Chapter

Insights of Cisplatin Resistance in Cervical Cancer: A Decision Making for Cellular Survival

Elizabeth Mahapatra, Salini Das, Souvick Biswas, Archismaan Ghosh, Debomita Sengupta, Madhumita Roy and Sutapa Mukherjee

Abstract

The clinical scenario of acquired cisplatin resistance is considered as a major impediment in cervical cancer treatment. Bulky drug-DNA adducts formed by cisplatin elicits *DNA damage response (DDR)* which either subsequently induces apoptosis in the cervical cancer cells or enables them to adapt with drug assault by invigorating pro-survival molecular cascades. When HPV infected cervical cancer cells encounter cisplatin, a complex molecular interaction between *deregulated tumor suppressors*, *DNA damage-repair enzymes*, and *prosurvival molecules* get initiated. Ambiguous molecular triggers allow cancer cells to cull apoptosis by opting for a survival fate. Overriding of the apoptotic cues by the pro-survival cues renders a *cisplatin resistant phenotype* in the tumor microenvironment. The present review undrapes the impact of deregulated signaling nexus formed due to crosstalk of the key molecules related to cell survival and apoptosis in orchestrating platinum resistance in cervical cancer.

Keywords: HPV, Cervical cancer, Cisplatin resistance, tumor suppressors, DNA-damage repair, prosurvival signaling

1. Introduction

Cervical cancer, one of the widespread gynecological cancers, accounts for the maximum deaths amongst women across the globe. As per GLOBOCAN 2018, cervical cancer is helmed as the fourth leading cause of mortality and morbidity in women after breast and ovarian cancers [1]. As revealed from the data collated by World Health Organization (WHO) in 2013, over 85% of the cervical cancer cases had surfaced mostly from developing countries with a poor socio-economic backdrop [2]. Women, owing to lack of awareness, often arrive for seeking medical help when the malignant growth of cervix has attained advancement [3].

Infections with a special class of oncogenic DNA viruses called *Human Papilloma Viruses (HPVs)*, hailing from the viral family *Papillomaviridae,* are highly accredited for the malignant transformation of cervix. Principally, HPVs are sexually transmitted [4]. On the basis of its carcinogenic potentials, HPVs can be categorized as –*(i) low-risk HPVs(lr-HPVs)* like *HPV 6, 11, 42, 43* and *44*, and *(ii) high-risk*

HPVs (hr-HPVs) like *HPV 16, 18, 31, 33, 34, 35, 39, 45, 51, 52, 56, 58, 59, 66, 68* and *70* [4, 5]. Persistent and prevalent infections with hr-HPVs contribute in development of cervical cancer alongside other cancers such as the cancer of vagina, vulva, penis, anus, head and neck. HPV infections may also give rise to anogenital warts and recurrent respiratory papillomatosis [5, 6]. Besides HPVs, several other risk factors have been implicated in the etiology of cervical cancer. These mainly include long term use of oral contraceptive [7], smoking [8] and infections with *Chlamydia trachomatis* [9].

Cervical cancer progresses through stages of *mild dysplasia*, *moderate dysplasia* and *severe dysplasia* to finally aggravate into *carcinoma in situ* and *invasive cancer* **stages** [10]. The International Federation of Gynecology and Obstetrics (FIGO) classify these developmental grades of *cervical intraepithelial neoplasia (CIN)* into various stages [11, 12]. Rise in the global disease burden is majorly due to *treatment failure* and *disease recurrence* [13]. The advent of vaccination has allowed for pre-infection protection [14]. However, lack of cost-effectiveness has limited its use to only a certain section of the society, particularly in low income countries like India. The therapeutic modality therefore, is skewed to *chemotherapy* and *radiotherapy*. Stage specific treatment regime is followed for treating cervical cancer [15]. As per FIGO conventions, *Stage IIB-IVA* denotes invasive stages where treatment is ensued in forms of conventional modes of chemotherapy and radiotherapy [11]. Traditionally, chemotherapy involves use of *platinum ligated drugs* like *cisplatin (cis-diamminedichloroplatinum; CDDP)* [16, 17]. Cisplatin in combination with other chemotherapeutics is often employed for treating invasive stages [16]. Patients are often subjected to treatment with cisplatin as a *'radiosensitizer'* prior to radiotherapeutic intervention in the *Concurrent Chemoradiotherapy (CCRT)* regime [16]. Accordingly, cisplatin is the *'drug of choice'* to oncologists for treating cervical cancer irrespective of its different stages.

In the process of HPV mediated cervical carcinogenesis several molecular changes are incited which remodels the metabolic profiles of the cervix [18]. HPV induced metabolic paradigm shift bestows the cells with therapy evasive properties. Consequentially, neoplastic cells emerge as highly dynamic and evolving entities [19]. On encountering drugs, the rewired signaling cascades of the tumor cells residing in the cervix get triggered. These eventuate in increased metabolism of chemotherapeutics like cisplatin, finally catering in reduced intracellular drug accumulation [20], paving a way for acquired cisplatin resistance. This chapter majorly discusses the mechanisms underlying the acquirement of resistance towards cisplatin as a result of deregulated activities of tumor suppressors, DNA damage repair enzymes and prosurvival molecules, mediated due to HPV infections.

2. HPVs: Integral to etiology of cervical cancer

HPVs are relatively small non-enveloped viruses with a diameter of 55 nm. It has a double stranded circular DNA genome which is 8 kb long and is enclosed within an *icosahedral capsid* composed of *72 capsomers* [21, 22]. Functionally, the HPV genome is regionalized into-i) a non-coding regulatory region called the *long control region (LCR)* or the *upper regulatory region (URR)*, ii) an early region which houses *E1, E2, E4, E5, E6* and *E7 genes*, and (iii) a late region which is made up of late expressing genes such as *L1* and *L2* [23]. LCR regulates the process of viral DNA replication via controlling the transcription of Open Reading Frames (ORFs). The lately transcribed proteins L1 and L2 are the structural proteins of the viral capsid. The early genes are dictators of viral replication, transcription, assembly and

oncogenesis. Particularly, E6 and E7 are oncogenic and they degrade the cell cycle regulators like p53 and pRb to eventuate in cervical carcinoma [23].

These miniscule infectious agents access the cervical epithelial layer through crevices or microabrasions that generally forms due to mechanical shock or injury. Following entry, HPVs integrate their genome with that of the host to initiate the process of malignant transformation of the cervix (**Figure 1**). The carcinogenesis of cervical epithelium begins with the onset of viral lifecycle which initiates with viral entry into basal cell layer of the epithelium [24]. The basal cell layer of the cervical epidermis enables multiplication and replication of the virus by providing them with a suitable microenvironment. Molecules expressed by the basal cells such as *integrins (α6β1, α6β4), heparan sulphate,* and *proteoglycans* are chemoattractants for HPVs [25, 26]. No sooner does the virus enter the basal cells the viral replication starts but owing to poor copy number the duplication of viral DNA becomes non-reproductive. However, as the infection load spreads into the parabasal and intermediate layers, which are majorly comprised of semi-differentiated cells or terminally differentiated keratinocytes, DNA copy number increases and productive viral replication commences [27]. Meanwhile, the process of cervical carcinogenesis gets driven as the virus multiplies and sustains itself in the host system.

