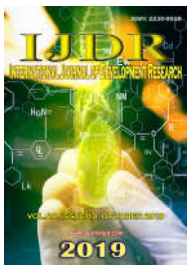
ISSN: 2230-9926

Available online at http://www.journalijdr.com

IJDR

International Journal of Development Research
Vol. 09, Issue, 10, pp. 30757-30759, October, 2019



RESEARCH ARTICLE OPEN ACCESS

GENOMIC CHARACTERISTICS OF HUMAN PAPILOMAVIRUS 16 AND 18

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ARTICLE INFO

Article History:
Received 20th July, 2019
Received in revised form
11th August, 2019
Accepted 06th September, 2019
Published online 23rd October, 2019

Key Words:
HPV 16,
HPV 18,
Genome,
Proteins.

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ABSTRACT

There are more than 200 Human Papilloma Virus serotypes, or commonly called HPV (Human Papillomavirus), they participate in a frequent number of pathologies that can affect various organs of the human body. Among high-risk HPVs, serotypes 16 and 18 can be highlighted, since most of them are associated with potentially pre-neoplastic lesions in certain anogenital carcinomas, with high tropism for cervical cells. The present work aims to demonstrate the mechanism of action and replication of the obligate intracellular parasite HPV, correlating its protein potential in relation to the neoplasms caused by serotype 16 and 18. It was based on a systematic and bibliographic research on the human papillomavirus genome. serotype 16 and 18. In general, HPV 18 in its integration with the host cell involves disruption of the E1 and E2 gene along with retention of the Long Control Region (CRL) at its first contact within the cell nucleus. Such disruption is believed to have a relief in E7 gene expression because of E2 involvement in viral regulation. Regarding HPV 16 proteins, it can be seen that E6 is made up of 150 aminoacids and has two regions called the zinc finger (composed of two antiparallel beta-leaves and one alpha helix) that interact with zinc, significantly altering the apoptosis mechanism and cell proliferation. These HPVs are in greater contact with the genital regions and the lack of condom use and poor hygiene corroborate intraepithelial lesions causing various pathologies to the organism.

Citation: ***Suzane Meriely da Silva Duarte et al*, 2019.** "Bradyrhizobium japonicum in no-tillage system under Urochloa ruziziensis¬¬ straw", *International Journal of Development Research*, 09, (10), 30757-30759.

INTRODUCTION

There are currently more than 200 Human Papillomavirus serotypes, or commonly called HPV (Human Papillomavirus), they participate in a frequent number of pathologies that can affect various organs of the human body depending on their risk classification. There are two pathological groups that classify them, HPV's with low oncogenic risk, which have tropism to the superficial squamous epithelium, such as skin, causing warts (papillomas), and the second group highlighted by HPV's with high oncogenic risk, have cell tropism. Mucosa, causing neoplasms as it occurs mainly in the regions of the uterus, vagina, penis and anus (MIRABELLO *et al.,* 2018). Among high-risk HPVs, serotypes 16 and 18 can be highlighted, since most of them are associated with potentially pre-neoplastic lesions in certain anogenital carcinomas, with a high tropism for cervical cells. Genetically, an interaction between both viral and cellular proteins can be perceived, in which case the E6 and E7 proteins are regularly expressed in the cervix and in the cell lines present in the epithelium. The genes also present in these viruses, such as E7 and E8, have cell transformation properties, such as blocking signals that induce cells to undergo apoptosis and other mechanisms (WEELE *et al.,* 2018). Many proteins of viral genetic load alone cannot be demonstrated in papillomas, carcinomas or any other alteration as they have only membrane destabilizing capacity, however, HPV 18 E4 protein and HPV 16 E7 protein can cause intraepithelial lesions, significantly assisting in the transformation process, replication within the cell, inducing morphophysiological transformations of host cells (MIRABELLO *et al.,* 2018). The present work aims to demonstrate the mechanism of action and replication of the

obligate intracellular parasite HPV, correlating its protein potential in relation to neoplasms caused by serotype 16 and 18, which are considered of high oncogenic risk and present in neoplasms that affect the genital region. and anal, with emphasis on cervical cancer.

METHODOLOGY

It was based on a systematic and bibliographic research on the human papillomavirus genome of serotype 16 and 18, in which the studies were identified and selected through references obtained from the database, using the following electronic search sites: PubMed, Google scholar and Scientific Electronic Library Online (SciELO). The guidelines identified and specifically related to the theme were evaluated according to their validity and recommendations, criticized and summarized, highlighting the evolution of the virus.

