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Review

The current state of therapeutic and T cell-based vaccines against human papillomaviruses

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ABSTRACT

Human papillomavirus (HPV) is known to be a necessary factor for many gynecologic malignancies and is also associated with a subset of head and neck malignancies. This knowledge has created the opportunity to control these HPV-associated cancers through vaccination. However, despite the availability of prophylactic HPV vaccines, HPV infections remain extremely common worldwide. In addition, while prophylactic HPV vaccines have been effective in preventing infection, they are ineffective at clearing pre-existing HPV infections. Thus, there is an urgent need for therapeutic and T cell-based vaccines to treat existing HPV infections and HPV-associated lesions and cancers. Unlike prophylactic vaccines, which generate neutralizing antibodies, therapeutic, and T cell-based vaccines enhance cell-mediated immunity against HPV antigens. Our review will cover various therapeutic and T cell-based vaccines in development for the treatment of HPV-associated diseases. Furthermore, we review the strategies to enhance the efficacy of therapeutic vaccines and the latest clinical trials on therapeutic and T cell-based HPV vaccines.

Contents

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1. Introduction

Human papillomavirus is the causative agent of a multitude of conditions including warts, cancer, and other diseases. In particular, HPV is responsible for nearly 100% of cervical cancer cases, which remains the fourth most common female cancer (Forman et al., 2012; Wakeham and Kavanagh, 2014). Furthermore, HPV has been shown to be a human biological carcinogen for five other types of cancers: penile, vaginal, vulvar, anal, and oropharynx including base of the tongue and tonsils (Forman et al., 2012; Maxwell et al., 2015; Mehanna et al., 2013; Wakeham and Kavanagh, 2014). Over 200 types of HPV had been identified and categorized into high risk and low risk groups according to their degree of oncogenic capacity (Egawa et al., 2015). Among high-risk HPV types, type 16 and 18 are the most carcinogenic and are responsible for inducing over 70% of cervical cancer cases (Walboomers et al., 1999). To date, HPV infections remain extremely common and represent a significant global health burden (Forman et al., 2012).

Most sexually active women will be infected by HPV during their lifetime; the majority of these infections will remain asymptomatic and be cleared by the immune system. However, for a handful of infected women whose immune system fails to clear the infection, these can develop into persistent HPV infections, which may further progress into low and high-grade cervical intraepithelial neoplasia (CIN) and consequently cervical carcinoma, or regress at any stage of this process (for review see (Ghittoni et al., 2015; Ostor, 1993)).

The identification of HPV as an etiological factor for HPV-associated malignancies allows for the opportunity to control these cancers through immunization and other target therapies. Vaccines have been traditionally used as a preventative measure against infectious disease. Several successful prophylactic vaccines have been developed to prevent disease-causing HPV types targeting the major capsid protein L1 of the viral particle (for review see (Harper, 2009; Kash et al., 2015)). Prophylactic vaccines have been effective in preventing vaccinated, healthy patients from acquiring HPV infections. They have also been effective in preventing previously infected patients who do not have active infections from being re-infected by the same HPV type. However, there is no strong evidence demonstrating any therapeutic effects of these prophylactic vaccines in treating and clearing established HPV infections and HPV-associated lesions (for review see (Harper and Williams, 2010; Ma et al., 2012)).

While there have been giant strides in the prevention of HPV infections and HPV-associated malignancies, there is still a need to develop treatments for the control of existing HPV infections and its associated diseases. Our review will cover various therapeutic and T cell-based vaccines in development for the treatment of HPV-associated cancers and lesions. Moreover, we will review strategies designed to enhance the efficacy of these vaccines and review the latest clinical trials on both therapeutic and T cell-based HPV vaccines.

2. Therapeutic vaccines

Due to the prevalence of HPV infections worldwide, there is an urgent need to develop effective treatments for established HPV infections and HPV-associated diseases. One potential treatment method involves the use of therapeutic vaccines. Unlike preventative vaccines, which are intended to generate neutralizing antibodies against viral particles, therapeutic vaccines are intended to stimulate cell-mediated immune responses to specifically target and kill infected cells. In many occasions, as HPV-associated lesions develop into cancer, the HPV viral DNA will be integrated in to the host's genome (Klaes et al., 1999). Typically, the integration process leads to the deletion of many early (E1, E2, E4, and E5) and late (L1 and L2) genes. The deletion of L1 and L2 genes during HPV DNA integration renders the prophylactic vaccines ineffective in targeting infected cells. In addition, E2 is a negative regulator of the HPV oncogenes E6 and E7; therefore, the deletion of the E2 gene during integration leads to the increased expression of these oncoproteins (for review see (Doorbar, 2016; zur Hausen, 2002)). This process is believed to contribute to the carcinogenesis of HPV-associated lesions, and the uncontrolled expression of E6 and E7 is considered a biological hallmark of HPV-associated cancers. Since HPV oncoproteins E6 and E7 are necessary for the generation and maintenance of HPV-associated malignancies, they are, consequently, constantly expressed and remain present and transcriptionally active in the transformed cells in HPV-induced cancer and precancerous lesions. Furthermore, since E6 and E7 are foreign proteins they are able to circumvent the setback of immune tolerance against self-antigens, a challenge presented by many other cancers. Thus, E6 and E7 serve as ideal targets for therapeutic HPV vaccines (for review see (Yang et al., 2016)). These findings have initiated many efforts to create an optimal immunotherapeutic treatment against HPV infections and diseases.

There are several types of therapeutic HPV vaccines that have been developed and tested in preclinical and clinical trials, most of which mainly target HPV E6 and E7. These include live vector, protein or peptide, nucleic acid, and cell-based vaccines. Most therapeutic vaccines contain E6 and E7 antigens in various forms, and aim to deliver these antigens to antigen-presenting cells (APCs) to stimulate antigen presentation through major histocompatibility complex (MHC) class I and MHC class II. This leads to the generation of CD8+ cytotoxic T cell or CD4+ helper T cell responses, respectively. Before the E6 and E7 antigens can be presented on the MHC class I molecule for the stimulation of CD8+ T cell responses, they are processed and digested in to smaller peptides by the proteasome in the APCs. Not all peptide fragments can be successfully