

The Potential Therapeutic Usefulness of Targeting BK Polyomavirus in Prostate Cancer

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Introduction

Prostate cancer (PCa) is a slow-growing, organ-confined tumor usually accompanied with a favorable overall prognosis. Current standard-of-care chemotherapy, and recently immunotherapies, for patients suffering from this disease may prolong overall survival and improve quality of life, but they do not prevent tumor recurrence and thus are not curative. Underlying reasons are not completely understood. Recent investigations support a possible carcinogenic activity of the human BK polyomavirus (BKPyV) in the prostate. In this commentary, we envisage the development of BKPyV-related therapeutic strategies to be beneficial for individuals at risk of developing PCa.

For 2015, the American Cancer Society predicted that prostate cancer (PCa) would account for 26% (220,800) of all new cancer cases in men and for 9% (27,510) of all male cancer deaths in the United States [1]. The high incidence-to-mortality ratio predominantly reflects the favorable prognosis of localized disease, which is often curable with surgery/radiation. Recurrence occurs in 20%-30% of the patients [2]. For these cases, androgen deprivation therapy is most likely effective, but a large proportion eventually develops a hormone-independent disease that often progresses to castration-resistant prostate cancer (CRPC). Current chemotherapy and immunology-based therapies for CRPC may prolong survival and quality of life but are not curative [3]. Chemotherapy is the treatment of choice after second and third-line hormone ablation therapy. First-line chemotherapy with docetaxel and prednisone was considered the standard-of-care for CRPC with detectable metastatic disease [4]. Therapeutic interventions at the immunological level have also been explored for the treatment of PCa. For instance, autologous dendritic-cell-based agents (Sipuleucel-T), whole cell- (GVAX) and PSA-targeted viral vector-based (PROSTVAC) agents have been extensively studied in the context of metastatic CRPC [5]. Although these emerging treatments provided better results in terms of efficacy in phase II clinical trials, as compared to standard chemotherapeutic treatments, they did not yield satisfactory progression-free survival and hazard ratio (HR) of death in phase III trials [5]. Nevertheless, cancer immunotherapy is a promising lead [5]. Taken together, new therapies that more specifically reduce the risk of PCa progression are urgently needed. Here, we propose to address these needs by generating specific tools targeting viral agents involved in the genesis of PCa, such as BK polyomavirus (BKPyV). We envision corresponding therapies to be especially effective in a preemptive regimen when initiated following removal of the primary tumor, prior to the establishment of gross metastases.

The oncogenic potential of BKPyV is mainly due to the activity of its regulatory protein Large T antigen (LTag). The antigen is primarily involved in the initiation of the proliferation of the virus as soon as

permissive cells are infected [6]. Beside its major activity in viral replication, LTag also binds to and inactivates the products of tumor suppressor genes, such as Retinoblastoma family proteins (pRb) and, particularly, p53 [6]. In non-permissive cells, in which an abortive infection takes place (by uncoupling of early gene expression from late gene expression), the LTag binding to pRb and p53 triggers a carcinogenic process [7], as observed *in vitro* and *in vivo* in animals [8]. In humans, the only evidence on the involvement of this virus in the neoplastic process of the prostate is given by its detection at pre-early stages of PCa, such as the proliferative inflammatory atrophy [9, 10].

The detection of the virus at molecular levels in tumor specimens correlates with BKPyV-specific immune responses that might be involved in the progression of PCa [11]. Indeed, in PCa patients with evidence of disease recurrence and BKPyV-positive tumors, the LTag induced an immune tolerogenic response able to sustain the malignancy and favor a bad prognosis [12]. Therefore, exploiting the immunogenic activity of LTag in PCa patients with a BKPyV-driven tolerogenic signature is of utmost importance. We are thus currently working on the generation of a vaccinia vector encoding immunogenic peptides within BKPyV LTag, which are able to revert the regulatory profile enhanced by specific portions of BKPyV LTag [13]. In addition, we recently found that the antibody response to LTag might play a central role in informing about the prognosis of this malignancy. Indeed, the preoperative BKPyV LTag serostatus of patients undergoing surgery at first diagnosis might act as an independent predictor of biochemical recurrence and serve as a promising novel therapeutic approaches targeting LTag [14].

Owing to its function, LTag localizes to the nucleus of infected cells. In abortive infections, the presence of the LTag/p53 complex in the cytoplasm of transformed cells is a peculiar sign [15]. By the accumulation of LTag in the cytoplasm this antigen becomes an immunogenic determinant which is able to provide effective cellular and humoral immunosurveillance against infected cells [16]. In addition, LTag production is regulated by viral microRNAs [17]. Indeed, the latter could not only control LTag expression but also modulate its antigenic activity [18].

Therefore, targeting BKPyV LTag may lead to innovative approaches in the treatment of PCa based on sound immunological findings in either preventive or

Authors' Contribution

MP designed, coordinated and drafted the manuscript. EXK participated in the designing of the manuscript and helped to draft it.

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