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Drug Re-purposing to Defeat the Complex Adaptive Network of HPV-derived Cancer

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Abstract

Three decades of basic research have largely elucidated the oncogenic mechanisms of human papilloma virus (HPV). HPV protein E5 achieves a takedown of antigen presentation to evade immune evasion while also impairing the ubiquitin turnover of EGFR. HPV E6 and E7 causes turnover of key tumor suppressor genes, p53 and PTPN13, and Rb1 and PTPN14, respectively. The signaling pathway consequences and resulting transcriptional reorganization that results in malignant behavior is discussed regarding the complex, self-perpetuating network of HPV. The potential utility of network-targeting combination therapy by re-purposing rimantidine, withaferin A, and curcumin to rescue the tumor suppressor proteins and re-establish immune recognition is discussed as a strategy to achieve deactivation of the malignant network that leads to collapse of the disease and reversal of therapeutic resistance. Investigation of this re-purposing regimen to block hypoxia by achieving cell cycle arrest could permit the use of lower doses of radiation that have potential to enhance treatment efficacy and survival while also decreasing the long-term side effects of radiotherapy.

Keywords: HPV • E5 • E6 • E7 • Drug re-purposing • Rimantidine • Withaferin A • And curcumin • Network-targeting combination therapy

Introduction

Viral infections are responsible for 15 to 20% of human cancers [1]. One of the most notorious oncoviruses, Human Papilloma Virus (HPV) causes more than 650,000 cases of these cancers, including those below the belt, i.e., the uterine cervix, anus, vagina, and penis, as well as in the oropharynx with potentially fatal outcomes for as many as one-third to one-half of patients [2]. For HPV, the mechanisms or oncogenesis mediated by the viral proteins E5, E6, and E7 have been clearly delineated. Inevitably, signaling pathway dysregulation leads to transcriptional reorganization that drives a complex and relentless disease network. On the other hand, the detailed understanding of the HPV-related mechanisms has led to the possibility of defeating the key drivers of malignancy and overcoming therapeutic failure. This review discusses the potential use of re-purposed medicine and plant-derived agents to achieve collapse of the HPV network and the potential utility for developing more effective and less toxic therapy in the future.

Viral oncogenesis

The immune system fails to eradicate HPV-infected cells. To some extent the basis for this failure has been related to unique polymorphisms in Human Leukopcyte Antigen (HLA) proteins needed for MHC2 function compromise antigen presentation and impair the immune system's ability to eliminate cancer, constituting an hereditary predisposition [3,4]. However, even PD-L1 immune checkpoint targeting with pembrolizumab generates only marginal benefits in survival limited to patients less than 65 years of age, with intact PD-L1 expression, and no metastatic disease [5]. Not surprisingly, the virus also mediates takedown of the immune response. HPV E5 channelizes membranes to cause collapse of the proton (H+) gradient used by lysosome to achieve proteolysis that is required for antigen loading into the MHC reading frame [6,7] and interferes with migration of the MHC1 from the endoplasmic reticulum to the Golgi and plasma membrane [8]. Cancers expressing high levels of HPV E5 are entirely resistant to anti-PD-L1 immunotherapy and exhibit substantially worse survival. Concomitantly, HPV E6 interferes with the phosphorylation of the transcription factor interferon releasing factor-3 (IRF3) at serine-396 leading to impairment of interferon-ß release which augments T cell response [9]. Additionally, the transcriptional consequences that follow from signaling pathway dysregulation including, MYC, STAT3, and HIF1A culminate in a profoundly immune-evasive tumor microenvironment that antagonizes T cell activation and function.

HPV E5 also inhibits c-CBL, thus disrupting the mechanism that leads to EGFR ubiquitination and proteasomal turnover [10]. The consequences of HPV E5 for lysosomal function also impedes the turnover of proteins whose stability and half-life is determined by lysosomal turnover [11]. Thus, HPV causes EGFR accumulation in the plasma membrane and enhanced activation downstream pathways that drive the malignant phenotype.

HPV E6 is famously known for causing ubiquitination and turnover of p53, one of the cell's key tumor suppressors that regulate transcription to control proliferation, the cell cycle G2/M checkpoint during which replication errors are resolved, and triggers apoptosis when genomic integrity is compromised beyond repair [12]. The takedown of p53 results in blockade of apoptosis and genomic instability, including the accumulation of chromosomal copy number aberrations. HPV E6 also promotes turnover of PTPN13, a key phosphatase that regulates ß catenin, UPAR, PIK3R1 activation, and NFKB signaling to promote cancer progression through activation of numerous transcription factors that propel malignant behaviour [13-15].

