

Periodontitis as a reservoir of human papillomavirus in the causation of oral squamous cell carcinoma: a review

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Abstract

Human papillomavirus (HPV) is a DNA virus from *Papillomavirus* family, and is one of the most widely reported sexual infection, which is not only related to ano-genital malignancies, but also associated with head and neck cancers, with chronic periodontitis being one of the risk factor for the same. Chronic periodontitis leads to loss of tissue structures of and around periodontium and is clinically detectable in the form of periodontal pocket and loss of alveolar bone. A variety of other systemic diseases have also been found to be linked to chronic periodontitis, such as cardiovascular diseases, respiratory diseases, etc., and recent data show that it is also related to malignancies of oral cavity. Junctional epithelium of periodontal pocket helps HPV to survive by facilitating the cellular functions to grow and hence, acts as a reservoir for the virus. *Porphyromonas gingivalis*, a Gram-negative anaerobic bacteria and HPV interacts both directly and indirectly in a series of complex reactions and as a result of some inflammatory reactions, this association further leads to commencement and progression of head and neck squamous cell carcinoma or oral squamous cell carcinoma. This article reviews the pathophysiology of oral human papillomavirus infection and its role in head and neck cancers, with chronic periodontitis as one of the causative factors.

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Key words: human papillomavirus, chronic periodontitis, *Porphyromonas gingivalis*, oral squamous cell carcinoma.

Introduction

Epidemiological data reveals human papillomavirus (HPV) as one of the most widely reported sexually transmitted infection worldwide [1]. It not only leads to anal and genital cancer but has an active role in etiopathogenesis of several oral malignancies [2, 3]. Certain points of evidence support that uterine cervical epithelium and junctional epithelium of periodontal pocket shares some similarity in terms of their rapidly dividing basal layer, which provides greater affinity to HPV [4]. This indicates that chronic inflammation of periodontium that facilitates HPV life cycle may play a pivotal role in increasing the risk of oral cavity

cancer. This review intends to explain the basic structure of HPV virus and its possible relation between periodontitis, which acts as a reservoir for the virus and helps in the progression of oral cavity carcinoma.

Human papillomavirus structure

HPV belongs to category of DNA viruses of family *Papovaviridae*, including *Polyomaviruses* and *Papillomaviridae* [5]. It is a non-enveloped virus having icosahedral capsid with double stranded DNA, and as it is a genetic material, is circular in shape [5].

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Human papillomavirus classification

Phylogenetically, HPV can be classified into genera, species, and types [5]. Based on tropism, it can be further categorized as cutaneous type, causing lesions of skin and mucosal type, which is associated with anogenital and upper aerodigestive tract, initiating oral cancer [5]. HPV can also be classified based on oncogenicity [5].

Human papillomavirus and chronic periodontal disease

Periodontitis is a local inflammatory but chronic disease of oral cavity that is related to Gram-negative anaerobic bacteria present in dental plaque or biofilm, which damage periodontal tissues, and are clinically seen as periodontal pocket and loss of alveolar bone [6, 7]. HPV gains its entry either through a breach in mucosa or through normal exposure of parabasal cells, exclusively infecting basal cells of epithelium. In addition, the replication of HPV is closely related to proliferation of epithelial basal cell layer and parabasal cell layer. Initial HPV infection occurs in periodontal pocket, which consists of stratified squamous epithelium, and is characterized by continuous epithelial proliferation, migration, rete ridge formation, and ulcerations [8]. The bottom layer of periodontal pocket, i.e. the junctional epithelium, consists of suprabasal and basal cell layers only, have a tremendously high turnover ratio, and provides cellular functions required by the virus. Therefore, in a way, the periodontal pocket serves as a reservoir or tank for latent HPV that requires infected and undifferentiated cells for its survival. Before the process of differentiation, the basal cells become exfoliated from the gingival crevice [9].

Association between chronic periodontal disease and oral cancer

A close association between chronic periodontitis and oral cancer have been reported in literature. More than a four-fold increase in the risk of head and neck cancers has been reported with each millimeter loss of alveolar bone [10].

Interaction of *Porphyromonas gingivalis* and human papillomavirus in the development and progression of oral carcinoma

An interaction between oral bacterium, especially *Porphyromonas gingivalis*, and viruses occur either directly or indirectly. Lipopolysaccharides in the form of endotoxins, lytic enzymes like proteases, collagenases etc., and metabolic products in the form of hydrogen sulphide, ammonia etc., may directly carry out or induce changes at the genic level in adjacent cellular medium [11-13]. Additionally, it leads to an increased production of some substances like acetaldehyde [14-16] and nitrosamines [17, 18], which are quite carcinogenic in nature. Inflammatory reactions, on the other hand, explains the indirect association between these two. Neutrophils, lymphocytes, macrophages, fibroblasts, and epithelial cells of the host immune system respond to *P. gingivalis* by generating inflammatory mediators including: 1. Cytokines, chemokines, prostaglandins, growth factors, and other signals that provide an environment for various cellular functions like their survival, ability to proliferate, to migrate, to form new blood vessels (i.e. angiogenesis), and inhibition of apoptosis such as programmed cell death [19]. This new environment further