DISCUSSION

Viral genome of human papillomavirus serotype 18 and its proteins: Human papilloma is understood to be a strongly conservative family of DNA viruses in their transcriptions. Some individual HPV types have a genetic conservation above 90%, when they have some particularity of less than 10% in nucleotide composition they are still considered the same HPV type, but it becomes a variant belonging to that group. What sets them apart are the characteristic risks for intraepithelial neoplasia. This lineage and carcinogenicity have a specific correlation; in the case of HPV 18, it has three lineages and eight sublines (MORGAN *et al.,* 2018). Although HPV virus genotyping studies are numerous, a large proportion of HPV 18 studies come from serotype 16, as it is more present in cervicovaginal carcinomas, much is currently being studied about the interaction of HPV DNA in genomic DNA. because they cause various changes at the cellular and tissue levels (XU *et al.,* 2018). In a general sense, HPV 18 in its integration with the host cell involves disruption of the E1 and E2 gene along with retention of the Long Control Region (LCR) at its first contact within the cell nucleus. This disruption is believed to soften E7 gene expression because of E2 involvement in viral regulation. This integration also stabilizes messenger RNA transcriptions using a cellular polyadenylation signal (MORGAN *et al.,* 2018). The following table shows the correlation of the Human Papillomavirus in relation to histology, showing the predominant HPV type and the type of carcinoma, in order to understand the great role of serotype 18 in neoplasms.

Table I. HPV genotyping carcinoma types and age and differentiation factors

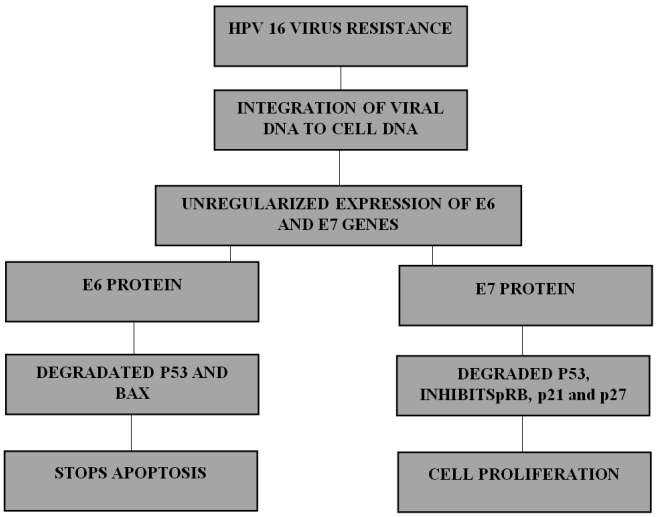
Type of carcinoma	Differentiation	Cell state	Age	HPV type
Scaly	Moderate / good	Involved	30	16 e 18
Scaly	Moderate / poor	Involved	35	18
Scaly	Moderate / poor	Involved	36	18
Scaly	Poor	Involved	37	18
Adenocarcinoma	No changes	Not involved	41	16 e 18
Scaly	Moderate	Not involved	46	18
Adenocarcinoma	Moderate / good	Involved	51	18
Scaly	Moderate / good	Involved	58	18
Scaly	Moderate	Not involved	69	18

SOURCE: Adapted from Corden *et al.,* 1999.

In order to accurately understand the proposed theme, it is clear that since the twentieth century there are studies that seek to demonstrate the prevalence of HPV 18 in the cervix (KARDANI and BOLHASSANI, 2018). According to Corden *et al.* (1999) a study of 13 women showed that the HPV most found and capable of generating a neoplasm was 18, even though 16 was present. In this case, HPV 16 enhanced cell differentiation, thus elevating carcinomas in the undeveloped squamous epithelium and adenocarcinoma (tumor in the granular cells) in development in women over 30 years of age, most of the cells in these age groups were involved and with neoplastic changes. Much is concerned about this high incidence, as it is clear that over time the number of cases tends to increase, according to the Pan American Health Organization (PAHO) cervical cancer is the 3rd most common in women. Latin America (PAHO / WHO Brazil, 2019). Worldwide, cervicovaginal cancer is the second type that causes most deaths in women and mostly caused by HPV infection (WHO, 2011). In HPV 18 proteins perform primordial functions for their multiplication and survival within the cell, but in contrast, cell organization becomes outdated and inconsistent for normalization of basic activities. The E7 protein induces DNA damage responses, denoted by the acronym DDR (DNA Damage Response), which protects the proper cellular replication of cellular DNA needed to amplify HPV virus DNA replication (KARDANI & BOLHASSANI, 2018). It is important to note that the response to DNA damage alters some mechanisms of the cell cycle, the G2 phase is significantly prolonged as this cell replication work becomes available to support viral load replication by reproducing new virions with such damage to the cell cycle. DNA, which causes kinases, which are phosphate group transfer enzymes to specific target molecules, to have dysfunctions, promoter protein phosphorylation and destabilization 53 which are mostly destabilized by the E6 protein. The S phase of the cell cycle affected by the virus is always renewed, because it is in this phase that the cell DNA duplication occurs (MORGAN *et al.,* 2018).