HPV E7 is best known for taking down Retinoblastoma-1 (Rb1) by accelerating its ubiquitination and proteasomal turnover [16]. The canonical effect of causing E2F1 activation leads to broad transcriptional activation, i.e., including FOXM1, MYC, SOX2, ZEB1, responsible for uncontrolled proliferation, upregulation of DNA repair Foxhead box M1 (FOXM1, MYC) [17,18] and the cancer stem cell phenotype (SOX2, ZEB1) [19-21] which make the cancer intrinsically therapy-resistant and responsible for tumor cell repopulation.

Non-canonical effects of Rb1 include inhibition of SKP2, [22-24] a member

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of the ubiquitin ligase complex SCF^{SKP2} which targets p21 and p27, crucial brakes regulating the G1/S checkpoint of the cell cycle. Loss of Rb1 results in the ubiquitin-mediated turnover of p21 and p27 leading to uncontrolled replication. Rb1 also regulates EZH2 [25,26] a crucial histone methylase of H3K27, such that loss of Rb1 leads to hypermethylation and gene silencing that leads to tumor suppressor gene and differentiation gene silencing. Additionally, E7 promotes the takedown of another phosphatase, PTPN14, responsible to preventing YAP1 translocation to the nucleus [27] where it activates MYC, survivin, STAT3, ß-catenin, AREG, and other drivers of the malignant phenotype [28,29]. A summary of signaling pathway consequences for HPV E5, E6 and E7 is listed in Table 1.

The HPV cancer network

Rb1, p53, PTPN13, and PTPN14 turnover activates a network of Transcription Factors (TF) that function as master regulators that determine the regulatory logic of the cell, its gene expression, and malignant cell fate (Figure 1). The pattern of TF activation determines the cell's functional organization by which each TF activates hundreds to thousands of genes whose proteins conduct the business of generating hallmark behaviours of cancer, e.g., proliferation, apoptosis blockade, angiogenesis, immune evasion, replicative immortality, etc. In turn, these TF have secondary network effects by stimulating each other's transcription, inducing activation of target proteins, or altering ubiquitin turnover to enhance oncogene stability or limit tumor suppressor stability. For example, E2F1 becomes liberated by loss of Rb1 and leads to activation of FOXM1, MYC, and SOX2 gene expression. In turn these lead to the activation of HIF1A and STAT3 expression. As a result of remarkable interconnectedness, network effects exhibit convergence, redundancy, reciprocal stimulation, and feed forward activation resulting in a set of vicious cycles that leads to an autonomous and self-perpetuating activation. As the latent capacity for malignant behaviour exists in every cell, the activated HPV network crosses a tipping point whereupon the possibility of malignant behaviour is triggered by the activation of an amplifying and self-reinforcing transcriptional network.

Network-Targeting Combination Therapy (NTCT)

While drugs for transcription factor targeting constitute an unmet need in cancer therapy, rimantadine, withaferin A (WA) derived from *Withania somnifera*, commonly known as Indian ginseng or ashwagandha, and curcumin derived from *Curcuma longa* are capable of targeting HPV E5, E6, and E7. Rimantidine and the sister agent amantadine were originally developed as a prophylactic drug for influenza the 1960's and subsequently abandoned for relative lack of efficacy against influenza, later they were

Table 1. Signaling pathway consequences of HPV oncoproteins.

HPV Protien	Pathway
E5	Lysosome_H^+↓ → TAP1 → Proteolysis of peptides → MHC1 → Antigen_presentation → Immune_Evasion MHC1↓ → Antigen presentation → Immune_Evasion c-CBL↓ → EGFR-Ub → Proteasomal_turnover Lysosome_H^+↓ → EGFR↓ → [MAPK → MYC, PI3K →[HIF1A, SOX2], PKC, STAT3] → Cancer_progression
E6	IRF3_S396-398_Phos↓ → IFN-ß → Immune_Evasion p53↓ (proteasomal turnover) → [apoptosis, G2/M checkpoint, genomic integrity,] PTPN13↓ → UPAR↓ → [Invasion, metastases] PTPN13↓ → ß-catenin → Cancer_progression PTPN13↓ → PIK3R1↓ → PI3K↓ → AKT → [FOXO3A↓, p21↓, MTOR, NFKB, MDM2, BCL2, SOX2, HIF1A, etc.] → Cancer_progression PTPN13↓ → NFKB↓ → [CCND2, MYC, PTGS2, IL6, etc.] → Cancer_progression
E7	Rb1↓ → E2F1↓ → [FOXM1, MYC, SOX2, ZEB1] → Cancer_progression Rb1↓ → EZH2↓ → [MYC, YAP1]↓ → Cancer_progression Rb1↓ → SKP2↓ → [p21,p27]↓ → G1/S↓ → Proliferation PTPN14↓ → YAP1↓ → [MYC, BIRC5 → STAT3, ß-catenin, HIF1A] → Cancer_progression

