Mini Review

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Pathology Of Human Papillomavirus (HPV)

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Abstract

The human papilloma virus (HPV) plays a role in human pathology and is responsible for a variety of different patterns of pathogenesis, ranging from inflammatory conditions to cancers. The primary purpose of this research was to analyze the most recent developments in the body of literature concerning the pathogenic facets of HPV. During their investigation, the writers made use of a variety of search engines, including Google, Google scholar, Science direct, and PubMed. According to the findings of this research, the HPV is linked to several different cancers, including oral squamous cell carcinoma and cervical cancer (OSCC). The findings of the research team led them to the conclusion that the significance of human papillomavirus (HPV) is through its association with a wide variety of diseases, ranging from inflammatory conditions to malignancies. Getting vaccinated is absolutely necessary in order to protect oneself from this infection. In addition, we recommend that screening programs be established for this virus in order to detect cases at an early stage and, as a result, halt the development of the disease into a malignant condition.

Keywords: Hpv, Cervical Tumor, Oral Squamous Cell Carcinoma (Oscc), Inflammatory, Malignancy.

Introduction

The current study looked into recent discoveries that have been made in the scientific literature about the pathophysiological aspects of human papillomavirus (HPV). In the subsequent sections, we will discuss a comprehensive overview of the pathophysiology of HPV, in addition to its associated elements.

An overview of the HPV

The Papillomaviridae virus family is home to the human papillomavirus, which is also abbreviated as HPV. This viral family is responsible for causing cervical cancer. According to Monteiro et al, there are over 130 distinct species of HPV, and researchers have identified nearly 228 distinct genotypes of HPV up to this point [1]. Every one of these genotypes carries the possibility of having a tropism for mucosal and cutaneous epithelia, such as squamous tissue. The International Committee on the Taxonomy of Viruses (ICTV) describes the human papillomavirus (HPV) as "a small non-enveloped double-stranded circular DNA virus that ranges in diameter from approximately 52 to 55 nm".

It is composed of a protein shell called an icosahedral capsid, which is made up of 72 pentameric capsomeres that surround the viral genome and contain 8000 nucleotide base pairs [2,3].

The human papillomavirus is responsible for the outbreak of genital war. When a person engages in sexual activity without protection, HPV has the potential to infect the epithelial surface through microlesions that occur in the basal layer. Because of the morphological similarities, this can then result in a proliferative benign or malignant lesion both in the skin and in the oropharyngeal mucosa, as well as in the vaginal or anal tract [4].

Based on the likelihood that they will cause cancer in humans, HPVs are currently categorized as having either a high oncogenic risk (HR) or a low oncogenic risk (LR). The human papillomavirus (HPV) 16, 18, 26, 31, 33, 35, 39, 45, 51, 52, 53, 56, 59, 66, 68, 72, and 81 are all examples of HR subtypes. These subtypes are

associated with malignant lesions such as squamous cell carcinoma (SCC) [5]. LR subtypes 6, 11, 40, 42, 43, 44, 54, 61, and 70 are linked to benign lesions like condylomatous warts [4]. The ability of the HPV virus to insert two specific genes into hosts, known as E6 and E7, that encode viral oncoproteins, and thereby infect the genome of the cells, is the basis for HPV's potential to cause cancer [6].

This capability of HPV promotes the invalidation of the activities of important tumor suppressor and apoptosis proteins, such as Retinoblastoma Protein and Tumor Protein p53. This can lead to an increased risk of developing cancer (TP53). Both of these proteins play an important role in the battle against cancer as well as the process of apoptosis (pRb). Interaction between E6 viral oncoproteins and TP53, which ultimately results in the degradation of TP53 as a consequence of its connection to E6-Associated Protein [7].

Because of the attachment of E7 viral oncoproteins to pRb, which inhibits pRb's ability to prevent an excessive advancement of the cell cycle and, as a result, leads to the formation of cancer, carcinogenic activity can be linked to the oropharyngeal and vaginal epithelium [7].

Epidemiology of HPV

HPV is a serious concern all over the world, mostly because it is one of the most common sexually transmitted diseases (STIs). There are variances across continents in the incidence of HPV infection due to the varying levels of socioeconomic development and vaccination programs in each country. The global prevalence of HPV infection is roughly 12%. There are cases of cancer caused by HPV in both men and women and at a wide variety of anatomic sites.

