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Lung and prostate epithelial tissues defects oncogenic opportunities of human papillomavirus

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ABSTRACT

The oncogenic role of human Papillomavirus (HPV) types in human tissues is a renewed subject since the discovery of probable HPV tumorigenesis mechanisms in cervical tissues and other tumor types. The cancerous tissues were observed to be high infected with HPV in comparison to healthy ones. But the HPV carcinogenesis mission at prostate, lung and other epithelial tissues are still controversial. Although this role is very possible, epidemiological studies did not confirm significant correlations between infection ratios in cancerous and healthy tissues. In this insight, we revised the potential HPV histological strategy for infecting lung and prostate epithelial tissues. Our suggestions are based on the previous HPV infection mechanisms regarding cervical and other reproductive system tumors and link this to histological manifestations before tumors initiation. Other recommendations to investigate the HPV oncogenic role in lung and prostate were presented.

1. INTRODUCTION

Scientists consider the Human papillomavirus (HPV) to be one of the closest microbial human enemies. Various types of HPV found spreading on the epithelial tissues particularly the sexual tract, and vary by type and number of infections through world populations. The pathogenesis of this virus has been associated with dermal pimples, but molecular biology techniques have soon allowed the discovery that this virus has an active role in cervical cancer development. Among more than 200 HPVs types, the oncogenic HPVs are well known to be the main cause of cancer, especially cervical cancer and involved as well in other urinogenital tumors such as uterine, vulva, penile, anal, and suspected oncogenic to breast and ovary [1- 3].

The accepted dynamics of tumorigenesis role are based on a pair of proteins E6 and E7 that inhibit the action of each of the P53 and Rb tumor suppressor genes. The role of HPV E5 oncoprotein previously revealed, that engaged in the early cervical cancer carcinogenesis progression by delaying epithelial cell differentiation through modulating cellular signaling pathways [4- 6].

Chronic inflammation harm effects on the cell microenvironment and inducing cancer cell proliferation well established, the presence of HPV together with inflammations increase the tumorgenesis opportunities, certainly with high-grade lesions in oncogenic HPV-infected women, and patients with head and neck squamous cell carcinoma, oral cavity and laryngeal squamous cell carcinoma. The presence of HPV at inflammation sites is widely recognized by observing the association between HPV presence inflammatory mediators secretion such as cytokines (IL-1, IL-6, IL-17, TGF-β, TNF-α, and NF-kB) [7- 10].

2. Mechanism of adhesion of HPV

However, there is controversy surrounding the mechanism of adhesion of this virus to the surfaces of epithelial cells, and how the viral particles enter until it reaches the basal membrane of epithelial tissue. The controversy also relates to the mechanisms of penetration of the plasma membrane, even though it is a nonenveloped virus, and the way the genome reaches the nucleus.

Let's talk here about what is most acceptable regarding the previous questions: The virus attaches the "exposed" basal membrane of epithelial tissue. Then contact a specific factor called heparan sulfate proteoglycans on the surface of epithelial cells. And the "Slow" endocytoses clathrin-dependent or caveolar process, are the primary suggested pathway of the entrance to the cytoplasm. Recent evidence suggested that tetraspanin (which is a membrane protein interacting among each other and other types of membrane proteins) could serve as a virus entry platform; the initial notice was that human papillomavirus aggregate on the cell surface of tetraspanin overexpressing keratinocytes. Furthermore, obscurin-like protein 1 (OBSL1), might be engaged with filamentous actin as a cytoskeletal adaptor [11]. Others argue that the entire intact viral capsid can enter the nucleus within a transport vesicle as a novel mechanism explaining by which a virus accesses the nuclear cellular machinery [12]. Or specific modifications such as phosphorylation of L2 capsid protein could be playing a potential role in infectious entry [13]. The viral particles thought to be carried into the cytoplasm through microtubules, the viral genome copy numbers amplifications then increased. The oncogenic mechanisms induced by E6 and E7 oncogenic proteins interactions with tumor suppressors Tumor protein P53 and retionoplasma protein (Rb). Thereby, inactivation of p53 by E6 can activate unregulated cell cycle, cell growth, and early tumorigenesis begins [14- 17].

3. Other tumorgenesis roles of HPV in Prostate and lung cancer

There is another puzzling and more pressing question about this virus, Are there other unknown tumorgenesis roles? The major role of HPV in cervical cancer development was revealed since years ago, To the extent that global health authorities consider that vaccination against this virus (especially high-risk types of HPV) could prevent cervical cancer development. This can be applied to uterine, ovarian, and genital tumors. But some studies talk about suspected roles of viruses in head and neck cancer, nasopharyngeal and lung cancers. It is not surprising that the virus is transmitted to these places from the body by the fluid contact within the human being and between males and females [18- 20]. We think that the presence of the virus in the reproductive or respiratory tract is acceptable to be more than its presence in other tissues, and subsequently its role of cancer development in these organs. It is assumed that the virus remains on the surfaces of epithelial tissue until chronic infections occur, which can lead to chronic cracks in the upper surfaces of epithelial tissue. This enables the virus to reach the basic membrane due to its permanent presence on the surfaces of epithelial tissues. This is very likely to occur in the reproductive and respiratory channels because these tissues are more vulnerable than others to contamination with the virus, thus the role of this virus has been discovered in many tissues of the reproductive and respiratory tract. Thus, at least we have two conditions for the occurrence of HPV infection, first: the epithelial tissue has injury points within, such as previous chronic inflammations, and the second the tissue is exposed to external communication, such as the genital and respiratory tracts.

