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HPV AND IMMUNE SYSTEM: AN EXAMINATION OF THE COMPLEX INTERACTIONS BETWEEN HPV AND HOST IMMUNE SYSTEM

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ABSTRACT

Cervical intraepithelial neoplasia (CIN) and cervical cancer are primarily attributed to human papillomavirus (HPV) infection. The virus can remain undetected for extended durations due to its ability to evade the immune system and disrupt normal cell cycle regulation through its integration into host cells. Following HPV infection, the host's immune system may develop a state of immunotolerance, which affects the maturation and function of various immune cells, including regulatory T cells, dendritic cells, natural killer cells, CD4+/CD8+ T cells, and macrophages. This immunological alteration encompasses the differentiation of tumorassociated macrophages, a compromised cellular immune response, an imbalance between Th1 and Th2 cells, infiltration of regulatory T cells, and a reduction in the activation and maturation of dendritic cells. In response to these immune changes, therapeutic vaccines aimed at activating the immune response are becoming increasingly prominent for the treatment of HPVrelated conditions, alongside the development of preventive vaccines designed to mitigate the risk of carcinogenesis. Evidence suggests a correlation between T cell infiltration and the regression of disease. In studies involving animal models, especially rabbits and canines, there is a significant elevation of CD11c, CD4, and CD8+ T cells observed during the early stages of regression and adaptive immune responses.

KEYWORDS: CIN, Regression, persistence, papillomavirus, innate immunity, adaptive immunity, epidermis, and immune evasion.

INTRODUCTION

Human papillomavirus (HPV) is a small, non-enveloped DNA virus, approximately 50-55 nm in diameter, known for its impressive resilience to heat, acid, and ether.[1] This virus is particularly common in tropical regions, where it targets stratified squamous cells, and it depends on the differentiation of skin and mucosal epithelial cells for replication.[2] HPV types are classified based on their genetic characteristics, with a new type being recognized when the E6, E7, and L1 gene regions show less than 90% sequence homology with any previously identified HPV strains. Currently, more than 90 distinct genotypes have been documented, with new variants continuously emerging.[3] L1 and L2 are two fundamental encapsulating structural proteins observed in the HPV genome.[4]

Adherence to and invasion of human cells depend on the L1 protein, which is a core component of the capsid (CAP).[5] The main surface-exposed areas of L1 are composed of hypervariable amino acid loops, as evidenced by studies showing that antibodies against a particular kind of HPV only weakly interact with other varieties. Different papillomavirus kinds have modified these loops in response to host immunological selection pressures. As a result, the current prophylactic vaccinations are mainly useless because of their inadequate cross-protective characteristics.[6]

The early segment of the virus has a substantial amount of genes, while the L2 gene product serves as essential for the early phases of viral genome production.[7] Unlike L1, the primary capsid protein, E1 has high conservation value and encodes a virus-specific DNA helicase that is needed for viral genome replication and amplification.[8] The N-terminal and C-terminal domains of E2 remain stable across different HPV types, and it serves as key for viral transcription, replication, and genome dispersion. It has the capacity to affix itself to specific regions in the genomes of the virus and the host cell.[9]

E6 and E7's transcriptional expression can be controlled by E2. These proteins are responsible for facilitating all HPV strains to enter the cell cycle, stimulating genome replication in the epithelium's mid-layers, and inhibiting specific innate immune components.[10] During the early

stage of genome amplification that follows infection, the proteins E1 and E2, which are involved in viral replication, are essential. They might no longer be required for episome maintenance, though, once the copy number reaches equilibrium.[11]

E2 binding proteins play a significant part in replication, division, and genome transfer. The exact roles of the E6 and E7 proteins found in infected basal cells are still unresolved despite the fact that they have a key in maintaining the cell cycle. While the mechanism of wound healing is vital for boosting early cellular development in low-risk HPV types, E6 and E7 are known to enhance cell proliferation in the basal and parabasal layers in high-risk types.[12]

HPV AND IMMUNE EVASION

Mechanism of immune evasion used by HPV

MHC class I alleles, which serve as necessary ligands for the inhibitory proteins on natural killer (NK) cells, specifically HLA-C and HLA-E, are evaded in immune evasion.[13] This approach relies on MHC class I molecules, namely HLA-A and HLA-B, which are mostly in charge of delivering viral peptides. Additionally, it should be noted that the HPV-16-associated E6 and E7 oncoproteins are commonly expressed in both precancerous and cancerous lesions.[14] These proteins disrupt the dynamics of the cell cycle and the death of cells, which in turn leads to cellular immortality, transformation, and the start of carcinogenesis. They do this by interacting with the regulatory pathways of the PRB and P53 genes in – cells.[15]

The genomic instability caused by E7 and E6 results in the silencing of tumor suppressor genes and the activation of oncogenes.[16] Reduced immune responses from infected cells establish an environment that is primarily immunosuppressive, which promotes the growth of cancer and hinders communication with neighbouring immune cells.[17] HPV deliberately targets DNA sensors and starts a chain of events to combat viral infection. HPV modifies DNA sensor function and inhibits interferon generation via controlling IRF transcription factors.[18]