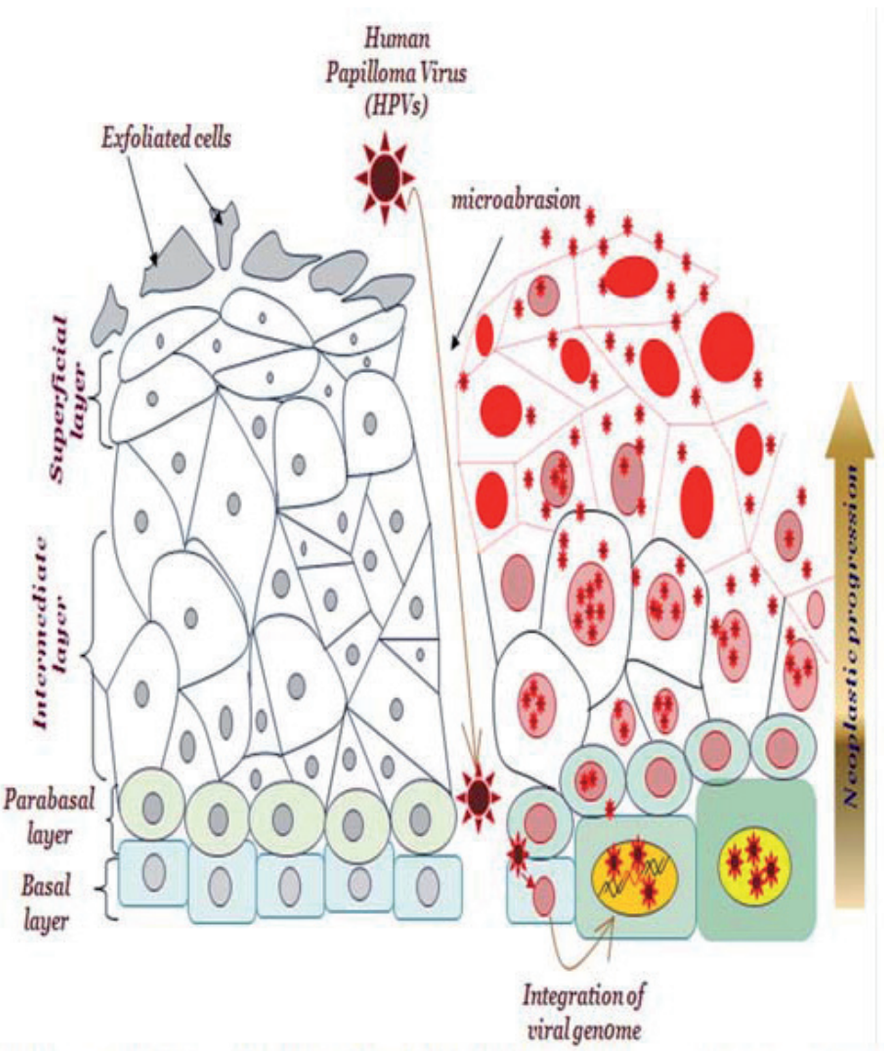

Figure 1.
Host cell hijacking by HPVs. HPVs enter the cervical epithelium through micro abrasions to finally integrate its genome into the DNA of the basal cells to promote loss of genomic integrity. Carcinogenesis is accompanied by viral multiplication in the cervical epithelium.

3. Concomitant molecular changes during cervical carcinogenesis upon HPV infection: an escape route to cisplatin therapy

3.1 Onslaught of HPVs deregulates tumor suppressors

HPV mediated neoplastic transformation of cervix kick starts with the abridgement of tumor suppressor functions. An array of experimentations conducted in *in vitro* and *in vivo* models have successfully established the immortalizing capacities of E6 and E7 viral gene products; ensued via degradation of cell cycle controllers like p53 and pRb [28, 29]. E6 promotes ubiquitin mediated degradation of p53 in assistance with *E6-associated protein (E6AP),* a homolog for *MDM-2* expressed in cells infected with hr-HPVs [30, 31]. As per reports, E6AP very efficaciously reduces the half-life of p53 in HPV infected cervical carcinoma cells, precisely as *MDM-2,* the conventional p53 inhibitor [32]. The guardian of the genome, p53, controls and coordinates the major genetic players involved in *cell cycle arrest* [33]. On top of this, p53 choreographs *DNA damage repair*, and *apoptotic events* [34]. As the episome formation is successfully accomplished by the virus, *DNA damage response (DDR)* is triggered. Absence of functional p53 allows the cervical cells to skip *G1-arrest* [35]. These functions which are central to cell survival and death get violated in the HPV immortalized cervical cells owing to reduced p53 levels. A higher E6 level is inversely proportional to cellular p53 levels [36]. Contrarily, the oncoprotein E7 binds with hypophosphorylated retinoblastoma protein (pRb); releasing the growth promoter E2F from the Rb-E2F complex. E2F translocate to the nucleus to enable expression of genes that drive the infected cells through S-phase of the cell cycle [37]. Cumulative loss of function of both of these tumor suppressors enables the infected cells to progress through G1 and S phases even with genetic errors. Shortfall of repair processes ultimately paves a way for genomic disintegrity to prevail; mediating neoplastic growth. Recent reports suggest that E6 and E7 intervene into the tumor suppressor activity by recruiting methyl groups on their promoter region [38, 39]. These oncogenic viral proteins also methylate *cyclinA1* promoter and deregulate cell cycle progression to mediate tumorigenesis [40].

3.2 Cisplatin insensitivity: a consequence of HPV driven deregulation of tumor suppressors

HPV immortalized cervical cancer cells, especially those at the invasive stages, are subjected to treatment with platinum-ligated drugs like cisplatin. Following its cellular entry, cisplatin transforms into a very strong electrophilic species by hydrolytic activation. Such an activated drug generates an electrophilic attack on cellular nucleophiles like DNA and results in formation of bulky drug-DNA adducts which are beyond repair [41]. Inevitably, cancer cells harboring complex cisplatin modified DNA will be arrested in the G1 phase of the cell cycle particularly; due to generation of DDR response and subsequent activation of p53. Generation of cisplatin-DNA adducts activates *Ataxia Telangiectasia Mutated (ATM) vis a vis ATM- and Rad3-related (ATR)* proteins; culminating into phosphorylation at serine 15 residue and stabilization of p53 [42]. ATR along with various other proteins form an axis of ATR/CHK2/p53/p21; which ultimately mediates apoptosis [43–46]. Therefore, p53 functional status is central to mediation of cisplatin cytotoxicity. This was first demonstrated in a study conducted with small-cell lung cancer cells where adenoviral delivery of p53 sensitized them to cisplatin and resulted in apoptosis [47]. A similar study carried out with ovarian cancer cells, reflected cisplatin induced apoptotic death upon adenovirus mediated delivery of p53 [48]. This tumor suppressor takes up multi-modal routes to facilitate cisplatin-induced cell death. Specifically, p53 increases the susceptibility of cancer cells towards cisplatin by degrading *FLIP*

(FLICE-like inhibitory protein) and by binding with the anti-apoptotic mediator *Bcl-xl* to inactivate its function [49, 50]. It further activates other tumor suppressors like *phosphatase and tensin homolog (PTEN)* to shut down PI3K/Akt pathway [51]. Sometimes, hyperinduction of p53 can disable *AMP-kinase (AMPK)* [52]**;** thereby forcing the cancer cells to succumb to cisplatin cytotoxicity**.**

In HPV infected cells, this entire p53 dictated cell-death inducing pathway is compromised owing to functional absence of the tumor suppressors. E6 mediated prior degradation of p53 in cervical cancer cells, unprecedentedly makes them tolerant to the drug. It has been experimentally demonstrated that p53-Bax signaling axis elicited cisplatin induced apoptosis in cervical cancer cells [53]. Even in multiple clinical studies, patients retaining wild-type p53 have been found to respond better to platinum based chemotherapy [54]. Expression patterns of p53 are predictive of success rate of cisplatin treatment in adeno-carcinoma of the uterine cervix [55]. A very recent report has envisaged the contribution of p53 in restoring cisplatin sensitivity in CDDP resistant cervical cancer cells, particularly during combination treatment with doxorubicin [56].

