller, Hiroshi Yamaguchi, Ryo Hayashi and Scott Cherry, J, et al. "Two Distinct Motifs within the P53 Transactivation Domain Bind to the Taz2 Domain of P300 and are Differentially Affected by Phosphorylation." *Biochem* 48(2009): 1244-1255.

52. Reed, Sara M and Dawn E Quelle. "P53 Acetylation: Regulation and Consequences." *Cancers* 7(2015): 30-69.

53. Kaypee, Stephanie, Smitha Asoka Sahadevan, Shilpa Patil and Piya Ghosh, et al. "Mutant and Wild-Type Tumor Suppressor P53 Induces P300 Autoacetylation." *Iscience* 4(2018): 260-272.

54. Comel, Anna, Giovanni Sorrentino, Valeria Capaci and Giannino Del Sal. "The Cytoplasmic Side of P53's Oncosuppressive Activities." *FEBS Letters* 588(2014): 2600-2609.

55. Green, Douglas R and Guido Kroemer. "Cytoplasmic Functions of the Tumour Suppressor P53." *Nature* 458(2009): 1127-1130.

56. Pietsch, E Christine, Stephen M Sykes, Steven B Mcmahon and Maureen E Murphy. "The P53 Family and Programmed Cell Death." *Oncogene* 27(2008): 6507-6521.

57. Warren, Chloe FA, Michelle W Wong-Brown and Nikola A Bowden. "BCL-2 Family Isoforms in Apoptosis and Cancer." *Cell Death Dis* 10(2019): 1-12.

58. Petros, Andrew M, Edward T Olejniczak and Stephen W Fesik. "Structural Biology of the Bcl-2 Family of Proteins." *Biochimica Et Biophysica Acta (BBA). Mol Cell Res* 1644(2004): 83-94.

59. Kruse, Jan-Philipp and Wei Gu. "MSL2 Promotes Mdm2-Independent Cytoplasmic Localization of P53." *J Biol Chem* 284(2009): 3250-3263.

60. Jiang, Peng, Wenjing Du, Klaus Heese and Mian Wu. "The Bad Guy Cooperates with Good Cop P53: Bad is Transcriptionally Up-Regulated by P53 and Forms a Bad/P53 Complex at the Mitochondria to Induce Apoptosis." *Mol Cellular Biol* 26(2006): 9071-9082.

61. Aubrey, Brandon J, Gemma L Kelly, Ana Janic and Marco J Herold, et al. "How Does P53 Induce Apoptosis and How Does this Relate to P53-Mediated Tumour Suppression?" *Cell Death Different* 25(2018): 104-113.

62. Moll, Ute M and Alex Zaika. "Nuclear and Mitochondrial Apoptotic Pathways of P53." *FEBS Letters* 493(2001): 65-69.

63. Elkholi, Rana, Thibaud T Renault, Madhavika N Serasinghe and Jerry E. Chipuk. "Putting the Pieces Together: How is the Mitochondrial Pathway of Apoptosis Regulated in Cancer and Chemotherapy?" *Cancer Metab* 2(2014): 1-15.

64. Toledo, Franck and Geoffrey M Wahl. "MDM2 and MDM4: P53 Regulators as Targets in Anticancer Therapy." *Int J Biochem Cell Biol* 39(2007): 1476-1482.

65. Fischer, M. "Census and Evaluation of P53 Target Genes." *Oncogene* 36(2017): 3943-3956.

66. Sanz, Gema, Madhurendra Singh, Sylvain Peuget and Galina Selivanova. "Inhibition of P53 Inhibitors: Progress, Challenges and Perspectives." *J Mol Cell Biol* 11(2019): 586-599.

67. Wallace, Maura, Erin Worrall, Susanne Pettersson and Ted R Hupp, et al. "Dual-Site Regulation of MDM2 E3-Ubiquitin Ligase Activity." *Mol Cell* 23(2006): 251-263.

68. Ferru, A, G Fromont, H Gibelin and J Guilhot, et al. "The Status of CDKN2A Alpha (P16 INK4A) and Beta (P14 ARF) Transcripts in Thyroid Tumour Progression." *British J Cancer* 95(2006): 1670-1677.

69. Haupt, Sue, Javier Octavio Mejía-Hernández, Reshma Vijayakumaran and Simon P Keam, et al. "The Long and the Short of It: The MDM4 Tail So Far." *J Mol Cell Biol* 11(2019): 231-244.