The heightened activity of HPV38 E6E7 leads to a notable reduction in the expression levels of both channel IRF-1 and MHC I. When the transfer mechanism for IRF is obstructed, HPV16 E6 diminishes the production of interferons, specifically IFN-α, IFN-β, and IFN-κ. Furthermore, IRF has the capacity to influence the transcription of HPV through a feedback mechanism.[19] The immunosuppressive signals that emerge during the neoplastic transformation of precancerous epithelial cells may significantly contribute to the carcinogenic processes linked to HPV by potentially modulating the activity and functionality of antigen-presenting cells (APCs). Cells transformed by HPV secrete immunomodulatory factors that recruit regulatory T cells, tumor-associated macrophages, and suppressor cells.[20] By using CTLA-4 to suppress the expression of CD80 and CD86, regulatory T cells (Treg) are essential for the maturation of dendritic cells. Tumor cells can effortlessly evade the host immune system's detection via this process. The benefits of CTLA-4 inhibition in individuals with cervical cancer and tumors of the head and neck (HNSCC) are being studied in ongoing clinical trials.[21]

INNATE HPV RESPONSE TO HPV

A number of membrane and cytoplasmic pattern recognition receptors (PRRs) are compromised by the human papillomavirus (HPV). Among these, membrane sensors called Toll-like receptors (TLRs) play a crucial role in the initiation of both innate and adaptive immunological responses.[22] Higher expression levels of TLRs 3, 7, 8, and 9 have been connected to patients' efficient virus clearance, according to research into biomarkers that may predict HPV clearance.[23]

Research indicates that human papillomavirus (HPV) specifically targets the immune pathway associated with 'sitesol DNA sensors.' The Toll-like receptor 9 (TLR-9), which plays a crucial role in the immune response to infections from double-stranded DNA viruses, has been found to have diminished expression in cervical cancer samples positive for HPV16, as well as in HPV-positive cell lines and keratinocytes that express the E6 and E7 proteins of HPV16 and HPV18.[24] The use of small interfering RNA (siRNA) to inhibit E6 and E7 can lead to a restoration of TLR-9 expression. Furthermore, the upregulation of interferon gamma-inducible DNA sensor protein 16 (IFI16) has been shown to inhibit the transcription and replication of HPV18.[25]

TLR9 can identify unmethylated CpG sequences found in DNA as well as synthesized CpG oligodeoxynucleotides (CpG ODNs). Additionally, TLR7 and TLR8, which are involved in the detection of single-stranded RNA, can be activated by synthetic oligoribonucleotides and tiny imidazoquinoline derivatives.[26] Cytoplasmic dsRNA sensors, including retinoic acid-inducible gene I (RIG-I), melanoma differentiation-associated gene 5 (MDA5), and protein kinase R (PKR), are continuously expressed by keratinocytes (KCs). Type I and type II interferons (IFNs) and poly(I·C) increase the expression of these four dsRNA sensors (TLR3, PKR, RIG-I, and MDA5) in KCs, which improves their capacity to detect viral infections.[27]

NK cells perform as our primary defenses against infections and are necessary components of the innate immune response. Its two main methods for identifying and destroying virus-infected or transformed cells are the production of cytotoxic granules and the triggering of apoptosis in the afflicted cells.[28]

The relationship between NKT cells and tumor immunity has been gradually elucidated. NKT cells play a role for regulating early tumor growth, yet their impact seems to diminish as tumors progress, according to research using a mouse model of adoptive immunotherapy with tumors expressing HPV16 E7 (TC-1).[29] Although the exact involvement of NKT cells in HPV lesions' spontaneous remission is still unknown, research from patients with and without immunocompetence shows that the immune system plays a major role in the possibility of haphazard remission.[30]

Recently, a transgenic mouse model that produces the HPV16 E7 protein in epidermal keratinocytes has been used to clarify the immunosuppressive properties of NKT cells. By generating IFN-γ, infiltrating CD1d-restricted NKT cells within E7-positive skin grafts help to prevent rejection.[31] The ability of NKT cells isolated from lymph nodes draining these skin grafts to restrict CD8 T cells multiplying, cytokine generation, and cytotoxic activity is also demonstrated.[32]

Research indicates that tumors associated with HPV exhibit the expression of genes that are pertinent to adaptive immune responses, leading to significant T cell-mediated immune activity. Additionally, proinflammatory chemokines, including CXCL 9, 10, and 100, as well as their corresponding receptors such as CXCR3, are found to be highly expressed within the HPV microenvironment.[33]

These variables have a major impact on the recruitment of tumor-infiltrating lymphocytes (TILs), especially CD8+ cytotoxic T cells. When it comes to targeting neoplastic cells, CD8+ cytotoxic T cells are the main effector cells.[34] Accordingly, CD8+ T cells are essential for the immune system's shielding against intracellular infections as well as tumor cells.[35]

VACCINATION

The most successful method of treating viral infections is prevention through vaccination, and the invention of the HPV vaccine was an important technological breakthrough in the past 20 years.[36]