3.3 HPV mediated impairment of DNA repair machinery: an auto-corrector of cisplatin-DNA adducts in cervical cancer

Early genes E1 and E2 drive the process of viral replication in the host by acting as an *origin recognition factor (ORF)* and by imparting helicase [57]. Mostly, the viral replication is dependent upon host cell factors, especially those which are involved in DNA damage repair pathways [58]. Not only HPVs, but other viruses like hepatitis C virus (HCV), Epstein–Barr virus (EBV) and human cytomegalovirus (HCMV) concocts the components of DNA damage repair pathway to survive in the host cells [59, 60]. HPV, while attempting to integrate its genome into the host cell's DNA, incurs DNA damage that eventually evokes DDR.

The host cell has various repair pathways working in a well-knitted fashion to clear off irrelevant mistakes that may arise during the process of DNA replication. Some of these include- *base excision repair (BER), nucleotide excision repair (NER)*, *mismatch repair (MMR)*, *homologous recombination (HR)* and *non-homologous end joining (NHEJ)*. This machinery actively functions to correct errors incorporated in DNA during replication while the cell is gradually traversing through different stages of the cell cycle. In instances of assault to DNA architecture hurled as single strands or double strand breaks, recruitment of ATM or ATR proteins occur at the site of damage. Protein complex comprised of *MRN (MRE11-RAD50-NBS1)* and *Tip60* recognizes and recruits these proteins to the site of damage. ATM phosphorylates a series of downstream effectors which includes *CHK2* and the *histone H2A (H2AX)* to begin with the repair process. For correcting double strand breaks, ATM switches over to HR pathway wherein the process of repair is executed by *breast cancer 1/2 (BRCA1, BRCA2), RAD51* and *Partner and Localizer of BRCA2 (PALB2)* molecules [61–63]. In all cases, p53 is found to be the sole dictator of the process as it allows repair to occur by arresting cells with erroneous DNA.

Cervical cancer cells infected with hr-HPVs exhibit an upregulation of *ATM pathway*. Throughout the viral lifecycle, ATM response is constitutively kept activated owing to phosphorylation of its downstream effectors namely CHK2, NBS1 and BRCA1 [62, 63]. Oncogenic early protein E7 along with higher levels of E1 keeps ATM activity always at a hike. E1, the ORF while imparting helicase action, forms pseudo-viral replication origins which initiate the process of DDR by stalling replication forks [64, 65]. In high-risk HPV infected cervical cells, the candidates of ATM pathway accumulates in the nucleus [66]. The differentiated and undifferentiated cells of the cervical epithelium packed with viral genomes also exhibit an upregulation of homologous recombination factors [67, 68]. Studies with pharmacological inhibitors

have further delineated that ATM remains activated all throughout the viral life-cycle. It aids in amplification of viral genome within the differentiated squamous cells [69].

In addition to ATM, HPVs also activate ATR pathway. In HPV infected cells considerably higher levels of *ATR-interacting protein* or *ATRIP* and *DNA topoisomerase 2-binding protein 1* or *TopBP1* were noted [70]. Multiple studies have shown that in cells infected with HPVs has remarkably higher levels of total and phosphorylated forms of ATR as well as its downstream effectors, CHK1 [70]. ATM and ATR pathways provide the virus with an access to the host replicative machinery. E7 destroys Rb along with other related tumor suppressors such as p107 and p130, comprising the family of pocket proteins to control the transit of the cells from G1 phase to S-phase. Moreover, the released E2F translocates to the nucleus and lead to translational activation of the responsive gene, some of which are candidates of DNA damage repair pathways [70].

3.4 HPV seized DNA repair machineries of cervical cancer cells encourages acquired Cisplatin resistance

Upregulated activities of DNA damage repair enzymes empower cervical cancer cells to quickly repair the cisplatin-DNA adducts. Cisplatin generates intrastrand cross-links in the DNA to primarily activate *nucleotide excision repair (NER) system* [71]. It has been proposed that NER prevents apoptosis in cisplatin treated cells via activation of the members of the ATM pathway followed by its recruitment to the site of damage in the DNA. In cervical cancer cells, already activated ATM, immediately starts chewing away drug-DNA adducts; leading to resistance. Over 20 proteins hailing from the *excision repair cross-complementation group 1 (ERCC1)* partake in this process of clearing away the cisplatin-DNA conjugates [72]. At the 5′ site of the bulky cisplatin-DNA lesions, ERCC1 gets co-recruited with ERCC4 for excising away DNA-adducts [73]. In HCA-1R, a cisplatin resistant cervical cancer cell line, an upregulation of ERCC1 expression is recognized. Poor cisplatin responders with locally advanced cervical squamous cell carcinoma exhibit elevated levels of ERCC1 [74]. ERCC1, therefore, is considered as a prognostic biomarker for assessing the survival rate of patients receiving chemotherapy or CCRT [75, 76]. Another evolutionarily conserved DNA repair pathway is *Mismatch Repair (MMR)* pathway which is highly implicated in cisplatin resistance of cervical cancer cells [77]. Amongst the MMR proteins, *MutS homolog 2 (MSH2)* has been identified as a contributor of cisplatin resistance in cervical cancer cells [78]. *Post-meiotic segregation 2 (PMS2),* another key member of the MMR system is found to be negatively correlated with cervical cisplatin resistance [79–82].

3.5 HPV mediated upregulation of prosurvival signaling cascades: Another contributor of cisplatin resistance in cervical cancer

'Abortive infection' often referred to active HPV infection, induces the genesis of both benign and malignant neoplasms of the cervix [83]. The oncogenic viral early gene products initiates cervical carcinogenesis by interacting with the crucial prosurvival signaling cascades of the host cell [84]. Besides abrogating p53 and pRb functions, HPVs opportunistically modulate four important cellular survival pathways by interacting with their upstream effectors such as *growth factor receptor, notch receptor, Ras* along with *phosphatidylinositol 3-kinase subunit C (PI3KCA)* gene which is second messenger activating Akt kinases [85, 86].

3.5.1 Activation of PI3K/Akt signaling

PI3K, particularly was found to be amplified and overtly activated in HPV-induced cervical cancers [87, 88]. The activation of MAPK/ERK in turn alters

transcription of multiple genes that are important for regulation of cell-cycle progression and cell proliferation. Thus, activation of PI3K begets in Akt activation via phosphorylation of the protein in most of the HPV infected cancers. HPV16 E6 activates receptor protein tyrosine kinases (RTKs) viz. epidermal growth factor receptor (EGFR), insulin receptor beta and insulin-like growth factor receptor beta; lying upstream of the PI3K/Akt pathway [89]. Activation of Akt results into a series of changes in downstream targets. Akt, furthermore can phosphorylate E6 to promote its ability to interact with 14–3-3σ, an important protein required for carcinogenic progression [90]. A strong association between HPV and surged c-myc expression has been evidenced [91–93]. Reportedly, interaction between E6 and c-myc activates the enzymatic function of *telomerase* [94, 95]. In a clinical study, thirty nine out of 46 cervical cancer specimens evinced phosphorylation of Akt at serine 473 [96]. Akt activation was obtained in about, forty-eight percent of stage Ib2-IIb cervical cancer patients. HPV infection destabilizes the host genome for which mutations may be incurred in PIK3CA gene. Some mutations may be activator mutations accounting in Akt hyperactivation in cervical as well as many other HPV-induced cancers [95]. Oncogenic mutations and translational amplification of PIK3CA gene, switch on PI3K/Akt signaling invigoratingly; driving HPV mediated tumorigenesis.

