Editorial

Therapeutic vaccines for human papillomavirus-related cancer: progress and challenges

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Human papillomavirus (HPV) is the most global widespread sexually transmitted disease. In public health, the epidemiological importance of HPV infection is related to its ability to induce malignancy in epithelial cells (1). In fact, high-risk HPV is associated with virtually all cases of cervical cancer, which is the fourth most prevalent in women worldwide, and one of the leading causes of death. Actually, a woman dies of cervical cancer every two minutes (2). In this concern, a global strategy to eliminate cervical cancer was recently launched by the World Health Organization (WHO) (3). Importantly, persistent HPV infection is also related to other forms of cancer, including the vagina, vulva, anus, penile, tongue, and oropharynx. Prophylactic vaccines are one of the most essential disease-prevention practices, and screening early HPV lesions with different approaches can prevent cancer development. However, the landscape of HPV-related cancer and the recurrence rates following usual treatments highlights emerging trends in cancer treatment (4).

In the field of therapeutic vaccines, the focus of HPV research relies on strategies that deliver HPV oncoproteins to target immune cells (5-7), eliciting an antitumor response capable of controlling tumor development and achieving partial or total tumor remission. Furthermore, treatment combinations are required to boost the antitumor potential of a vaccine candidate (8-11). In this proposal, Lee *et al.* [2022] design vaccines based on HPV-16 E7 short or long peptides and tested different treatment approaches in a tumor-mouse model (12). The authors emphasize the importance of combining therapeutic vaccines with adjuvant and immune checkpoint inhibitor to reach a better outcome. Interestingly, an improved antitumor effect was observed when long peptides (E7-PL35) were adjuvanted with flagellin, especially when associated with anti-PDL1. The efficacy of synthetic long peptides of HPV-16 combined or not with chemotherapy or immune checkpoint inhibitors was well documented in clinical and preclinical trials (13-18), highlighting the potential of vaccines based on HPV-16 E7 long peptides to treat HPV pre-malignant and malignant lesions. Importantly, combined therapies showed to be essential to achieve strong and protective immune responses, especially for invasive cancer (18).

In preclinical studies, other vaccine platforms showed strong antitumor activity against HPV-related tumors. Diniz *et al.* [2010] and Porchia *et al.* [2011] developed two vaccine strategies with therapeutic potential against HPV 16-related tumors, one using naked DNA (19) and the other using recombinant protein (20). These vaccines are based on the production of a hybrid protein formed by the fusion of Herpes simplex virus-1 (HSV-1) glycoprotein

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D (gD) and the HPV 16 E7 oncoprotein (gDE7), which activate $CD8^+$ E7-specific T cells and elicit a significant antitumor response in mice models. When combined with other techniques such as electroporation (10), IDO inhibitors (9), melatonin (9), polyinosinic:polycytidylic acid [poly(I:C)] (20), spores (11), chemotherapies (7,8), and IL-10 inhibitors (21), the antitumor potential of gDE7-based vaccines was boosted.

In recent years, a great advance in cancer research was observed regarding therapeutic vaccines. There is no doubt that cancer vaccines are the new frontiers of immunotherapy. High demand and expectations reside on cancer vaccines, with promising immuno-therapeutics possibility to reach a better outcome in cancer patients. Further studies targeting immune system mechanisms are necessary for translational research of ongoing vaccine candidates and for future vaccine designs.

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