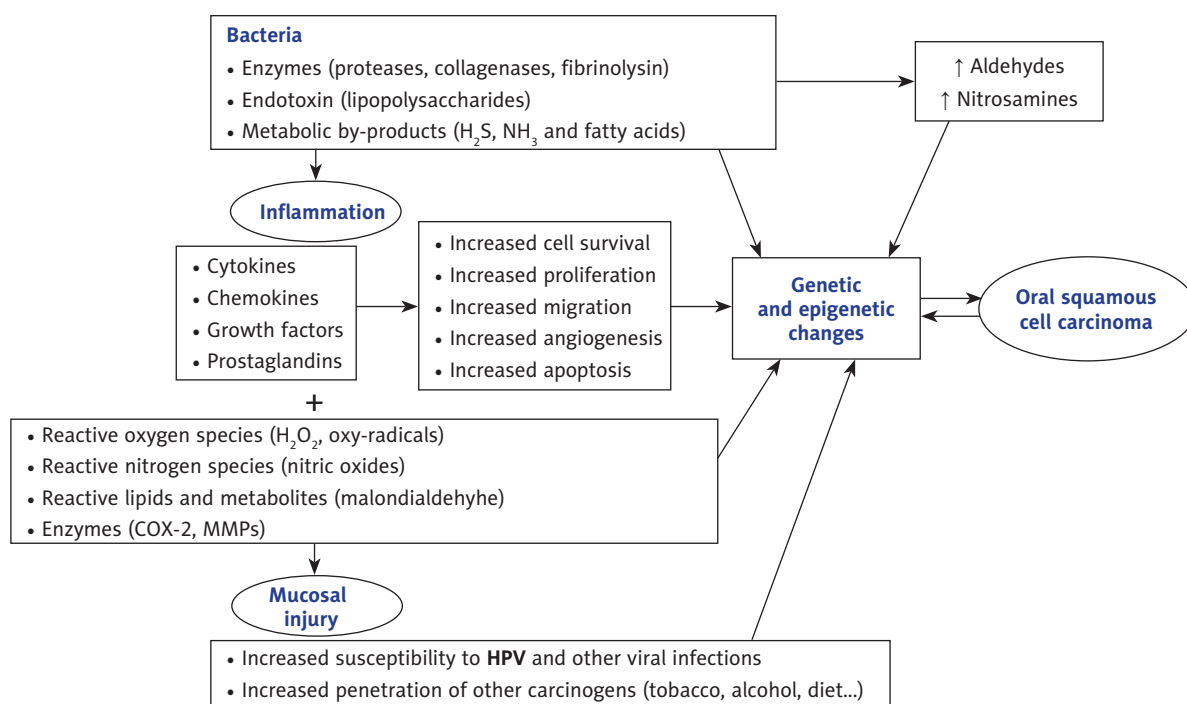


Figure 1. Inter-relationship between chronic periodontitis, HPV and oral squamous cell carcinoma [33]

accumulates mutations in epithelial cells, and forces these mutant epithelial cells to migrate and proliferate at distant site and further allows them to grow; 2. Along with inflammatory reactions, few other substances can also bring genetic and epigenetic changes by acting as endogenous mutagens. These substances include reactive oxygen species (H_2O_2 , oxy-radicals), reactive nitrogen species in the form of nitric oxides, reactive lipids, and few metabolites such as malondialdehyde and matrix-metalloproteinases [20-30]. Chronic inflammation may cause a breach in the mucosal barrier, which may further lead to an increased penetration of other carcinogenic substances like alcohol, tobacco, and dietary metabolites [31, 32].

However, it is yet determined whether it is the direct effect of bacteria or its indirect effect through stimulation of inflammation that links oral HPV infection with chronic periodontitis. Both the mechanisms are likely to be involved, but the majority of present data suggests that the periodontopathogenic bacterium travels via salivary pathway and bloodstream from affected sites to distant normal sites and carry out tissue injury through inflammatory reactions.

Conclusions

As literature has shown, chronic periodontitis is associated with various systemic diseases and other complications of oral cavity, such as oral carcinoma. This can act as an independent causative factor or in conjugation with HPV virus for the progression of oral carcinoma. Therefore, the management of chronic periodontitis patients becomes crucial in the maintenance of oral hygiene and health in order to prevent such potential life-threatening diseases like oral cancer.

Conflict of interest

The authors declare no conflict of interest with respect to the research, authorship, and/or publication of this article.

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