At this point, we can say that there are two factors that determine the success of the virus to starting integration into the epithelial cell genome in many human organs. First: the heavy presence of the virus particles on the surfaces of epithelial tissues, knowing that most laboratory studies agree on the presence of the virus integrated with the genome of cells, although this tissue is completely healthy. Second: The presence of cracks or lacerations on the upper surfaces of epithelial tissues down to the basal membrane gives the virus great opportunities to spread accidentally and to adhere to the epithelial cell through the supposed adhesion mechanisms that we talked about previously [21].

We think that the location and histological structure of any tissues is the key to understand the HPV infections and future roles of tumorgenesis. Let us here discuss this regarding two locations: prostate gland and lungs. Prostate cancer and lung cancer two of the most common tumors around the globe, and the HPV participation in the tumorgenesis process still controversial. Evidence regarding HPV infections in prostate biopsies strengthens the hypothesis that HPV infection could be one of the cofactors associated with the progression of prostate cancer. There is more than one mechanism of virus involvement in cancer development, viruses could elevate cancer risk through cellular transformation, interrupting the cell-cycle control, amplifying cell turnover rates, and immune suppression. One of the most important of these aspects is chronic inflammation. Several epidemiologic and molecular methods detected HPV in malignant, benign, or normal prostate tissues. Three cancerous prostate samples (2.3%) out of 133 samples were HPV positive as one study stated. In Mexico, results showed that high risk (HR) HPVs were detected in 37/189 (19.6%) Prostate cancer specimens compared to 16/167 (9.6%) of Benign Prostatic Hypertrophy/hyperplasia (BPH) specimens. In India, The data demonstrate HPV infection in 41% of prostate tumor biopsies and 20% in BPH [22- 25]. These results suggest that HPV infection plays an essential or assistant role in prostate cancer development.

Anatomically, the only way for this virus toward the prostate tissue should go through the urethra, and exactly the area with contact with the prostate, the area that surrounds the urethra called the prostatic urethra. Remarkably, the vast majority of prostate cancer cases originate from this region [26]. The virus may cross through the urethral stratified epithelial tissues; the urethra may be originally damaged or the HPV might enter the peripheral zone of the prostate gland through a prostatic utricle: the blind hole in the urethra. At that moment, the virus entered one of the prostate ducts in the lumen and became face-to-face with the epithelial cells of the prostate cavity. Here there must be laceration or cracks resulting from previous stress effects, a point to consider, one of the most important manifestations of prostate progress, especially in the early stages of prostate cancer, is the loss of the basal membrane. So that the virus reaches the basal membrane in the same way that it follows in cervical cancer.

Although urethral cancer is rare, it can also occur as a secondary consequence of prostate cancer, we expect that the epithelial channels in the body open to the outside effects are more likely than others to be infected with this virus. We also believed that channels with dense fluid streams, such as the gut and urethra, are not appropriate for slow HPV behavior on epithelial cell surfaces.

As for the lungs, in principle, the virus and through inhalation or nasal passages of the mouth can easily reach the tissues of the lungs. There are various studies and conclusions that believe that the presence of this virus in the genome of the epithelial cells of the lungs is related to specific types of lung tumors [27]. According to Klein, and others after screening 4508 cases the mean incidence of HPV in lung cancer was 24.5% around the globe. In Europe and America, the average reported frequencies were 17% and 15%, but the mean number of HPV in Asian lung cancer specimens was 35.7% [28]. Other conclusions declare that lung tissue with HPV infection has a strong association with lung tumors, especially, high-risk types: HPV16/18 [29].

It is assumed that this virus follows the same strategy agreed upon and is currently accepted, which is the presence of vertical voids between the rows of epithelial cells that make the basal membrane exposed so that it can bind to the receptors on the surfaces of the epithelial cells and the rest of the dynamics we talked about previously.

However, in the case of the lungs, the matter seems a little different, as the structure of the lung tissue, is characterized by the presence of a mucous layer covering the epithelial cells and then the basal membrane. For the virus to be able to come into contact with the basal membrane, two things need to have occurred before that. The first is the erosion of the mucous layer and its decay in certain places, and the presence of vertical spaces between the epithelial cells.

Clinically, this means that the lungs have been subjected to stress, which may be related to previous infections or pre-symptoms that lead to the decay of the mucus layer and lead to the detection of voids or the creation of new voids within epithelial tissue.

Figure 1 describes a model for human Papillomavirus interaction locations with transitional epithelial tissues of prostate and lung cancer. The model based on assumed previous stress of these Tissues which could lead the viral particles to densely invade prostate gland or lung tissues, this paves the way to launch the actual tumorgenesis mechanism in the cytoplasm. In sum, the HPV could follow the same histological infection strategy in all human epithelial tissues before entering the cytoplasm, and the number of virus copies in the human genome might be correlated with non-viral previous chronic inflammations.