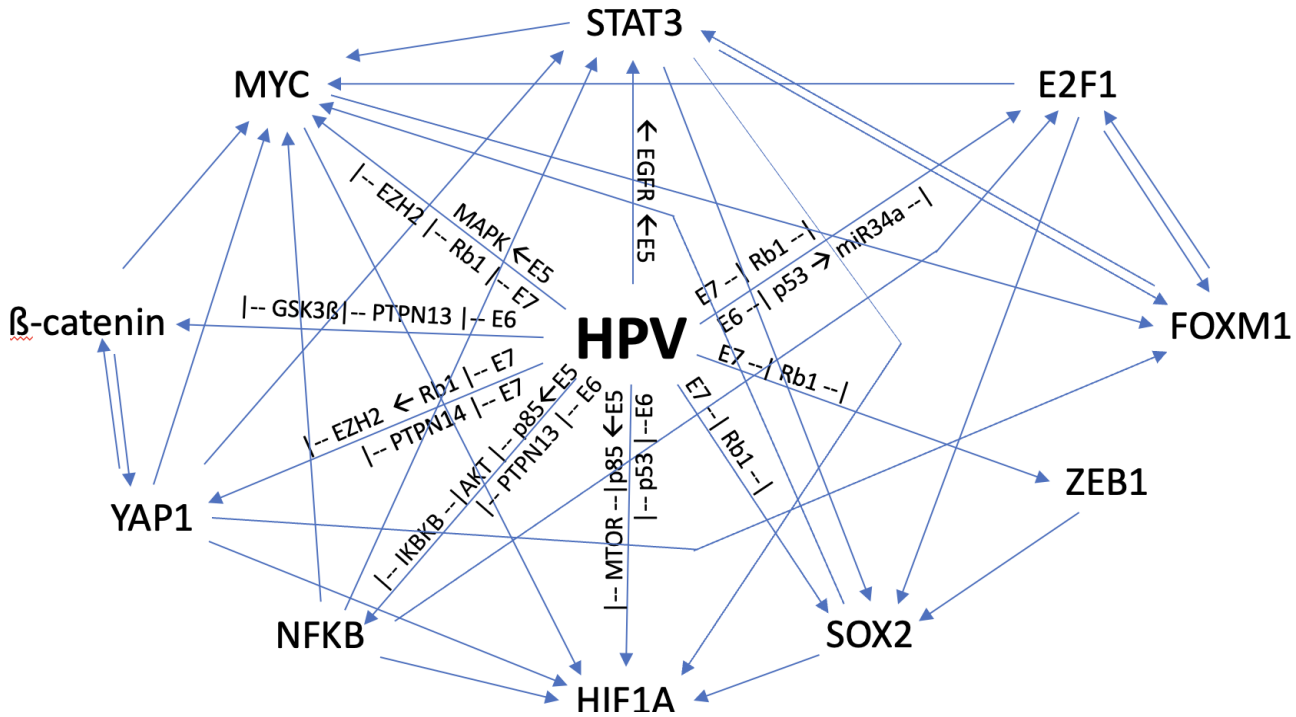

Figure 1. HPV oncogenic network. Signaling pathway consequences of HPV proteins E5, E65, and E7 activate key transcription factors that function as master regulators of the malignant phenotype.

