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Emerging immunotherapeutic strategies targeting telomerases in genitourinary tumors

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ABSTRACT

Telomerase activity and telomere length are essential for the pathogenesis of several human diseases, including genitourinary tumors. Telomerase constitutes a complex system that includes human telomerase reverse transcriptase (hTERT), human telomerase RNA component (hTR) and telomerase associated protein 1 (TEP1), which are overexpressed in tumor cells compared to normal cells and are involved in the carcinogenesis and progression of renal cell carcinoma (RCC), bladder (BC) and prostate cancer (PCa). In addition, telomerase degraded peptide fragments expressed on the surface of tumor cells lead to their recognition by immune cells. On this scenario, *in vitro* and *in vivo* studies have shown effective anti-tumor activity of hTERT-tailored strategies in genitourinary tumors, including active immunotherapy with hTERT-peptide vaccines and passive immunotherapy with hTERT-transduced T cell infusion. This review emphasizes the role of telomerase in the carcinogenesis and progression of genitourinary tumors, thus underlying the potential of emerging telomerase-tailored immunotherapies in these patients.

1. Introduction

In the last decade, immunotherapy has completely changed the therapeutic armamentarium of patients with genitourinary tumors. In particular, the approval of anti-Programmed-death-1 (PD-1) agents in patients with renal cell carcinoma (RCC) and bladder cancer (BC) has increased their life expectancy, with a generally tolerated toxicity profile. On the contrary, patients with prostate cancer (PCa) seem to scarcely benefit from this strategy.

Due to the enthusiastic results obtained by immunocheckpoint inhibitors in cancer patients, researchers have increased their efforts to identify novel and more effective targets for immunotherapeutic approaches. Based on its pivotal activity, telomerase is emerging as a potential candidate for future therapeutic strategies in genitourinary tumors. Telomerase is a ribonucleoprotein complex that maintains the length and integrity of telomeres, the ends of chromosomes, by restoring their repetitive sequences (TTAGGG) that would be lost during cell divisions (Hayflick, 1998). Telomerase is overexpressed in about 80–95% of cancers and is present at very low levels or almost undetectable in normal cells (Shay and Bacchetti, 1997). Telomerase constitutes a complex system of large molecules that cooperate to maintain the chromosomal stability. They include three main components, called respectively human telomerase reverse transcriptase (hTERT), human telomerase RNA component (hTR) and telomerase associated protein 1 (TEP1) (Blackburn, 2010). In addition, the two human telomeric repeat binding factors 1 and 2 (TRF1, TRF2) also contribute to telomerase activity (Matsutani et al., 2001). Basically, hTR binds to the last few bases to 5′-3′ strand and, successively, hTERT starts synthesizing new bases, leading to telomere lengthening and cell immortalization (Huang et al., 2013).

The expression of the telomerase degraded peptide fragments on tumor cell surface constitutes one of the means by which cancer cells are recognized and attacked by immune cells (Jafri et al., 2016). This is a standard event in cancer tissues and represents one of the key events

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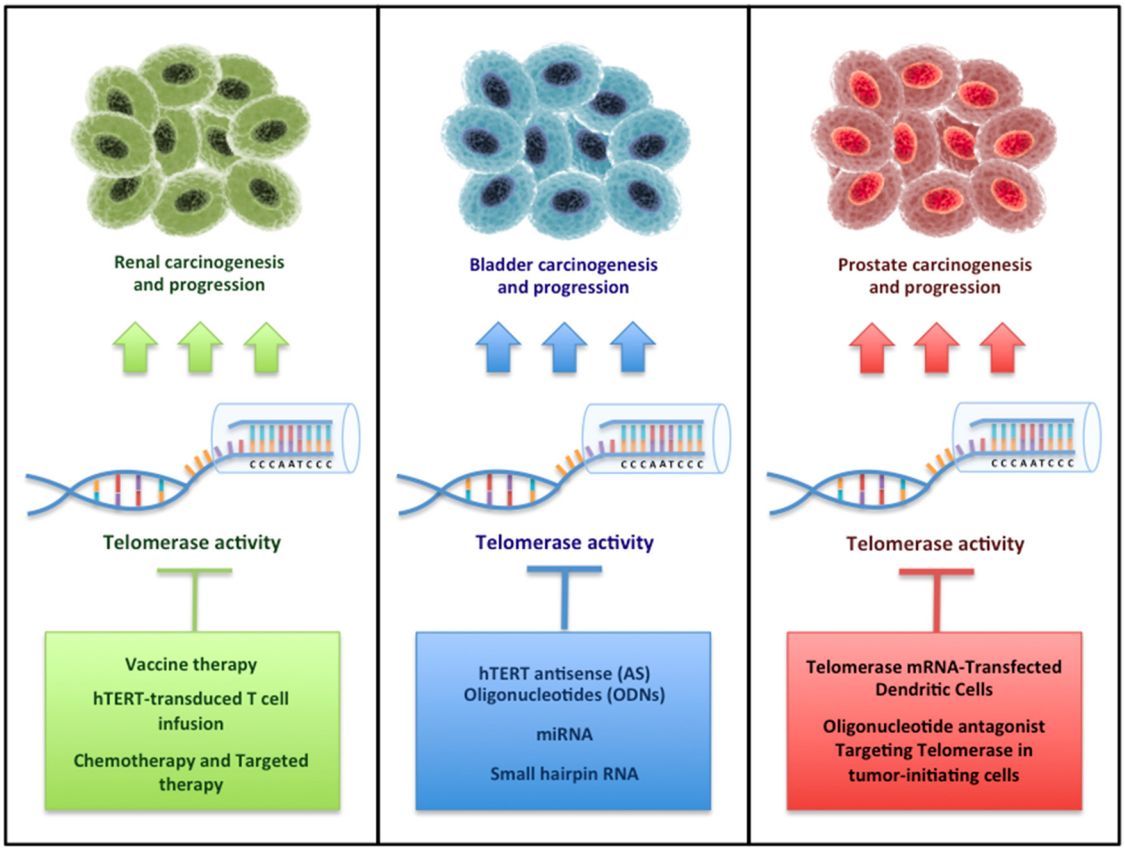