Viral genome of human papillomavirus serotype 18 and its proteins: HPVs capable of causing cervical cancer are classified as high-risk oncogenic HPVs including HPV 16, 18, 31, 33, 35, 39, 45, 51 52 and 58. Currently clinical and diagnostic methods for HPV detection that are available at low cost are: clinical examination capable of observing macroscopic changes, colposcopy, oncotic and histological cytology (WORLD HEALTH ORGANIZATION, 2002). These methods do not really identify the viral genotype, only the lesions caused by the microorganism. Biotechnological methods such as hybridization and PCR (Polymerase Chain Reaction) identify genotyping and the group in which HPV is inserted (KENTER *et al.,* 2009). HPV 16 can cause multifocal papular lesions in the anogenital region, this lesion is also called Bowenoid Papulosis and is characterized by multiple brownish-colored papules and is present in young people who have an active sex life. Cervical cancer is also closely linked to HPV 16 due to its high capacity for cellular transformation inducing other significant processes within the cell (OLIVEIRA; HAGA; VILLA, 2018). Human papillomavirus 16 is the most commonly observed in vulvar neoplasms, but in recent decades, HPV findings 18, 21, 31, 33 and 34 have been observed in these lesions due to the proliferation of warts in the region, and as untreated they may lead to various pathologies when they are associated with inflammation of other microorganisms, such as bacteria, fungi and protozoa (BOURGUIGNON; EARLE; SHIINA, 2019). Regarding HPV 16 proteins, it can be seen that E6 is made up of 150 amino acids and has two regions called the zinc finger - a zinc finger

(composed of two antiparallel beta-sheets and an alpha helix) that interact with zinc. . Thus, the property bound to E6 protein is characterized by the intimacy with the E3 family protein of ubiquitin ligase (E6-AP), inducing the formation of trimeric complex with p53 protein, promoting proteolytic degradation and reduction in p53 level. preventing activities that regulate the cell cycle, giving greater flexibility in DNA synthesis, allowing for more developed and unbridled replication (HOOI *et al.,* 2018).For a better understanding of HPV16 viral proliferation, the scheme below shows the multiplication processes and mechanisms of cell differentiation.



SOURCE: Adapted from FERRAZ; SANTOS; DISCACCIATI, 2012.

Figure I. Cellular Alteration Caused by HPV 16

Human Papillomavirus E2 protein serotype 16 significantly alters keratinocyte cell differentiation due to the intervention of notch - slit signaling (acts on cell coordination and differentiation, proliferation and programmed cell death). This interference natively regulates notch signaling, unbalancing the degradation of GAP (GTPase Activation Protein) proteins and inhibiting the degradation of protein kinases, evidencing the transformation and immortalization of these keratinocytes. E7 (OLIVEIRA; HAGA; VILLA, 2018).

Final considerations

In fact, HPV has been the subject of many studies on viral genotyping, as they undergo constant differentiation as they may include cellular genes in their DNA. Papillomavirus-associated infections and pathologies are becoming more and more common in adult and sexually active men and women. It is estimated that in about 10 years a large proportion of men and women worldwide suffer from HPV neoplasms, and more than 80% cause vaginal cervical cancer. In order to prevent and reduce these deaths, greater characterization in biotechnological tests and rapid diagnostics is required for the detection and treatment of HPV lesions. In short, HPV 16 and 18 have been the subject of much research as they cause various diseases such as vaginal and uterine cervix cancer, penile cancer, anal cancer and oropharyngeal cancer. In this sense, it is necessary that the population has clear and objective information about the pathogenicity and risk factors of the virus, and it is irrefutable that the best way to a quality of life in relation to HPV infection is, condom use, hygiene. genitals, body knowledge, HPV vaccination, and information about the diseases.

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