adopted for Parkinson Disease management as NMDA receptor antagonist. Remarkably rimantadine inhibits HPV E5 and has been shown to reverse the deleterious effect on antigen presentation [7]. Though the IC50 of rimantadine is 100-150 μM and the drug only achieves a Cmax of 17 μM, intra-lysosomal accumulation provides tissue concentrations 48.2 to 386 μM capable of inhibiting E5 at ordinary clinical doses [30]. In this case the acidic milieu of the lysosome concentrates the drug, thus surpassing the concentration needed to inhibit E5. WA downregulates expression of HPV E6 and E7 viral proteins and restores expression Rb1 and p53 tumor suppressor's proteins. As a result of p53 accumulation, increased levels of p21, G 2 /M cell cycle arrest, decreased levels of STAT3 and activated STAT3 phosphorylation at tyrosine_705 and serine_727 are observed. Animal models in athymic nude mice experiments revealed reduction of 70% of the tumor volume [31]. A variety of other wide-ranging pleiotropic antitumor effects are also attributed to WA [32]. While the literature related to Cmax of WA is not persuasive that it can function like a drug, investigators have shown that as little as 1,100 mg per day of WA is capable of inducing alteration of mRNA levels for a wide variety of genes, thus providing plausibility for clinical utility [33].

Perhaps better known, curcumin suppresses also suppresses E6 and E7 albeit by another mechanism. In this case, E6 and E7 expression are upregulated by the transcription factor AP-1. Curcumin inhibits AP-1 and thus interferes with E6 and E7 transcription [34]. Additionally, curcumin inhibits thioredoxin to upregulate oxidative stress that can precipitate cell death through ferroptosis in cervical cancer cell lines [35]. Curcumin also down regulates ß-catenin and NFKB which are upregulated in the HPV network [36]. A phase 1 trial of intravaginal curcumin reported no significant toxicity, although dose escalation was limited, [37] and a curcumin-based intravaginal cream Vacurin has been under development [38]. Co-targeting E6 and E7 transcription may be synergistic with targeting the proteins in the proteome, with lower effective doses being required by the combination than by either agent individually. Given the limited absorption and half-life issues of these agents, combination therapy makes practical as well as mechanistic sense.

By targeting E6 and E7 and regenerating Rb1, p53, and the phosphatases, PTPN13 and PTPN14, the transcriptional consequences of signaling pathway activation can be dialed back to achieve virtuous deactivation of cancer causing network, thereby causing collapse of the disease and its therapeutic resistance mechanisms. For example, by deactivating the impact of E5, HIF1A, MYC, STAT3, NFKB activation is reduced, while deactivation of E6 and E7 reduces the activation of E2F1, ß-catenin, HIF1A, YAP1, MYC, ZEB1, and SOX2 (Table 2). In turn, the network effects are reversed and the disease drivers become deactivated. Incidentally, tobacco has also been identified as a driver of HPV oncoprotein transcription. Benzopyrene upregulates E6 and E7 expression and increases viral load [39]. Women who smoke are more susceptible to cervical cancer compared to non-smokers [40] It is also worth pointing out that cannabis appears to accelerate the growth of HPV [41]. These agents bind to cannabinoid receptos which in turn upregulate the p38-MAP kinase pathway to promote the disease. Cannabis also promotes the phenomenon of netosis to antagonize the benefit of PD-L1 immunotherapy and is associated with impaired survival among patients receiving immunotherapy for cancer [42,43]. Thus, cannabis and tobacco avoidance should be strongly recommended for HPV-afflicted patients.

Table 2. Re-purposing regimen to take down oncogenic consequences of HPV.

Target	Agent	Mechanism of Action	Transcription Factor Impact
E5	Rimantidine	Inhibits E5 and rescues lysosomal function allowing for peptide processing and EGFR turnover	HIF1A, MYC, STAT3, NFKB
E6, E7	Withaferin A	Inhibits ubiquitination of Rb1, p53, PTPN13, PTPN14	E2F1, ß-catenin, HIF1A, YAP1, MYC, ZEB1, SOX2
	Curcumin	Rescues or enhances transcription of *RB1* and *TP53*	

Future

Chemoradiotherapy has been an indispensable mechanism of eradicating squamous cancer without the need for surgery. However, hypoxia has been found to be a key driver of radiation and chemotherapy resistance leading to treatment failure [44-47] The latest innovation of using 18F-fluoromisonidazole (FMISO) positron emission tomography scan, now commonly referred to as "hypoxia PET scan" has allowed radiation oncologists to use relative non-toxic doses of radiation 30 Gy for oropharyngeal cancer patients whose cancers are not hypoxic, and to reserve 70 Gy of radiotherapy for patients with positive hypoxia PET scans [48]. As a result, significant acute toxicities related to radiation treatment are decreased while chronic toxicities are completely eliminated in the low dose non-hypoxic group, thus sparing patients from severe mucositis and odynophagia upfront, and permanent chronic, life-altering xerostomia, dysphagia, and lymphedema.