High-risk HPV strains 16 and 18 are the focus of widespread vaccination campaigns. The structural proteins L1 and L2, found on virus-like particles, are used in modern vaccines.[37] L1 neutralizing antibodies fall into two categories: the first prevents binding to cell surfaces, while the second prevents attachment to basement membranes. Through direct interaction or by interfering with crucial conformational changes, both groups seem to hinder viral internalization.[38] The injectable Gardasil®4 vaccine, which is made from the yeast Saccharomyces cerevisiae, contains amorphous aluminum sulfate hydroxyphosphate (AAHS) as an adjuvant.[39] The primary capsid protein linked to the human papillomavirus, the purified, C-terminally shortened L1 protein, is used in this vaccine to create a self-assembled virus-like particle (VLP). development of this technology employs recombinant DNA methodologies.[40] The vaccine offers approximately 90% efficacy in preventing genital warts caused by HPV types 6 and 11, and it provides around 70% protection against anal and cervical cancers associated with HPV types 16 and 18. It is particularly effective for individuals aged 15 to 45 years for women and 16 to 26 years for men.[41]

CervarixTM, a bivalent HPV vaccine manufactured by GlaxoSmithKline (GSK), received FDA approval in October 2009, following its earlier approval by the European Medicines Agency (EMA) in September 2007. This vaccine is effective in providing protection against the two most common carcinogenic HPV types, HPV16 and HPV18.[42] The formulation of CervarixTM includes HPV strains HPV16/18 along with AS04, which acts as an adjuvant. AS04 is composed of aluminum hydroxide and monophosphoryl lipid A (MPL), a detoxified bacterial lipopolysaccharide that functions as an agonist for Toll-like receptor 4, thereby stimulating both innate and adaptive immune responses.[43] The principal aim of prophylactic HPV vaccination is to induce neutralizing antibody responses against viral particles, which is crucial for preventing future HPV infections.[44] Virus-like particles (VLPs) are generated by recombining HPV capsid proteins that lack viral DNA, ensuring that they are non-infectious and non-carcinogenic.[45]

Beyond its efficacy in preventing cancer and precancerous conditions, vaccination with L2 protein virus-like particles (VLPs) may also offer protection against a range of benign skin lesions, consequently reducing the public health burden associated with cutaneous warts.[46] Importantly, peptide fragments derived from the L1 protein of HPV-16 have been incorporated into chimeric L2 vaccines to enhance the immune response to L2 particles, thereby broadening the scope of vaccination efforts.[47]

DISCUSSION

Human papillomavirus (HPV) infection is responsible for approximately 30% of cancers associated with infections globally, and it is implicated in nearly all cases of cervical cancer among women. The established causal relationship between HPV and the majority of anogenital cancers is well-documented, although its role in non-anogenital and skin cancers remains ambiguous.[48] Recent studies on immunotherapy have shown promise in addressing tumour-induced immune suppression; however, a significant number of patients exhibit limited responses to immune checkpoint inhibitors.[49] Tumour regression appears to be associated with a cell-mediated immune response to early HPV antigens, including E2, E6, and E7, with CD4+ T cell infiltration being crucial, as CD8+ T cells alone are insufficient for effective regression.[50] Furthermore, regulatory T cells (Tregs) contribute to local immune suppression in chronic lesions. Additionally, the presence of specific HLA molecules affects immune recognition, as certain HLA

types are linked to an increased risk of HPV-related cancers due to their ability to bind HPV peptides.[51] The review articulates the advancing knowledge regarding effective host responses to HPV infection, as well as the possible deficiencies in these responses that could lead to viral persistence and the formation of premalignant lesions.[52] Neutralizing antibodies in serum against the major capsid protein L1 are protective against viral challenges in natural infections.[53] Toll-like receptors (TLRs) serve as molecular adjuvants, presenting a new avenue for the prevention of HPV infections and guiding the development of effective vaccines.[54] The epidemic nature of HPV infection is particularly concerning in developing countries, where it is linked to high mortality rates. Additionally, the E1 protein may play a significant role in immune evasion, thereby enhancing the replicative cycle and contributing to cancer development.[55]

CONCLUSION

The important part that human papillomavirus (HPV) plays in the development of cancer, particularly cervical cancer, which makes up a sizable percentage of HPV-related cancers globally. It emphasizes the way HPV contributes to viral persistence and carcinogenesis by avoiding immune detection and interfering with immune responses through mechanisms such as immune checkpoint suppression, regulatory T cell activity, and altered HLA molecule expression. The restricted efficacy of CD8+ T cells alone and the significance of cell-mediated immune responses, especially the function of CD4+ T cells, in tumour regression and the possible application of Toll-like receptors (TLRs) as molecular adjuvants in vaccine development, as well as the protective function of neutralizing antibodies against the viral capsid protein L1. Even with improvements in treatment and prevention strategies, HPV remains a major health issue and a contributing factor to high death rates, particularly in areas with little resources. Future approaches that concentrate on immune modulation, novel vaccinations, and resolving inequalities in vaccine availability may considerably lessen the prevalence of diseases linked to HPV worldwide.

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