71. Li, Li, Binwei Deng, Guichun Xing and Yan Teng, et al. "PACT is a Negative Regulator of P53 and Essential for Cell Growth and Embryonic Development." *Proc National Acad Sci* 104(2007): 7951-7956.

72. Yang, Wensheng, David T Dicker, Jiandong Chen and Wafik S El-Deiry. "Carps Enhance P53 Turnover by Degrading 14-3-3σ and Stabilizing MDM2." *Cell Cycle* 7(2008): 670-682.

73. Moll, Ute M and Oleksi Petrenko. "The MDM2-P53 Interaction." *Mol Cancer Res* 1(2003): 1001-1008.

74. Olivier, Magali, Monica Hollstein and Pierre Hainaut. "TP53 Mutations in Human Cancers: Origins, Consequences, and Clinical Use." *Cold Spring Harbor Persp Biol* 2(2010): A001008.

75. Bouaoun, Liacine, Dmitriy Sonkin, Maude Ardin and Monica Hollstein, et al. "TP53 Variations in Human Cancers: New Lessons from the IARC TP53 Database and Genomics Data." *Human Mutat* 37(2016): 865-876.

76. Barnoud, Thibaut, Joshua LD Parris and Maureen E Murphy. "Common Genetic Variants in the TP53 Pathway and their Impact on Cancer." *J Mol Cell Biol* 11(2019): 578-585.

77. Scheckenbach, Kathrin, Oliver Lieven, Karl Götte and Ulrike Bockmühl, et al. "P53 Codon 72 Polymorphic Variants, Loss of Allele-Specific Transcription, and Human Papilloma Virus 16 And/Or 18 E6 Messenger RNA Expression in Squamous Cell Carcinomas of the Head and Neck." *Cancer Epidemiol Preven Biomarkers* 13(2004): 1805-1809.

78. Zhang, Yu, Lan Cao, Daniel Nguyen and Hua Lu. "TP53 Mutations in Epithelial Ovarian Cancer." *Translat Cancer Res* 5(2016): 650.

79. Olivos, David J and Lindsey D Mayo. "Emerging Non-Canonical Functions and Regulation by P53: P53 and Stemness." *Int J Mol Sci* 17(2016): 1982.

80. He, Hongtao, Jiangdong Ni and JUN Huang. "Molecular Mechanisms of Chemoresistance in Osteosarcoma." *Oncol Letters* 7(2014): 1352-1362.

81. Brooks, Christopher L and Wei Gu. "P53 Ubiquitination: MDM2 and Beyond." *Molecular Cell* 21, No. 3 (2006): 307-315.

82. Eymin, Béatrice, Sylvie Gazzeri, Christian Brambilla and Elisabeth Brambilla. "Mdm2 Overexpression And P14 ARF Inactivation Are Two Mutually Exclusive Events In Primary Human Lung Tumors." *Oncogene* 21(2002): 2750-2761.

83. Piette, Jacques, Henry Neel and Vincent Maréchal. "MDM2: Keeping P53 under Control." *Oncogene* 15(1997): 1001-1010.

84. Bond, Gareth L, Wenwei Hu, Elisabeth E Bond and Harlan Robins, S, et al. "A Single Nucleotide Polymorphism in the MDM2 Promoter Attenuates the P53 Tumor Suppressor Pathway and Accelerates Tumor Formation in Humans." *Cell* 119(2004): 591-602.

85. Zhao, Yan, Xiaoer Yang, Xiaojiao Hao and Xiaolin Pan, et al. "Common Variant on MDM2 Contributes to Endometrial Cancer Susceptibility: Evidence Based on 7 Studies." *Tumor Biol* 35(2014): 7555-7560.

86. Zhang, Jianxin, Yang Zhang and Zhenyu Zhang. "Association of Rs2279744 and Rs117039649 Promoter Polymorphism with the Risk of Gynecological Cancer: A Meta-Analysis of Case–Control Studies." *Medicine* 97(2018): 2-4.

87. Nayak, Surendra K, Gopal L Khatik, Rakesh Narang and Vikramdeep Monga, et al. "P53-MDM2 Interaction Inhibitors as Novel Nongenotoxic Anticancer Agents." *Curr Cancer Drug Targets* 18(2018): 749-772.

88. Melling, Nathaniel, Sonja Norrenbrock, Martina Kluth and Ronald Simon, et al. "P53 Overexpression is a Prognosticator of Poor Outcome in Esophageal Cancer." *Oncol Letters* 17(2019): 3826-3834.

