

Do human papilloma viruses play a role in the genesis of cutaneous malignancies?

Abstract

The role of human papillomavirus (HPV) infection in the genesis of cutaneous malignancies with special reference to cutaneous squamous cell carcinoma (SCC) remains a mystery. Recent evidence suggests that certain circumstances, such as allograft transplantation or genetic predisposition may allow infection with HPV to result in cutaneous malignancy.

Keywords: human papillomavirus, cutaneous malignancies, bak, viral genome, skin carcinogenesis

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Abbreviations: HPV, human papillomavirus; SCC, squamous cell carcinoma; EV, epidermodysplasia verruciformis; UV, ultraviolet; MAML-1, mastermind-like protein-1

Introduction

The human papillomavirus is a double-stranded DNA virus that infects the epithelial cells of skin and mucosa.¹ The family of papillomaviridae consists of around 200 different human papillomavirus types.² The various types and subtypes of HPV are distinguished on the basis of their nucleic acid sequence.³

HPVs have been divided into 5 genera: Alpha-papillomavirus, Beta-papillomavirus, Gamma-papillomavirus, Mu-papillomavirus and Nu-papillomavirus.^{4,5} Members of the genus alpha HPV types are known to induce benign skin warts, genital warts and cervical cancer.⁶⁻⁸ Genus beta HPV were identified in flat warts and in cutaneous squamous cell carcinomas in epidermodysplasia verruciformis (EV) patients.^{9,10} EV effected individuals are often infected with HPV types and many develop squamous cell carcinomas (SCCs) at body sites exposed to sunlight.¹¹ EV specific HPV types include HPV5 and HPV8 and to a lesser extent HPV14, and HPV20.^{12,13} It has been suggested that, the increase of risk of cutaneous malignancies in sun exposed area in EV patients may indicate correlation between DNA damage induced by Ultraviolet irradiation (UV) and the infection with beta HPV virus.¹⁴⁻¹⁶

The prevalence of beta-HPV DNA was found to be higher in premalignant lesions and SCC in immunocompromised individuals in comparison to immune competent patients.^{17,18} The higher rate of cutaneous malignancies among immunocompromised patients suggests that HPV may play a role in the genesis of this type of malignancies.

Previous studies showed that HPV viral load is decreased during skin carcinogenesis and significantly higher in actinic keratosis than in SCC.^{14,19} This led to the suggestion that the virus may play a role in the early stages of SCC development and that the role of HPV would be initiation of malignancies rather than maintenance.¹⁴ This may indicate that the beta-HPV is playing a role in the initiation

of malignancy by destabilizing the host genome by allowing the persistence of mutations that can drive tumorigenesis independently of the viral genome.²⁰

Discussion

The HPV genome may explain how this mysterious virus may contribute to malignancy. It consists of approximately 8000 base-pairs of double stranded, circular DNA that encode 9-10 open reading frames.^{21,22} The HPV genes are designated as early (E) and late (L) genes.²³ The early genes include E1, E2, E3, E4, E5, E6 and E7.²¹ The late genes include L1 and L2 genes.²¹ The L1 and L2 are major and minor capsid subunits respectively, and these are the structural proteins of the virion.^{21,22}

The viral E1 and E2 proteins are responsible for perverting normal cellular processes in order to reproduce the viral genome.²⁴ It has been shown that the early genes E6 and E7 encode the viral oncoproteins and they are the major transforming proteins of HPV.^{25,26}

Other studies indicated that E5 of high risk types of HPV may play a role in the genesis of cervical cancer.²⁷ The cellular target of E6 oncoprotein of alpha HPV in cervical cancer, is the tumor suppressor gene p53.^{26,28,29} The interaction of E6 oncoprotein with p53 results in its degradation and this may contribute to this type of malignancy.²⁶

The E7 oncoprotein of alpha HPV in cervical cancer destabilize pRB through proteasomal degradation.³⁰ Deactivation of pRB results in displacement and thereby activation of E2F and thus contributing to cellular transformation.³¹ In regard to the oncoproteins E6 and E7 of beta HPVs, previous studies conducted in tissue culture and in transgenic mice showed clearly that E6 and E7 display transforming activities and the transformation activities are enhanced following exposure to Ultraviolet irradiation.^{32,33} These finding may further confirm the potential role of this HPV type in the genesis of cutaneous carcinogenesis. It has been proposed that the genus beta HPV E6 proteins inhibit at least some p53 target genes, although perhaps not by the same mechanism or to the same degree as the high-risk genus alpha HPV E6 proteins.³⁴

Furthermore, the E6 protein of cutaneous HPV types was shown to interfere with DNA damage repair³⁵ and to inhibit apoptosis in keratinocytes in response to UV irradiation.^{36,37} The inhibition of apoptosis in keratinocytes was due to the capabilities of the E6 protein of HPV to degrade cell mediated apoptosis protein “Bak.”³⁸ The capabilities of E6 protein of beta HPV to interfere to some degrees with the tumor suppressor gene p53 and with the DNA damage repair mechanisms and to inhibit the induction of apoptosis may explain how this virus may contribute to cutaneous malignancies.

The E6 protein of beta HPV is also shown to target Mastermind-Like protein-1 (MAML1), which is known to act as transcriptional co-activator for NOTCH protein.^{39,40} NOTCH pathways play an important pro-differentiation role and have a tumor suppressing function in keratinocytes.⁴¹

On the other hand, the cutaneous beta HPV E7 oncoprotein is shown to bind pRB with lower efficiency than the high-risk HPV E7 proteins.⁴² However, this could be contributed to the type of beta HPV type involved, this suggestion was supported by previous work by Cornet I et al.,⁴³ who compared the properties of E6 and E7 oncoproteins from six uncharacterized beta HPVs types (14,22,23,24,36,49) and found that only HPV49 E6 and E7 immortalized primary human keratinocytes and efficiently deregulated the p53 and pRb pathways.⁴⁴

Conclusion

It appears that HPV is playing somehow a role in the initiation and genesis of cutaneous malignancies and more studies are needed in order to determine the carcinogenic properties of HPVs and their potential role in skin cancer development.

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Conflicts of interest

The author declares no conflicts of interest.

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