

Viruses and Head and Neck Cancers

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Received date: Dec 21, 2015; **Accepted date:** Dec 22, 2015; **Published date:** Dec 29, 2015

Keywords: Head and neck cancer; HPV; EBV; RV

Introduction

Viruses have often been termed as double edged swords. Many cancers including the head and neck group of cancers (HNC) are caused by oncogenic strains of viruses like Human papillomavirus (HPV) and Epstein - Barr virus (EBV) [1]. Interestingly certain viruses also possess the cancer eliminating properties and reovirus (RV) a double stranded RNA virus is a prominent one with significant research guided relevance [2]. The primary question arises as to what are the salient properties of the virus that makes it a causative agent versus a therapy. To understand the mechanism of viral interactions in cancer environment the head and neck group of cancers (HNC) are the best ones to follow. In a prominent fraction of this cohort the malignancy has been affected by viruses like HPV and EBV and many HNC patients have received RV mediated virotherapy through enrolment in phase I, II and III clinical trials (ClinicalTrials.gov identifier NCT00753038).

Head and neck cancer includes a wide array of carcinogenicity involving tissue and organs of head and neck. This cohort accounts for about 3% of all cancers in the United States and about half a million cases worldwide annually. In 2015 an approximate 59,340 people (43,390 men and 15,950 women) will develop head and neck cancer with an estimate of 12,290 deaths (8,900 men and 3,390 women) in United States alone (Statistics adapted from the American Cancer Society's publication, Cancer Facts and Figures 2015 and the National Cancer Institute).

Since the discovery of HPV type-16 (HPV-16) in the 1970s, the role of HPV in human malignancies has become established. Approximately 200 different HPVs have now been characterized and new types are regularly added to the list [3]. HNC has been convincingly sub classified with prominent distinctive difference between tumors that are caused by infection with high-risk types of HPV, and those that do not contain HPV. These viruses can be classified into mucosal and cutaneous HPVs. Within each of these groups, individual viruses are designated high risk or low risk according to the propensity for malignant progression of the lesions that they cause [3]. The HPVs of most concern in HNC is the mucosal, high-risk types that can infect the epithelium of the aerodigestive tract. Most frequently, HPV-16 and, to a lesser extent, HPV-18 have been detected and identified as two such types, playing important roles in head and neck carcinogenesis. HPVs have a unique mechanism of infection

that has likely evolved to limit infection to the basal cells of stratified epithelium, the only tissue in which they replicate. More than 95% of head and neck cancers are squamous cell carcinomas where cancer begins in squamous epithelial cells that line the moist surfaces inside the head and neck. HPV is a strictly epitheliotropic, circular double-stranded DNA virus that is known to be the primary cause of cervical cancer and also contributes to a significant fraction of head and neck carcinogenicity [3]. The HPV contains two oncogenes, E6 and E7, the expression of which inactivates p53 and retinoblastoma (RB), respectively, causing perturbation of cell cycle regulation in the infected cells and is considered to be the onset of HPV-mediated carcinogenesis. The virus is not easily cultured, therefore the involvement of the virus in tumors is usually determined by detection of the viral DNA genome or expression of the viral genes using PCR methods [4]. The detection of viral E6 and E7 transcripts is a reliable assay for the detection of an oncogenic HPV infection in HNC.

EBV is a γ (gamma)-herpes virus and a member of the Herpesviridae family. The herpes viruses consist of generally large, complex DNA viruses, able to encode about 100 different proteins, and are one of the largest virus groups [1]. This virus affects more than 90% of the world's adult population in some form or other. EPV is also associated with variety of malignant disorders. In the head and neck, the establishment of a latent transforming EBV infection and the potential viral genetic changes that occur in epithelial cells may contribute to the development, growth, and invasive capabilities of cancer specially the subclass of nasopharyngeal carcinoma. Unlike HPV the Epstein Barr Virus poses the larger risk of becoming tumorigenic when in its latent state, rather than in its active state. When EBV induces growth transformation in its host cell, the production of progeny virions is ceased, and the virus undertakes a tumorigenic pathway of replication.