3.5.2 Activation of mTOR signaling

mTOR kinase functions as a cellular rheostat that amalgamates cellular signaling pathways after sensing growth factor, starvation and energy status. Recently, it has been reported that Akt/mTOR activation occurs immediately after exposure to HPV16 pseudovirions [96]. mTOR activation is frequently observed in cervical squamous cell carcinoma, as well as in most HPV positive head and neck squamous cell carcinomas (HNSCC), and oropharyngeal cancers (OPSCC) [93, 97]. HPV oncoproteins E7 and E6 can chronologically activate AKT through pRb binding and subsequently stimulate mTOR in its complex 1 (mTORC1). These upregulated prosurvival signaling molecules lead to a shift in metabolic paradigm of the cancer cells. When subjected to cisplatin treatment, the HPV infected cervical cancer cells start to metabolize the drug faster than usual. This result in rapid drug efflux and eventually lessens intracellular cisplatin levels to orchestrate cisplatin resistance. Therefore, most cisplatin resistant cervical cancer cells are often characterized by the presence of greater levels of cisplatin efflux pumps [98, 99]. Of late, Li et al. showed in their study that in cisplatin resistant cervical cancer cells with upregulated PI3K/Akt pathway, espouses surged levels of *Lysosome-associated protein transmembrane 4β-35 (LAPTM4B-35)* which is another cisplatin exporter [100, 101].

3.5.3 Activation of the Wnt pathway

Nuclear accumulation of β-catenin due to activation of the canonical Wnt/β-Catenin pathway leads to transcriptional activation of a plethora of proliferative genes. This is highly characteristic to HPV16-positive invasive cancers as well as early dysplastic lesions [102, 103]. This phenomenon of nuclear accumulation of β-catenin positively correlates with progression of cervical cancer [104]. Accordingly, β-catenin was found in higher frequencies within the nucleus of cervical cancer cell line SiHa (bearing integrated HPV16) and HeLa (bearing integrated HPV18) [105]. Lichtig et al. proposed that HPV16 E6 could mechanistically activate Wnt/β-catenin pathway in a p53 independent fashion [106]. β-catenin signaling pathway exhibited a regulatory activity over acquired resistance to cisplatin via upregulation of Bcl-xl [107]. Cisplatin resistance got promoted in neoplasia due to shut down of GSK-3β owing to activation of Wnt/β-catenin signaling [108].

3.5.4 Activation of the Notch pathway

Cellular prosurvival juxtracrine signaling axis involving TGFβ/Notch1 is found to be exhilarated in invasive cervical cancer [109]. As the cervical lesions progressed from intraepithelial lesions III to microinvasive carcinoma, Notch1 translocated from the cytoplasm to the nucleus for ease of function [110]. HPV E6 has been identified as an activator of Notch protein in multiple cervical cancer cell lines [111]. Upregulated activities of notch protein induce stemness in cervical cancer cells, thereby enabling them to evade cisplatin driven cytotoxicity. Inhibition of Notch1was found to revert epithelial to mesenchymal transition (EMT); restoring cisplatin sensitivity [112].

3.5.5 Telomerase activation

Viral oncoprotein E6 escalates human telomerase activity by upregulating its catalytic subunit hTERT or telomerase reverse transcriptase [113, 114]. E6 on being

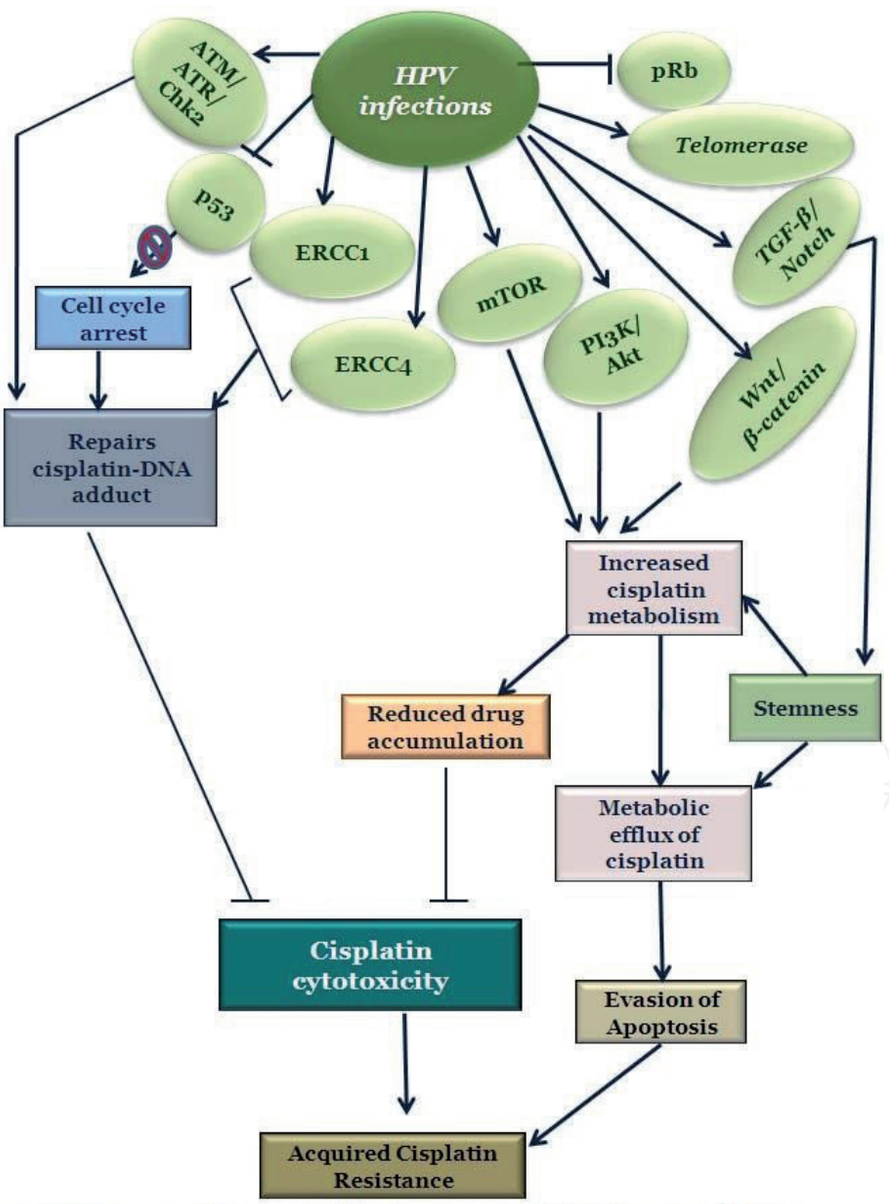

Figure 2.
Concomitant molecular changes induced by HPV contribute in cisplatin resistance in cervical cancer. The viral oncoproteins, particularly E6 and E7 deregulate the crucial molecules involved in cellular metabolism, cell cycle progression, DNA damage repair differentiation, survival, and apoptotic death. These changes provide the cervical cancer cells to evade cytotoxic cell death upon treatment with cisplatin; leading to acquirement of resistance.

aided by E6AP binds to the hTERT promoter region to increase its transcriptional activity [112]. NFX1–123, an mRNA interacting protein gets positively regulated by E6, to maintain higher telomerase expression [115]. E6 upon binding to hTERT protein increases telomerase activity via posttranscriptional modifications [116]. Telomerase reverse transcriptase was reported to promote cisplatin resistance by suppressing apoptosis.

Orchestration of HPV induced signaling nexus in promoting cisplatin resistance in cervical cancer is well depicted in **Figure 2**.

4. Perspective insights

As the virus hijacks the host system, it flips the molecular dynamics according to its own survival benefit. As discussed in this review, loss of function of tumor suppressors, magnified activities of DNA repair enzymes and constitutional activation prosurvival signaling cascades in the HPV infected cervix, make the situation precarious. The conundrum of drug resistance that arises as a result of these existent changes, stymies therapy. Tracking these prior change can aid in planning conventional therapeutic regimes. Thus, these molecules can act as valuable prognostic biomarker before administration of cisplatin based chemotherapy to cervical cancer patients.

Acknowledgements

The authors are indebted to the Director, Chittaranjan National Cancer Institute, Kolkata for encouraging the idea of the manuscript. The authors are grateful to Ministry of Health & Family Welfare, Govt of India for financial support to undertake the research.

Conflict of interest

Authors declare no conflict of interest.