The prevalence of cancer caused by HPV is 5.1%. Most countries have vaccination programs in place [8]. According to, the prevalence of HPV in Brazil is 25.41%, with some anatomic site variation as follows: penile area prevalence of 36.21%; anal region prevalence of 25.68%; and oropharyngeal prevalence of 11.89%. In addition, among this prevalence, 17.65 percent was linked to HR HPV subtypes [9]. One of the basic cancerous lesions that can be caused by invasive skin cancer is called squamous cell carcinoma. Oral squamous cell carcinoma (OSCC) may be present due to its anatomical similarities with oropharyngeal mucosa tissue; hence, OSCC may develop from any location of oropharyngeal mucosa [10]. The bottom of the tongue, the sublingual area, the gingiva, the hard palate, and the lips are the parts of the mouth that sustain the most damage on a regular basis, as stated by [11,12].

It is still a big problem in public health in Mexico, where it ranks second among diseases that impact women. Cervical cancer, commonly known as CC, is an abbreviation for cancer of the cervix. The presence of a persistent infection with human papillomaviruses is considered the single most important risk factor for the development of CC.

In addition, other cancers, such as those of the anus, oropharynx, and penis, have been connected to HPV infection in a significant number of cases. When it comes to cervical cancer, the high-risk HPV type that is found the most frequently is HPV-16, followed by HPV-18; these two types are jointly responsible for 70% of occurrences [13].

The nucleotide sequence of HPV intratype variant lineages can vary by between one and ten percent, while the nucleotide sequence of sublineages can vary by between half a percent and one percent. It has been postulated in a number of studies that the nucleotide variations that take place between HPV intratype variants are reflected in the functional differences as well as the pathogenicity of the virus. These studies have been conducted by a number of different researchers. Additionally, it has been demonstrated that intratype variations of HPV-16 and -18 can variably affect molecular processes in infected cells.

This, in turn, can affect the biological behavior of infected cells, which, in the end, can have an effect on the clinical outcome of patients. Mexico has contributed to the body of knowledge on the geographical distribution of intratype variations of the most frequent HPVs in the context of premalignant lesions of the cervix and CC, as well as in other HPV-related cancers. In addition, functional studies have been done to study the cellular impact of intratype variations in HPV proteins. These studies have been carried out. There is a possibility that these differences can occur within the same strain of the virus. This review will examine the current state of knowledge regarding the epidemiology of HPV-16 and HPV-18 intratype variants in the Mexican population, as well as their association with persistence, precancer, and cervical cancer, as well as functional aspects related to the biological behavior of the viruses. The purpose of this review is to examine the current state of knowledge regarding the epidemiology of HPV-16 and HPV-18 intratype variants in the Mexican populati [13].

Pathogenesis of HPV

It is highly likely that most women will become infected with HPV at some point in their lives [14]. This can happen at any time during their lives. On the other hand, it has been reported that approximately ninety percent of these HPV infections are temporary and will clear up within the first two years due to the immune system of the host [15].

A persistent infection with HPV is one of the most important factors in determining whether CC will develop. As a consequence of this, cancer brought on by HPV is a chance occurrence that does not contribute in any way to the viral replicative cycle or the generation of viral offspring. Only a small percentage of infections (between 10 and 20 percent) end up becoming chronic;

nevertheless, those who do have a greater chance of progressing to malignancy [16].

It has been demonstrated that the risk of CC was 12.4% in females who were continuously infected with one HR-HPV and tested over a period of 2 years. The testing took place over the course of two years. When compared to the risk of CC in women who had a repeatedly negative HPV test, which was 0.14%, this risk is significantly lower.

In addition, the risk of developing cancer increases with a woman's age, going from 5.5% for women aged 30 to 44 years to 14.4% for women aged 45 to 54 years and 18.1% for women aged 55 years or over [17]. .A genetic predisposition and lifestyle variables are both examples of features that are inherent to the host, while characteristics such as viral load, viral type, and intratype variations are examples of characteristics that are inherent to the virus [18].

All of these different aspects are taken into consideration as possible predictors of how long a virus will live. A number of clinical characteristics that are exclusive to HPV infection take place prior to the development of malignancy. The normal epithelium undergoes a transformation into epithelial precursor lesions during this process, which ultimately leads to cervical disease.