How can hypoxia be reversed? The impact of HPV E7 to cause turnover of Rb1 results in ungated cell cycle entry leading to continuous proliferation. Additionally, E6-mediated loss of p53 leads to loss of gene transcription of *CDKN1A*, thus compromising expression of p21, a key brake regulating G1/S progression in the cell cycle. Additionally, enhanced turnover of Rb1 removes a key restraint from the SKP2 ubiquitin complex leading to turnover of p21 and p27, thus facilitating unmitigated progression in G1/S phase. SKP2 is associated with radiation therapy failure in cervical cancer patients as well. Ultimately, continuous proliferation results in over-growing the blood supply and subsequently causing hypoxia [48] Therefore, the rescue of Rb1 and p53 expression with WA and curcumin to achieve cell cycle arrest and has the potential to eliminate proliferation as a key driver of hypoxia.

Additionally, the impact of NTCT to counter aerobic glycolysis (Warburg metabolism) also promises to reverse the activation of HIF1A and MYC to remove them as key mediators of therapy failure. Hence, the NTCT approach advocated above carries the promise of reducing the need for high doses of radiotherapy and the permanent long-term sequelae associated with this approach. This would not only save patients from treatment related disability but a change from 70 to 30 Gy of radiation would also decrease the cost of treatment by more than half. Hence, funding for NTCT trial using hypoxia PET would be of particular interest for payors with the potential that a positive trial could generate remarkable cost savings for the health care system.

Limitations

Loss of tumor suppressors Rb1 and p53 generates replication stress, a phenomenon where the cell cannot achieve genomic fidelity. Thus, the daughter cells resulting from cell division are not identical to the parent cell. Instead, profound genomic instability generates cells with evolutionary resources capable of enhancing the malignant phenotype and further complicating treatment efficacy. For example, *APC, BRCA2, FANCD2, MLH1, MSH3, PARP3, RAD18, RAD50, RB1, SETD2*, and *XPC* deletions are commonly present in cervical cancers. In anogenital cancers, copy number variations (CNVs) include amplification of *PI3KCA* and deletion of *APC* in both primary and recurrent tumors; amplifications of oncogenes *CCND1, MYC*, and *NOTCH1* and deletions of *BRCA2* and *RB1* in primary tumors; and deletions of *ATR, FANCD2*, and *FHIT* in recurrent tumors. As a result, simply targeting HPV with rimantidine, WA, and curcumin is unlikely to be sufficient to defeat HPV-driven cancers by itself.

By virtue of these acquired changes, genomic entropy enhances fitness of the cancer, i.e., *survival of the fittest*, by providing new resources to a cell under therapeutic stress. Hence the HPV-driven cancers not only possess a complex adaptive network but one which that is continually evolving resistance (C.A.N.C.E.R). The number of resources increases with the number of cell divisions and the size of the cancer, thus favoring treatment as early as possible.

Ultimately, new molecular diagnosis techniques such biosimulation will be able to reveal the enhancements to the HPV transcriptional network

afforded by genomic evolution and help define the therapeutic imperatives for designing combination targeting to accomplish network takedown.

Conclusion

The combination of rimantadine, WA, and curcumin can reverse the oncogenic effects of HPV by dialing back the transcriptional activation that drives the malignant phenotype. Though this combination does not resolve the HPV infection itself, it can defeat the mechanisms which lead to cancer. The possibility of reversing or eliminating premalignant dysplastic changes before they become invasive represents a promising chemoprevention strategy. For patients with established cancers, rescue of key tumor suppressor genes and antigen presentation may also be able to enhance antitumor immunity and overcome the mechanisms of radiation and chemotherapy resistance. As such, drug re-purposing with rimantadine, WA, and curcumin represents a critical opportunity to use adjunctive therapy to prevent the cancer for those with dysplasia identified in screening programs and to achieve superior treatment outcomes in patients who already have progressed to frankly invasive disease. The combination could also prove useful to decrease the intensity, morbidity, and cost of treating HPV-derived cancers. As few approaches in oncology promise an increase in therapeutic index by simultaneously increasing efficacy and diminishing toxicity, the re-purposing regimen described here constitutes a rare opportunity to improve upon standard management of this set of common and persistently challenging cancers.

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