Author details

Elizabeth Mahapatra, Salini Das, Souvick Biswas, Archismaan Ghosh, Debomita Sengupta, Madhumita Roy and Sutapa Mukherjee*
Department of Environmental Carcinogenesis and Toxicology, Chittaranjan National Cancer Institute, Kolkata, India

*Address all correspondence to: sutapa_c_in@yahoo.com

References

[1] Arbyn M, Weiderpass E, Bruni L, de Sanjosé S, Saraiya M, Ferlay J, Bray F. Estimates of incidence and mortality of cervical cancer in 2018: a worldwide analysis. *Lancet Glob Health*. 2020; 8(2): e191-e203.

[2] Bosch FX, Broker TR, Forman D, Moscicki AB, Gillison ML, Doorbar J, Stern PL, Stanley M, Arbyn M, Poljak M, Cuzick J, Castle PE, Schiller JT, Markowitz LE, Fisher WA, Canfell K, Denny LA, Franco EL, Steben M, Kane MA, Schiffman M, Meijer CJ, Sankaranarayanan R, Castellsagué X, Kim JJ, Brotons M, Alemany L, Albero G, Diaz M, de Sanjosé S. Comprehensive control of human papillomavirus infections and related diseases. *Vaccine*. 2013; 31 (7): H1-31.

[3] India State-Level Disease Burden Initiative Cancer Collaborators. The burden of cancers and their variations across the states of India: the Global Burden of Disease Study 1990-2016. *Lancet Oncol*. 2018; 19(10): 1289-1306.

[4] Day PM, Schelhaas M. Concepts of papillomavirus entry into host cells. *Curr Opin Virol*. 2014; 4: 24-31.

[5] De Brot L, Pellegrini B, Moretti ST, Carraro DM, Soares FA, Rocha RM, Baiocchi G, da Cunha IW, de Andrade VP. Infections with multiple high-risk HPV types are associated with high-grade and persistent low-grade intraepithelial lesions of the cervix. *Cancer Cytopathol.* 2017; 125(2): 138-143.

[6] Fortes HR, von Ranke FM, Escuissato DL, Araujo Neto CA, Zanetti G, Hochhegger B, Souza CA, Marchiori E. Recurrent respiratory papillomatosis: A state-of-the-art review. *Respir Med*. 2017; 126: 116-121.

[7] Gierisch JM, Coeytaux RR, Urrutia RP, Havrilesky LJ, Moorman PG, Lowery WJ, Dinan M, McBroom AJ, Hasselblad V, Sanders GD, Myers ER. Oral contraceptive use and risk of breast, cervical, colorectal, and endometrial cancers: a systematic review. *Cancer Epidemiol Biomarkers Prev*. 2013; 22(11): 1931-43.

[8] Puleo GE, Borger TN, Montgomery D, Rivera Rivera JN, Burris JL. A Qualitative Study of Smoking-Related Causal Attributions and Risk Perceptions in Cervical Cancer Survivors. *Psychooncology*. 2020; 29(3): 500-506.

[9] Zhu H, Shen Z, Luo H, Zhang W, Zhu X. *Chlamydia trachomatis* Infection-Associated Risk of Cervical Cancer: A Meta-Analysis. *Medicine(Baltimore)*. 2016; 95(13):e3077.

[10] Jain MA, Limaiem F. Cervical Intraepithelial Squamous Cell Lesion. *Treasure Island (FL): StatPearls Publishing*; 2021.

[11] Bhatla N, Berek JS, Cuello Fredes M, Denny LA, Grenman S, Karunaratne K, Kehoe ST, Konishi I, Olawaiye AB, Prat J, Sankaranarayanan R, Brierley J, Mutch D, Querleu D, Cibula D, Quinn M, Botha H, Sigurd L, Rice L, Ryu HS, Ngan H, Mäenpää J, Andrijono A, Purwoto G, Maheshwari A, Bafna UD, Plante M, Natarajan J. Revised FIGO staging for carcinoma of the cervix uteri. *Int J Gynaecol Obstet*. 2019; 145(1): 129-135.

[12] Ayhan A, Aslan K, Bulut AN, Akilli H, Öz M, Haberal A, Meydanli MM. Is the revised 2018 FIGO staging system for cervical cancer more prognostic than the 2009 FIGO staging system for women previously staged as IB disease? *Eur J Obstet Gynecol Reprod Biol.* 2019; 240: 209-214.

[13] Zhu H, Luo H, Zhang W, Shen Z, Hu X, Zhu X. Molecular mechanisms of cisplatin resistance in cervical

cancer. *Drug Des Devel Ther.* 2016 ; 10: 1885-95.

[14] Sankaranarayanan R, Basu P, Kaur P, Bhaskar R, Singh GB, Denzongpa P, Grover RK, Sebastian P, Saikia T, Oswal K, Kanodia R, Dsouza A, Mehrotra R, Rath GK, Jaggi V, Kashyap S, Kataria I, Hariprasad R, Sasieni P, Bhatla N, Rajaraman P, Trimble EL, Swaminathan S, Purushotham A. Current status of human papillomavirus vaccination in India's cervical cancer prevention efforts. *Lancet Oncol*. 2019; 20(11): e637-e644.

[15] Tsikouras P, Zervoudis S, Manav B, Tomara E, Iatrakis G, Romanidis C, Bothou A, Galazios G. Cervical cancer: screening, diagnosis and staging. *J BUON*. 2016; 21(2): 320-5.

[16] Rogers L, Siu SS, Luesley D, Bryant A, Dickinson HO. Radiotherapy and chemoradiation after surgery for early cervical cancer. *Cochrane Database Syst Rev.* 2012; 5(5): CD007583.

[17] Xiang M, Kidd EA. Benefit of Cisplatin with Definitive Radiotherapy in Older Women with Cervical Cancer. *J Natl Compr Canc Netw*. 2019; 17(8): 969-975.

[18] Ding Z, Yang X, Chernenko G, Tang SC, Pater A. Human papillomavirus type 16-immortalized endocervical cells selected for resistance to cisplatin are malignantly transformed and have a multidrug resistance phenotype. *Int J Cancer*. 2000; 87(6): 818-23.

[19] Navin N, Kendall J, Troge J, Andrews P, Rodgers L, McIndoo J, Cook K, Stepansky A, Levy D, Esposito D, Muthuswamy L, Krasnitz A, McCombie WR, Hicks J, Wigler M. Tumour evolution inferred by single-cell sequencing. *Nature*. 2011; 472(7341): 90-4.

[20] Martinho O, Pinto F, Granja S, Miranda-Gonçalves V, Moreira MA, Ribeiro LF, di Loreto C, Rosner MR, Longatto-Filho A, Reis RM. RKIP inhibition in cervical cancer is associated with higher tumor aggressive behavior and resistance to cisplatin therapy. *PLoS One*. 2013; 8(3): e59104.

[21] Favre M. Structural polypeptides of rabbit, bovine, and human papillomaviruses. *J Virol*. 1975; 15(5): 1239-1247.

[22] Baker TS, Newcomb WW, Olson NH, et al. Structures of bovine and human papillomaviruses. Analysis by cryoelectron microscopy and three dimensional image reconstruction. *Biophys J.* 1991; 60(6): 1445-1456.

[23] Burd EM. Human papillomavirus and cervical cancer. *Clin Microbiol Rev*. 2003; 16(1): 1-17.

[24] Doorbar J, Egawa N, Griffin H, Kranjec C, Murakami I. Human papillomavirus molecular biology and disease association. *Rev Med Virol*. 2015; 25(1): 2-23.

[25] Evander M, Frazer IH, Payne E, Qiy YM, Hengst K, McMillan NA. Identification of the alpha6 integrin as a candidate receptor for papillomaviruses. *J Virol*. 1997; 71(3): 2449-2456.

[26] Giroglou T, Florin L, Schäfer F, Streeck RE, Sapp M. Human papillomavirus infection requires cell surface heparan sulfate. *J Virol*. 2001; 75(3): 1565-70.