Plasma EBV DNA analysis has proven useful in detecting early nasopharyngeal carcinoma in individuals when there is no clinical suspicion of tumor [5]. Important member of EBV protein family includes the latency-associated proteins -1 and 2 (LMP-1 and LMP-2 and EPV nuclear antigen 1-6 (EBNA1-6) that play crucial role in development and progression of carcinogenesis [1]. It has been reported that the C-terminus and transmembrane-spanning domains of LMP-1 are required for the maximal activation of nuclear factor-kappa B (NF-kB),

the activation of which is linked to the inhibition of apoptosis a major way adopted by cancer cells for survival [6].

Reovirus a double stranded RNA virus that has gained novelty due to its oncolytic behavior in transformed cells. It is mildly pathogenic in infectivity profile and has been developed as a therapy that can be safely administered to cancer patients due to low toxicity and minimal side effects. Several clinical trials are in progress where the virus has been used in combination with approved chemotherapy to improve the disease outcome. In HNC the clinical trial of Phase I and Phase II showed significant promise which allowed the study to progress to phase III clinical trial. The phase III trial was conducted in combination with carboplatin and paclitaxel to evaluate the overall and progression free survival in patients with metastatic or recurrent squamous cell carcinoma of the head and neck. 167 patients were enrolled and the study continued for 4 years till its completion in May 2014. Although the outcome of the phase III trial was not very encouraging scientists and clinicians continue to document the oncolytic effect of reovirus in cell lines and preclinical animal models of HNC.

RNA dependent protein Kinase (PKR) has been identified as an important protein that plays crucial inhibitory role in efficient reoviral replication. Expression of PKR is up-regulated in response to interferon released by RV infected cells [7]. Once activated, PKR blocks the primary and secondary reovirus protein translation. In transformed cells, PKR is not activated, allowing unabated viral replication and effective assembly of viral proteins for production of infection efficient virions. Specific chemical inhibitors of PKR phosphorylation restore reovirus translation in untransformed cells providing evidence for a direct role of PKR in defining resistance to reovirus replication [8]. Activation of oncogenes like KRAS is suggested to release the translational blocks in the transformed cells. However, the exact molecular mechanism of coordination between transformation/oncogenic activation and inhibition of PKR-mediated viral translational remains elusive [2].

A critical question to ask is if a cancer cell can harbor two different classes of viruses and allow them to propagate freely? A study recently performed on a cohort of Japanese HNC to investigate the frequency of EBV and HPV in fresh frozen samples to analyze the effect of co- infection on different types of HNC. The findings revealed that although HPV and EBV are highly prevalent in subset of oropharynx and nasopharynx of HNC simultaneous infection or co- infection is rare [1]. Another report published this year by Cooper et al. reported that although oncolytic reovirus demonstrate significant destruction of HNC cells the oncolysis is significantly greater in HPV negative HNC cell lines as compared to HPV positive ones [9].

These findings clearly suggest that two classes of virus cannot be harbored within the same cell whether both are cancer causing particles or one is causative and the other is oncolytic in nature. Viruses thrive by utilizing host cellular machinery for their growth and propagation. In this process the virus can cause the cell to get transformed so that the virus

can better propagate in synergy with the unabated growth of the neoplastic cell or the fact that the cellular transformation itself favors generation of the oncolytic virus within itself until finally the viral propagation needs more resources than the transformed cells can provide hence after reaching a threshold the virus lyses the transformed cell (oncolysis) in search of another cell with better resources for virus proliferation.

In this whole event of viral infection and propagation there are several host proteins which plays very crucial role to modulate the process. Understanding the molecular characteristics of these proteins and the cross talk amongst them can shed valuable insight into the process of cancer dissemination and oncolysis. Can administering an attenuated virus as vaccine prevent or eradicate the virus mediated carcinogenesis of HNC? Can the double edged behavior be skillfully utilized in finding a therapeutic solution with improved prognosis?

Head and neck cancer is a molecularly and genetically heterogeneous disease. Within different subtypes of HNC a significant percent is affected by virus which makes it a valuable platform to discern the molecular events that favor virus proliferation. The fact that another subset of HNC which is not affected by carcinogenic viruses like HPV and EBV show significant cellular oncolysis upon administration of RV indicates that understanding the difference in molecular behavior of these two subsets of cancer might shed valuable insight to the cellular event that favors the propagation of carcinogenic or oncolytic viruses. This knowledge can then be effectively harnessed to search the poignant molecular event that determines carcinogenesis versus oncolytic fate of the cell. Such insight would provide invaluable guidance in better development of strategies both preventive and therapeutic.

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