89. Cogliano, Vincent James. "The IARC Monographs: A Resource for Precaution and Prevention." *Occup Environ Med* 64(2007): 572.

90. Lerman, Mark A, Soulafa Almazrooa, Neal Lindeman and Dimity Hall, et al. "HPV-16 in a Distinct Subset of Oral Epithelial Dysplasia." *Modern Pathol* 30(2017): 1646-1654.

91. Yeo-Teh, Nicole SL, Yoshiaki Ito and Sudhakar Jha. "High-Risk Human Papillomaviral Oncogenes E6 And E7 Target Key Cellular Pathways to Achieve Oncogenesis." *Int J Mol Sci* 19(2018): 1706.

92. Pinidis, Petros, Panagiotis Tsikouras, Georgios Iatrakis and Stefanos Zervoudis, et al. "Human Papilloma Virus' Life Cycle and Carcinogenesis." *Maedica* 11(2016): 48.

93. Munger, Karl and D Leanne Jones. "Human Papillomavirus Carcinogenesis: An Identity Crisis in the Retinoblastoma Tumor Suppressor Pathway." *J Virol* 89(2015): 4708-4711.

94. Giarrè, Marianna, Sandra Caldeira, Ilaria Malanchi and Francesca Ciccolini, et al. "Induction of Prb Degradation by the Human Papillomavirus Type 16 E7 Protein is Essential to Efficiently Overcome P16ink4a-Imposed G1 Cell Cycle Arrest." *J Virol* 75(2001): 4705-4712.

95. Lundberg, Ante S and Robert A Weinberg. "Functional Inactivation of the Retinoblastoma Protein Requires Sequential Modification by at least Two Distinct Cyclin-Cdk Complexes." *Mol Cellular Biol* 18(1998): 753-761.

96. Yim, Eun-Kyoung and Jong-Sup Park. "The Role of HPV E6 and E7 Oncoproteins in HPV-Associated Cervical Carcinogenesis." *Cancer Res Treatment: Official J Korean Cancer Assoc* 37(2005): 319.

97. Tomaić, Vjekoslav. "Functional Roles of E6 and E7 Oncoproteins in HPV-Induced Malignancies at Diverse Anatomical Sites." *Cancers* 8(2016): 95.

98. Thomas, Miranda, Paola Massimi, John Jenkins and Lawrence Banks. "HPV-18 E6 Mediated Inhibition of P53 DNA Binding Activity is Independent of E6 Induced Degradation." *Oncogene* 10(1995): 261-268.

99. Mantovani, Fiamma and Lawrence Banks. "The Human Papillomavirus E6 Protein and its Contribution to Malignant Progression." *Oncogene* 20(2001): 7874-7887.

100. Patel, Daksha, Shih-Min Huang, Laurel A Baglia and Dennis J Mccance. "The E6 Protein of Human Papillomavirus Type 16 Binds to And Inhibits Co-Activation by CBP and P300." *EMBO J* 18(1999): 5061-5072.

101. Kumar, Ajay, Yongtong Zhao, Gaoyuan Meng and Musheng Zeng, et al. "Human Papillomavirus Oncoprotein E6 Inactivates the Transcriptional Coactivator Human ADA3." *Mol Cellular Biol* 22(2002): 5801-5812.

102. White, Elizabeth A. "Manipulation of Epithelial Differentiation by HPV Oncoproteins." *Viruses* 11(2019): 369.

103. Yuan, Xiaotian, Catharina Larsson and Dawei Xu. "Mechanisms Underlying the Activation of TERT Transcription and Telomerase Activity in Human Cancer: Old Actors and New Players." *Oncogene* 38(2019): 6172-6183.

104. Hoppe-Seyler, Karin, Felicitas Bossler, Julia A Braun and Anja L Herrmann, et al. "The HPV E6/E7 Oncogenes: Key Factors for Viral Carcinogenesis and Therapeutic Targets." *Trends Microbiol* 26(2018): 158-168.

105. Vijayakumaran, Reshma, Kah Hin Tan, Panimaya Jeffreena Miranda and Sue Haupt, et al. "Regulation of Mutant P53 Protein Expression." *Front Oncol* 5(2015): 284.

106. Schulz-Heddergott, Ramona and Ute M Moll. "Gain-of-Function (GOF) Mutant P53 as Actionable Therapeutic Target." *Cancers* 10(2018): 188.

107. Mrakovcic, Maria and Leopold F Fröhlich. "P53-Mediated Molecular Control of Autophagy in Tumor Cells." *Biomolecules* 8(2018): 14.

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