[27] Flores ER, Allen-Hoffmann BL, Lee D, Sattler CA, Lambert PF. Establishment of the human papillomavirus type 16 (HPV-16) life cycle in an immortalized human foreskin keratinocyte cell line. *Virology.* 1999; 262(2): 344-54.

[28] Munger K, Howley PM: Human papillomavirus immortalization and transformation functions. *Virus Res*. 2002; 89:213-228.

[29] Howley PM, Scheffner M, Munger K: Oncoproteins encoded by the cancer-associated papillomavirus target the products of retinoblastoma and p53 tumor suppressor genes. *Quant Biol.* 1991; 56: 159-155.

[30] Henstermann A, Linares LK, Ciechanover A: Complete switch from Mdm2 to human papillomavirus E6-mediated degradation of p53 in cervical cancer cells. *Proc Natl Acad Sci USA.* 2001; 98: 1218-1223.

[31] Mantovani F, Banks L: The human papillomavirus E6 protein and its contribution to malignant progression. *Oncogene*. 2001; 20: 7874-7887.

[32] Werness BA, Levine AJ, Howley PM: Association of human papillomavirus types 16 and 18 E6 proteins with p53. *Science*. 1990; 248: 76-79.

[33] Di Leonardo A, Linke SP, Clarkin K, Wahl GM. DNA damage triggers a prolonged p53-dependent G1 arrest and long-term induction of Cip1 in normal human fibroblasts. *Genes Dev*. 1994; 8: 2540-2551.

[34] Smith ML, Chen IT, Zhan Q, O'Connor PM, Fornace AJ Jr. Involvement of the p53 tumor suppressor in repair of u.v.-type DNA damage. *Oncogene.* 1995; 10: 1053-1059.

[35] Thomas M, Pim D, Banks L. The role of the E6-p53 interaction in the molecular pathogenesis of HPV. *Oncogene.* 1999; 18(53): 7690-7700.

[36] Hwang ES, Riese DJ 2nd, Settleman J, Nilson LA, Honig J, Flynn S, DiMaio D: Inhibition of cervical carcinoma cell line proliferation by the introduction of a bovine papillomavirus regulatory gene. *Virology.* 1993; 67: 3720-3729.

[37] Syrj€anen SM, Syrj€anen KJ. New concepts on the role of human papillomavirus in cell cycle regulation. *Ann Med.* 1999; 31(3): 175-187.

[38] Sen P, Ganguly P, Ganguly N. Modulation of DNA methylation by human papillomavirus E6 and E7 oncoproteins in cervical cancer. *Oncol Lett*. 2018;15: 11-22.

[39] Yin F, Wang N, Wang S, Yu F, Sun X, Yu X, Luo B, Zhao C , Wang Y. HPV16 oncogenes E6 or/and E7 may influence the methylation status of RASSFIA gene promoter region in cervical cancer cell line HT-3. *Oncol Rep*. 2017; 37: 2324-2334.

[40] Yanatatsaneejit P, Mutirangura A, Kitkumthorn N. Human papillomavirus's physical state and cyclin A1 promoter methylation in cervical cancer. *Int J Gyneco.* 2011; 21: 902-906.

[41] Eastman A. The formation, isolation and characterization of DNA adducts produced by anticancer platinum complexes. *Pharmacology and Therapeutics*. 1987; 34 (2): 155-166.

[42] Efeyan A, Serrano M. p53: guardian of the genome and policeman of the oncogenes. *Cell Cycle*. 2007; 6(9): 1006-1010.

[43] Pabla N., Huang S., Mi QS, Daniel R, Dong Z. ATRChk2 signaling in p53 activation and DNA damage response during cisplatin-induced apoptosis. *Journal of Biological Chemistry. 2008,* 283(10): 6572-6583.

[44] Kondo S, Barna BP, Kondo Y, Tanaka Y, Casey G, Liu J, Morimura T, Kaakaji R, Peterson JW, Werbel B, Barnett GH. WAF1/CIP1 increases the susceptibility of p53 non-functional malignant glioma cells to cisplatin-induced apoptosis. *Oncogene*. 1996; 13(6): 1279-85.

[45] Zamble DB, Jacks T, Lippard SJ. p53-Dependent and -independent responses to cisplatin in mouse testicular teratocarcinoma cells. *Proc Natl Acad Sci U S A*. 1998; 95(11): 6163-8.

[46] Yang X, Fraser M, Moll UM, Basak A, Tsang BK. Akt-mediated cisplatin resistance in ovarian cancer: modulation of p53 action on caspase-dependent mitochondrial death pathway. *Cancer Res.* 2006; 66(6): 3126-36.

[47] Fujiwara T, Grimm EA, Mukhopadhyay T, Zhang WW, Owen-Schaub LB, Roth JA. Induction of chemosensitivity in human lung cancer cells in vivo by adenovirus-mediated transfer of the wild-type p53 gene. *Cancer Res*. 1994; 54(9): 2287-91.

[48] Kanamori Y, Kigawa J, Minagawa Y, Irie T, Oishi T, Shimada M, Takahashi M, Nakamura T, Sato K, Terakawa N. A newly developed adenovirus-mediated transfer of a wild-type p53 gene increases sensitivity to cis-diamminedichloroplatinum (II) in p53-deleted ovarian cancer cells. *Eur J Cancer*. 1998; 34(11): 1802-6.

[49] Persons DL, Yazlovitskaya EM, Pelling JC. Effect of extracellular signal-regulated kinase on p53 accumulation in response to cisplatin. *J Biol Chem*. 2000; 275(46): 35778-85.

[50] Abedini MR, Muller EJ, Bergeron R, Gray DA, Tsang BK. Akt promotes chemoresistance in human ovarian cancer cells by modulating cisplatin-induced, p53-dependent ubiquitination of FLICE-like inhibitory protein. *Oncogene*. 2010; 29(1): 11-25.

[51] Kutuk O, Arisan ED, Tezil T, Shoshan MC, Basaga H. Cisplatin overcomes Bcl-2-mediated resistance to apoptosis via preferential engagement of Bak: critical role of Noxa-mediated lipid peroxidation. *Carcinogenesis.* 2009; 30(9): 1517-27.

[52] Yan X, Fraser M, Qiu Q, Tsang BK. Over-expression of PTEN sensitizes human ovarian cancer cells to cisplatin-induced apoptosis in a p53-dependent manner. *Gynecol Oncol*. 2006; 102(2): 348-55.

[53] Sultana H, Kigawa J, Kanamori Y, Itamochi H, Oishi T, Sato S, Kamazawa S, Ohwada M, Suzuki M, Terakawa N. Chemosensitivity and p53-Bax pathway-mediated apoptosis in patients with uterine cervical cancer. *Ann Oncol*. 2003; 14(2): 214-9.

[54] Garzetti GG, Ciavattini A, Provinciali M, Di Stefano G, Lucarini G, Goteri G, Biagini G. Expression of p53 and apoptosis of tumor cells in locally advanced cervical carcinoma after cisplatin based neoadjuvant chemotherapy. *Anticancer Res*. 1996; 16(5B): 3229-34.

[55] Saito T, Takehara M, Tanaka R, Lee R, Horie M, Wataba K, Ito E, Kudo R. Correlation between responsiveness of neoadjuvant chemotherapy and apoptosis-associated proteins for cervical adenocarcinoma. *Gynecol Oncol*. 2004; 92(1): 284-92.

[56] Yi SA, Kim GW, Yoo J, Han JW, Kwon SH. HP1γ Sensitizes Cervical Cancer Cells to Cisplatin through the Suppression of UBE2L3. *Int J Mol Sci*. 2020; 21(17): 5976.

[57] Frattini, MG, Laimins, LA. Binding of the human papillomavirus E1 origin-recognition protein is regulated through complex formation with the E2 enhancer-binding protein. *Proc. Natl Acad. Sci. USA*. 1994; 91: 12398-12402.