These kinds of abnormalities have been histologically classified into one of three groups, which are referred to as cervical intraepithelial neoplasia (CIN) 1, 2, and 3; and they are arranged in descending order of the degree to which the lesion has progressed (mild, moderate to severe dysplasia). In addition, there is an additional classification that is based on cytological examination and divides the lesions into two groups known as low-grade squamous intraepithelial lesions (mild dysplasia) (LGSIL) and high-grade squamous intraepithelial lesions (moderate to severe dysplasia) (HGSIL) [19].

This classification divides the lesions into two groups that are known as mild dysplasia and moderate to severe dys Lesions that have been categorized as CIN1 or LGSIL have a low likelihood of progressing to CC. These lesions are brought on by short-lived HPV infections, and ninety percent of the time, the infected epithelium will transform into healthy tissue on its own. On the other hand, CIN2 and 3 or HGSIL are caused by persistent and unproductive HPV infections; yet, sixty percent of these lesions heal up on their own in immunologically competent people [20].

Within the framework of this discussion, it is common knowledge that 0.6% of HPV infections will ultimately result in cancer. A study that tracked participants for 16 years found that women who had persistent infections with any form of carcinogenic HPV had a 75.4-fold greater chance of acquiring cancer compared to those who did not have HPV [16].

HPV and oral malignancies

It is common knowledge that the highly oncogenic HPV is linked to and acts as a risk factor for a variety of oral carcinomas, including oral squamous cell carcinoma (OSCC). In order to analyze and describe the HPV-induced OSCC prevalence and genotyping in the city of Belém, which is located in northern Brazil, the purpose of this study was to conduct research. This study contains 101 individuals who sought diagnoses of oral lesions at an oral pathology referral facility located within a dentistry institution. The study is a cross-sectional investigation (OL).

The sociodemographic and epidemiological questionnaire was something that every participant had to go through after they had signed the consent agreement and satisfied the criteria for inclusion. Then, depending on the size of the OL, either an excisional or an incisional biopsy was performed to collect the OL. After that, the OL tissues were stored in paraffin blocks so that histological diagnoses could be made. After that, the blocks of paraffin were separated into benign, malignant, and premalignant lesions according to the classification of possibly malignant illnesses of the oral and oropharyngeal mucosa.

After that, the ReliaPrep FFPE gDNA Miniprep procedure was utilized in order to extract DNA from the paraffin blocks in order to differentiate between HPV DNA with a high oncogenic risk and HPV DNA with a low oncogenic risk. After that, the viral DNA was amplified and typed utilizing the Inno-Lipa genotyping Extra II procedure, and the gathered data were evaluated utilizing Chi-square tests and G-tests. In total, 59 out of 101 (58.4%) OL were malignant or premalignant lesions. Of these, OSCC was the most prevalent, accounting for 40 out of 59 (67.7%) cases, while benign lesions accounted for 42 out of 101 (41.6%) cases.

Upper gingiva was the most commonly affected area, accounting for 46/101 (45.5%), of all cases. Regarding the detection of HPV DNA, approximately 27 out of 101 (26.7%) had positive results; of these, 17 out of 59 (28.8%) were malignant or premalignant lesions, and the most prevalent genotypes detected were 16, 18, 52, and 58; however, among benign lesions, 10 out of 42 (66.6%) had HPV-positive results, and the most prevalent genotypes detected were 6, 11, and 42. The only risk factor that was found to have a significant connection between HPV and OSCC presence was age range (p-value: 0.0004). In our relatively small cohort, it was not possible to establish a connection between oral SCC and oral HPV among the samples that were analyzed [21].

HPV and immunology

As a result of the development of immunotherapies over the past few decades, immune cells that were discovered to be infiltrating tumors have attracted a significant amount of interest in the medical community. A point of fact, they may be biomarkers that can be used to predict the outcome of a patient's treatment, they may bear immune checkpoint markers that can be targeted by

therapeutic antibodies, and mechanistic studies may reveal how to modify their activation profile in order to re-direct them toward tumor cells.

These three possibilities are just the tip of the iceberg when it comes to the potential applications of these proteins. Because they are responsible for tissue remodeling and cleansing, the removal of altered cells, phagocytosis, and the regulation of inflammation through the generation of cytokines, macrophages hold a pivotal position in the maintenance of tissue homeostasis. This is due to the fact that macrophages are responsible for all of these things.