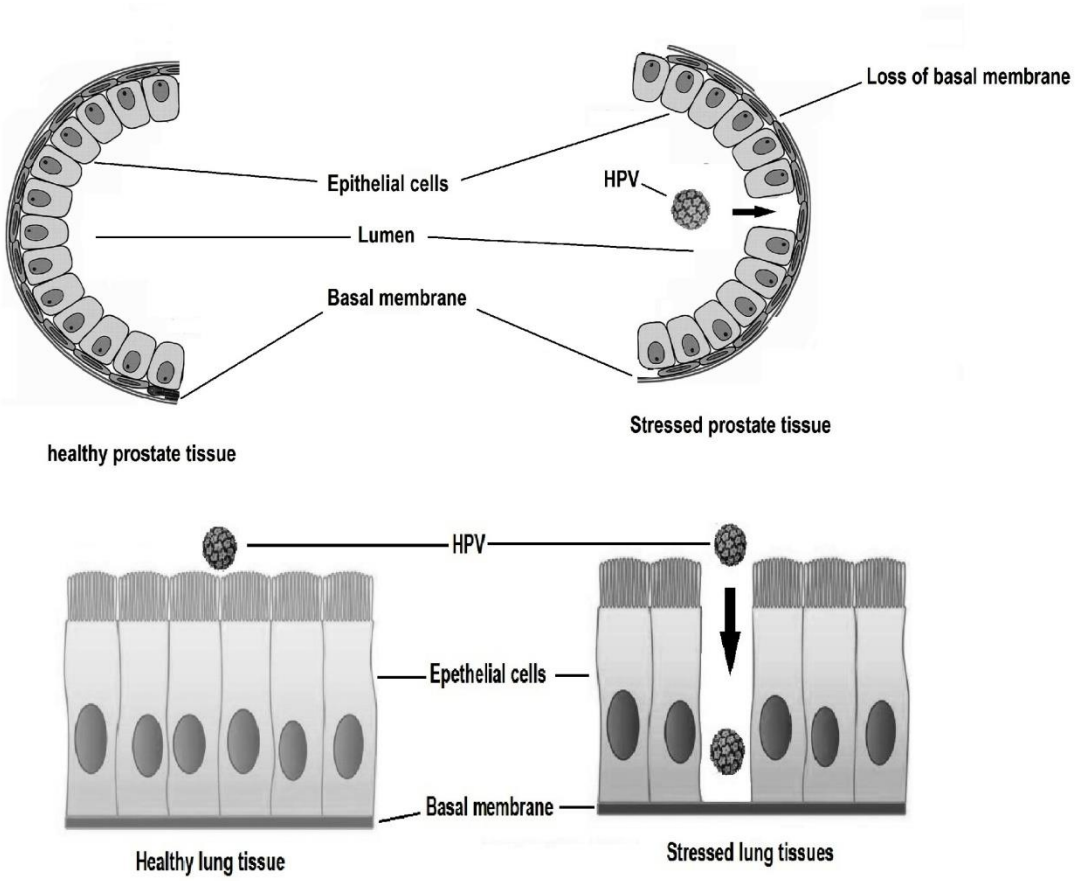

Figure 1: The suggested behaviour of human papillomavirus before and after epithelial tissue stress. The

HPV enters the prostate ducts lumen and attaches the basal membrane through the voids between epithelial cells (up). The HPV attaches the basal membrane of lung epithelial tissue after the decay of the mucus layer (down).

4. Conclusions and outlook

To assure rest to these discussion, two recommendations can be presented here, first: Further studies needed (mouse models, clinical case studies, bioinformatics researches based on integrated genomic databases...etc.) to explore the appearance of the epithelial tissues in the prostate gland resulted in age effect, chronic inflammations such as basal membrane loss and epithelial cells defects at the gland lumen. Then to be compared with the histological characteristics of prostate tumors especially the early-stage ones. These studies also could be correlated to HPV infection ratios or viral genome copy numbers found. The same manner can be introduced for lung cancer histological investigations and the suspected relevance between tissues stress resulted from certain nonviral symptoms and HPV infections.

Based on current shreds of evidence, certainly clinical and epidemiological studies of prostate and lung tumors, and also by analogy with the same adhesion strategy of HPV on epithelial tissues; it must be the findings will be accumulated revealing a confirmed role of this virus of initiation and progression of such tumors. Besides, the underlying tumorgenesis mechanisms in lung and prostate tissues could be accurately identified. This will be followed by introducing new subtypes of lung or prostate tumors, some of which might be concerning a pivotal role of HPV infections. Furthermore, it's possible to recommend HPV vaccines to avoid further human tumors, such as lung and prostate cancers.

Figure legends:

Figure 1: The suggested behaviour of human papillomavirus before and after epithelial tissue stress. The HPV enters the prostate ducts lumen and attaches the basal membrane through the voids between epithelial cells (up). The HPV attaches the basal membrane of lung epithelial tissue after the decay of the mucus layer (down).

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5. References

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