[58] Sedman J, Stenlund A. Co-operative interaction between the initiator E1 and the transcriptional activator E2 is required for replicator specific DNA replication of bovine papillomavirus in vivo and in vitro. *EMBO J*. 1995; 14: 6218-6228.

[59] Stracker TH, Carson CT, Weitzman MD, Adenovirus oncoproteins inactivate the Mre11-Rad50-NBS1DNA repair complex. *Nature*. 2002; 418: 348-352.

[60] Machida K, McNamara G, Cheng KT, Huang J, Wang, CH,

Comai L, Ou JH, Lai MM. Hepatitis C virus inhibits DNA damage repair through reactive oxygen and nitrogen species and by interfering with the ATM-NBS1/Mre11/Rad50 DNA repair pathway in monocytes and hepatocytes. *J. Immunol.* 2010; 185: 6985-6998.

[61] Hollingworth R, Grand RJ. Modulation of DNA damage and repair pathways by human tumour viruses. *Viruses*. 2015; 7(5):2542-91.

[62] Sy SM, Huen MS, Chen J. PALB2 is an integral component of the BRCA complex required for homologous recombination repair. *Proc Natl Acad Sci U S A*. 2009; 106 (17):7155-60.

[63] Helena JM, Joubert AM, Grobbelaar S, Nolte EM, Nel M, Pepper MS, Coetzee M, Mercier AE. Deoxyribonucleic Acid Damage and Repair: Capitalizing on Our Understanding of the Mechanisms of Maintaining Genomic Integrity for Therapeutic Purposes. *Int J Mol Sci*. 2018; 19(4):1148.

[64] Moody CA, Laimins LA. Human papillomaviruses activate the ATM DNA damage pathway for viral genome amplification upon differentiation. *PLoS Pathog*. 2009; 5.

[65] Sakakibara N, Mitra R, McBride AA. The papillomavirus E1 helicase activates a cellular DNA damage response in viral replication foci. *J. Virol*. 2011; 85: 8981-8995.

[66] Kadaja, M, Isok-Paas, H, Laos T, Ustav, E, Ustav M. Mechanism of genomic instability in cells infected with the high-risk human papillomaviruses. *PLoS Pathog*. 2009; 5.

[67] Gillespie KA, Mehta KP, Laimins LA, Moody CA. Human papillomaviruses recruit cellular DNA repair and homologous recombination factors to viral replication centers. *J. Virol*. 2012; 86: 9520-9526.

[68] McKinney CC, Hussmann KL, McBride AA. The role of the DNA damage response throughout the papillomavirus life cycle. *Viruses.* 2015; 7: 2450-2469.

[69] Hong S, Dutta A, Laimins LA. The acetyltransferase Tip60 is a critical regulator of the differentiation-dependent amplification of human papillomaviruses. *J Virol*. 2015; 89(8): 4668-75.

[70] Bristol ML, Das D, Morgan IM. Why Human Papillomaviruses Activate the DNA Damage Response (DDR) and How Cellular and Viral Replication Persists in the Presence of DDR Signaling. *Viruses.* 2017; 9(10): 268.

[71] Reinson T.; Toots, M.; Kadaja, M.; Pipitch, R.; Allik, M.; Ustav, E.; Ustav, M. Engagement of the ATR-dependent DNA damage response at the human papillomavirus 18 replication centers during the initial amplification. *J. Virol.* 2013; 87: 951-964.

[72] Hong, S.; Cheng, S.; Iovane, A.; Laimins, L.A. STAT-5 regulates transcription of the topoisomerase II beta-binding protein 1 (TopBP1) gene to activate the ATR pathway and promote human papillomavirus replication. *Am. Soc. Microbiol*. 2015; 6.

[73] Boyer, S.N.; Wazer, D.E.; Band, V. E7 protein of human papilloma virus-16 induces degradation of retinoblastoma protein through the ubiquitin-proteasome pathway. *Cancer Res*. 1996; 56: 4620-4624.

[74] Welsh C, Day R, McGurk C, Masters JRW, Wood RD, K¨oberle B. Reduced levels of XPA, ERCC1 and XPF DNA repair proteins in testis tumor cell lines. *International Journal of Cancer.* 2004; 110(3): 352-361.

[75] Martin LP, Hamilton TC, Schilder RJ. Platinum resistance: the role of DNA repair pathways. *Clin Cancer Res*. 2008; 14(5): 1291-1295.

[76] Galluzzi L, Senovilla L, Vitale I, et al. Molecular mechanisms of cisplatin resistance. Oncogene. 2012;31(15):1869-1883.

[77] Torii Y, Kato R, Minami Y, Hasegawa K, Fujii T, Udagawa Y. ERCC1 expression and chemosensitivity in uterine cervical adenocarcinoma cells. *Anticancer Res.* 2014; 34(1): 107-115.

[78] Park JS, Jeon EK, Chun SH, et al. ERCC1 (excision repair cross-complementation group 1) expression as a predictor for response of neoadjuvant chemotherapy for FIGO stage 2B uterine cervix cancer. *Gynecol Oncol*. 2011; 120(2): 275-279.

[79] Hasegawa K, Kato R, Torii Y, Ichikawa R, Oe S, Udagawa Y. The relationship between ERCC1 expression and clinical outcome in patients with FIGO stage I to stage II uterine cervical adenocarcinoma. *Int J Gynecol Cancer*. 2011; 21(8): 1479-1485.

[80] Guthrie OW, Li-Korotky HS, Durrant JD, Balaban C. Cisplatin induces cytoplasmic to nuclear translocation of nucleotide excision repair factors among spiral ganglion neurons. *Hearing Research*. 2008 ; 239(2): 79-91.

[81] Zhang Y, Shu YM, Wang SF, Da BH, Wang ZH, Li HB. Stabilization of mismatch repair gene PMS2 by glycogen synthase kinase 3beta is implicated in the treatment of cervical carcinoma. *BMC Cancer*. 2010; 10: 58.

[82] Doorbar J. The papillomavirus life cycle. *J Clin Virol*. 2005; 32 (1): S7-15.

[83] Burd EM. Human papillomavirus and cervical cancer. *Clin Microbiol Rev*. 2003; 16(1): 1-17.

[84] Keysar SB, Astling DP, Anderson RT, Vogler BW, Bowles DW, Morton JJ, Paylor JJ, Glogowska MJ, Le PN, Eagles-Soukup JR, Kako SL, Takimoto SM, Sehrt DB, Umpierrez A, Pittman MA, Macfadden SM, Helber RM, Peterson S, Hausman DF, Said S, Leem TH, Goddard JA, Arcaroli JJ, Messersmith WA, Robinson WA, Hirsch FR, Varella-Garcia M, Raben D, Wang XJ, Song JI, Tan AC, Jimeno A. A patient tumor transplant model of squamous cell cancer identifies PI3K inhibitors as candidate therapeutics in defined molecular bins. *Mol Oncol*. 2013; 7(4): 776-90.

[85] Lechner M, Frampton GM, Fenton T, Feber A, Palmer G, Jay A, Pillay N, Forster M, Cronin MT, Lipson D, Miller VA, Brennan TA, Henderson S, Vaz F, O'Flynn P, Kalavrezos N, Yelensky R, Beck S, Stephens PJ, Boshoff C. Targeted next-generation sequencing of head and neck squamous cell carcinoma identifies novel genetic alterations in HPV+ and HPV- tumors. *Genome Med*. 2013; 5(5): 49.

[86] Wu J, Chen J, Zhang L, Masci PP, Zhao KN. Four major factors regulate phosphatidylinositol 3-kinasesignaling pathway in cancers induced by infection of human Papillomaviruses. *Curr Med Chem*. 2014; 21 (26): 3057-69.

[87] Lee CM, Fuhrman CB, Planelles V, Peltier MR, Gaffney DK, Soisson AP, Dodson MK, Tolley HD, Green CL, Zempolich KA. Phosphatidylinositol 3-kinase inhibition by LY294002 radiosensitizes human cervical cancer cell lines. *Clin Cancer Res*. 2006; 12(1): 250-6.