Because of all of these qualities, it is now possible to discover immunotherapeutic techniques that specifically target macrophages that are associated with tumors (TAMs). A point of fact, TAMs are known to express immunological checkpoint markers including PD-L1, CD40, and Sirp in addition to prognostic markers like CD163, CD204, TREM2, and TREM1.

Because FC Receptors are present, there is a possibility that TAM can take part in antibody-dependent cell phagocytosis (ADCP) when it comes to the field of therapies. In this section, we are going to do a literature review on current research that concentrate on TAMs in relation to HPV+ cancers and look at the results of these investigations.

An infection caused by the HPV of mucosal tissue can lead to a number of different types of cancer, including cancer of the head and neck, CC, penile cancer, anal cancer, and vaginal cancer. It has been demonstrated that HPV-positive tumors contain a larger immune cell infiltrate than other types of cancers.

This immune cell infiltrate is determined by inflammation, immunosuppression, and an anti-viral response. In this context and considering the numerous roles that macrophages play, we will demonstrate the adaptability of TAMs in a tumor microenvironment that exhibits features of viral infection. This will be done while considering the various functions that macrophages perform [21].

HPV cancers

Infections of the skin and mucosa, which, in the majority of instances, result in lesions that are not malignant, are caused by HPV. Nevertheless, this is contingent on the particular type of HPV that is present. Carcinogenic strains of HPV have been identified, and they include 16, 18, and a number of other strains [22,23].

These high-risk strains generally infect the basal cell layers, which are more readily accessible at epithelial tissue transitions such as the squamo-columnar junction, which is located between the cervix and the uterus. At this junction, high-risk strains will proliferate in parallel with the epithelial cells when the epithelial cells divide. The cycle of HPV replication will result in the production of a locally inflammatory milieu (IL-1 and IL-6) and will also result in the recruitment of immune cells at the site of the lesion [24,25,26].

In parallel, HPV will ensure its own reproduction by locking infected epithelial cells in a replicative loop via early protein 6 and 7 (E6 and E7) [27]. This will result in abnormal replication of infected epithelial cells, which will lead to the development of low-risk squamous intraepithelial lesions (LSIL), followed by the potential development of high grade squamous intraepithelial lesions (HSIL) [22,23].

It is essential to take into consideration the fact that both E6 and E7 play a part in the epithelial-to-mesenchymal transition (EMT) [22,23]. The worst-case scenario is that the genome of the HPV virus will become integrated into the genome of the cell, which will ultimately lead to an increase in genomic instability and the development of cancerous tumors. The immune system will mount a reaction that is unique to the virus that is replicating at certain periods throughout the course of the disease's evolution.

A point of fact, the presence of proinflammatory cytokines (IL-1, IL-6, and TNF-) was documented in LSIL, but in HSIL, the recruitment of a mix of pro and anti-inflammatory cells (TGF-, IL-10) and cytokine was observed [28,29,30,31]. This was the case in both LSIL and HSIL. Immunosuppressive cells and cytotoxic cells that have been repressed are the primary components of the immune infiltration that can be seen within these tumors. Immune infiltration can also be found within the tumors themselves. This, as well as a few other topics connected to it, will be discussed in the following paragraph. The types of HPV-positive cancers that have garnered the most research include head and neck squamous cell carcinomas (HNSCC) and cervical malignancies.

[Note: HNSCC stands for head and neck squamous cell carcinomas.] {Note: It is essential to understand that HPV+HNSCC is not the same as HPVHNSCC}, which has a more dire prognosis and is brought on by the consumption of tobacco products and alcoholic beverages [32]. In spite of the fact that HNSCC can be either HPV+ or HPV-, over 95% of CCs are caused by HPV. In the case of HNSCC, this is not the situation. Other forms of cancer that can be caused by HPV include anal carcinoma, penile carcinoma, and vaginal carcinoma.

All of these types of cancer are exceedingly rare and are currently the subject of investigation. An immune reaction is always present after an HPV infection, as was discussed earlier. This is an unavoidable consequence of the virus. This immune response is characterized by the presence of a local inflammatory environment that shifts toward one that is immunosuppressive as the progression of lesions toward the formation of tumors continues to be active.

Conclusions

The HPV is an essential virus that has been linked to a wide variety of disorders, ranging from inflammatory problems to cancers. It

is imperative that individuals get vaccinated against this virus. In addition, we suggest that screening programs be implemented for this virus to detect instances at an early stage and so stop the progression of the disease to malignancy.

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