[88] Choi SK, Hong YO, Lee WM, Kim EK, Joo JE, Kim DW, Lee H. Overexpression of PI3K-p110α in the progression of uterine cervical neoplasia and its correlation with pAkt and DJ-1. *Eur J Gynaecol Oncol*. 2015; 36(4):389-93.

[89] Spangle JM, Munger K. The HPV16 E6 oncoprotein causes prolonged

receptor protein tyrosine kinase signaling and enhances internalization of phosphorylated receptor species. *PLoS Pathogens*. 2013; 9: e1003237.

[90] McFarlane M, Graham SV. Human papillomavirus regulation of SR proteins. *Biochem Soc Trans.* 2010; 38(4): 1116-21.

[91] Boon SS, Banks L. High-risk human papillomavirus E6 oncoproteins interact with 14-3-3ζ in a PDZ binding motif dependent manner. *Journal of Virology.* 2013; 87: 1586-1595.

[92] Hurlin P, Foley K, Ayer D, Eisenman R, Hanahan D, Arbeit J. Regulation of Myc and Mad during epidermal differentiation and HPV-associated tumorigenesis. *Oncogene*. 1995; 11: 2487-2501.

[93] Dellas A, Schultheiss E, Leivas M, Moch H, Torhorst J. Association of p27Kip1, cyclin E and c-myc expression with progression and prognosis in HPV-positive cervical neoplasms. *Anticancer Research*. 1997; 18: 3991-3998.

[94] DeFilippis RA, Goodwin EC, Wu L, DiMaio D. Endogenous human papillomavirus E6 and E7 proteins differentially regulate proliferation, senescence, and apoptosis in HeLa cervical carcinoma cells. *Journal of Virology*. 2003; 77: 1551-1563.

[95] Veldman T, Liu X, Yuan H, Schlegel R. Human papillomavirus E6 and Myc proteins associate in vivo and bind to and cooperatively activate the telomerase reverse transcriptase promoter. *Proceedings of the National Academy of Sciences*. 2003; 100: 8211-8216.

[96] Menges CW, Baglia LA, Lapoint R, McCance DJ. Human papillomavirus type 16 E7 up-regulates AKT activity through the retinoblastoma protein. *Cancer Res*. 2006; 66(11):5555-9.

[97] Surviladze Z, Sterk RT, Deharo SA, Ozbun MA. Cellular entry of human papillomavirus type 16 involves activation of the phosphatidylinositol 3-Kinase/Akt/mTOR pathway and inhibition of autophagy. *J Virol*. 2013; 87(5):2508-17.

[98] Sewell A, Brown B, Biktasova A, Mills GB, Lu Y, Tyson DR, et al. Reverse-phase protein array profiling of oropharyngeal cancer and significance of PIK3CA mutations in HPV-associated head and neck cancer. *Clin Cancer Res.* 2014;20(9):2300-11.

[99] Roy M, Mukherjee S. Reversal of resistance towards cisplatin by curcumin in cervical cancer cells. *Asian Pac J Cancer Prev*. 2014;15(3): 1403-1410.

[100] Meng F, Tan S, Liu T, Song H, Lou G. Predictive significance of combined LAPTM4B and VEGF expression in patients with cervical cancer. *Tumour Biol*. 2015.

[101] Li L, Wei XH, Pan YP, et al. LAPTM4B: a novel cancer-associated gene motivates multidrug resistance through efflux and activating PI3K/AKT signaling. *Oncogene*. 2010; 29(43):5785-5795.

[102] Pereira-Suárez AL, Meraz MA, Lizano M, Estrada-Chávez C, Hernández F, Olivera P, Pérez E, Padilla P, Yaniv M, Thierry F, García-Carrancá A. Frequent alterations of the beta-catenin protein in cancer of the uterine cervix. *Tumour Biol.* 2002; 23(1): 45-53.

[103] Fadare O, Reddy H, Wang J, Hileeto D, Schwartz PE, Zheng W. E-cadherin and β-catenin expression in early stage cervical carcinoma: a tissue microarray study of 147 cases. *World Journal of Surgical Oncology.* 2005; 3: 38.

[104] Shinohara A, Yokoyama Y, Wan X, Takahashi Y, Mori Y, Takami T,

Shimokawa K, Tamaya T. Cytoplasmic/nuclear expression without mutation of exon 3 of the beta-catenin gene is frequent in the development of the neoplasm of the uterine cervix. *Gynecol Oncol.* 2001; 82(3): 450-5.

[105] Rampias T, Boutati E, Pectasides E, Sasaki C, Kountourakis P, Weinberger P, Psyrri A. Activation of Wnt signaling pathway by human papillomavirus E6 and E7 oncogenes in HPV16-positive oropharyngeal squamous carcinoma cells. *Mol Cancer Res*. 2010; 8(3): 433-43.

[106] Lichtig H, Gilboa DA, Jackman A, Gonen P, Levav-Cohen Y, Haupt Y, Sherman L. HPV16 E6 augments Wnt signaling in an E6AP-dependent manner. *Virology*. 2010; 396(1): 47-58.

[107] Zhang J, Liu J, Li H, Wang J. β-Catenin signaling pathway regulates cisplatin resistance in lung adenocarcinoma cells by upregulating Bcl-xl. *Mol Med Rep.* 2016; 13(3): 2543-2551.

[108] Zhong Z, Virshup DM. Wnt Signaling and Drug Resistance in Cancer. *Mol Pharmacol.* 2020; 97(2): 72-89.

[109] Zagouras P, Stifani S, Blaumueller CM, Carcangiu ML, Artavanis-Tsakonas S. Alterations in Notch signaling in neoplastic lesions of the human cervix. *Proceedings of the National Academy of Sciences*. 1995; 92: 6414-6418

[110] Daniel B, Rangarajan A, Mukherjee G, Vallikad E, Krishna S. The link between integration and expression of human papillomavirus type 16 genomes and cellular changes in the evolution of cervical intraepithelial neoplastic lesions. *Journal of General Virology.* 1997; 78: 1095-1101.

[111] Zhang Y, Koneva LA, Virani S, Arthur AE, Virani A, Hall PB, Warden CD, Carey TE, Chepeha DB, Prince ME, McHugh JB, Wolf GT, Rozek LS, Sartor MA. Subtypes of HPV-Positive Head and Neck Cancers Are Associated with HPV Characteristics, Copy Number Alterations, PIK3CA Mutation, and Pathway Signatures. *Clin Cancer Res*. 2016; 22(18): 4735-45.

[112] Zeng D, Liang YK, Xiao YS, Wei XL, Lin HY, Wu Y, Bai JW, Chen M, Zhang GJ. Inhibition of Notch1 reverses EMT and chemoresistance to cisplatin via direct downregulation of MCAM in triple-negative breast cancer cells. *Int J Cancer*. 2020; 147(2): 490-504.

[113] Klingelhutz AJ, Foster SA, McDougall JK. Telomerase activation by the E6 gene product of human papillomavirus type 16. *Nature*. 1996; 380(6569): 79-82.

[114] Veldman T, Horikawa I, Barrett JC, Schlegel R. Transcriptional activation of the telomerase hTERT gene by human papillomavirus type 16 E6 oncoprotein. *Journal of Virology*. 2001; 75: 4467-4472.

[115] Vliet-Gregg PA, Hamilton JR, Katzenellenbogen RA. NFX1-123 and human papillomavirus 16E6 increase notch expression in keratinocytes. *Journal of Virology.* 2013; 87: 13741-13750.

[116] Liu X, Dakic A, Zhang Y, Dai Y, Chen R, Schlegel R. HPV E6 protein interacts physically and functionally with the cellular telomerase complex. *Proc Natl Acad Sci U S A*. 2009; 106(44): 18780-5.