Fig. 1. Telomerase-tailored strategies in genitourinary tumors. hTERT = human telomerase reverse transcriptase; miRNA = microRNA.

that lead to the activation of cytotoxic T lymphocytes (CTL), thus promoting immune anti-tumor response.

This review emphasizes the role of telomerase in the carcinogenesis and progression of genitourinary tumors, thus underlying the potential of emerging telomerase-tailored immunotherapies in these patients.

2. Telomerase as a target for cancer immunotherapy

Due to its key functions and its role as a hallmark of cancer cells, telomerase acts as an ideal target for cancer immunotherapy (Fig. 1). These approaches include anti-telomerase vaccines and the transfer of hTERT-specific cytotoxic T lymphocytes.

2.1. Telomerase vaccination

Telomerase-based vaccines are in course of evaluation in cancer patients. The majority of these vaccines are directed against hTERT, mostly due to its almost complete tumor specificity (Vonderheide, 2002) and to its ability to produce epitopes for both MHC class I and class II pathways (Vonderheide, 2008). At present, more than 25 different hTERT peptides have been exploited as epitope-mimicking structures or mimotopes. The majority of them are associated with MHC class I-mediated enhancement of CTL response, whilst a few of them are implicated in MHC class II-mediated induction of CD4 + T cell response (Schroers et al., 2002, 2003; Brunsvig et al., 2006a; Liu et al., 2010).

The list of vaccines includes several agents, such as GV1001 (in combination with Granulocyte Macrophage Colony-Stimulating-Factor, GM-CSF), GX301, GRNVAC1 and VX-001 (Xu and Goldkorn, 2016) (Table 1). GV1001 consists of 16 amino acids and offers the advantage of eliciting both $CD8^+$ and $CD4^+$ responses (Brunsvig et al., 2006b; Kokhaei et al., 2007). It has been recently reported that GV1001 acts as a cell-penetrating peptide (CPP) allows the cytosolic delivery of macromolecules including proteins, DNA and siRNA through extracellular heat shock protein 90 (eHSP90) and 70 (eHSP70) complexes (Lee et al., 2013). The eHSP-GV1001 complex may be taken up by antigen-presenting cells (APCs) and transferred to MHC class I molecules (cross-presentation), inducing a strong CTL response after recognition by CD8 + T cells (Kim et al., 2016).

As for GX-301, it is composed by four peptides (peptide540–548, 611–626, 672–686 and 766–780), each one with the possibility to induce specific T cell responses (Fenoglio et al., 2015). It has been shown that GX301 to have anti-tumor activity and be well tolerated in patients with stage IV RCC or PCa resistant to conventional treatments. Indeed, prolonged Progression-Free Survival (PFS) and Overall Survival (OS) were observed, without serious adverse events (Fenoglio et al., 2013).

On the other hand, GRNVAC1 (Table 1) is based on patient-derived dendritic cells pulsed with RNA encoding for a chimeric protein (lysosomal targeting signal LAMP fused to TERT) to enhance TERT peptide digestion and display (Stohr and Blackburn, 2008). Otherwise, VX-001 (Table 1) is composed by two peptides, ARG-Vx001 (TERT572) and TYR-Vx001 (TERT572Y). Vx-001 completed a randomized, placebo controlled, double blind phase IIb clinical trial in advanced NSCLC patients who did not progress after first line platinum based chemotherapy (NCT01935154). OS was longer in the 29% of patients with a Vx-001 specific immune response (21.3 *vs* 13.4 months, $p = 0.004$), and this advantage was stronger in never smokers (Gridelli et al., 2017).

2.2. Transferring hTERT-specific cytotoxic T lymphocytes

Another interesting immunotherapeutic approach targeting telomerase is based on engineering tumor-specific infiltrating lymphocytes (TILs). As for the other cells, extensive proliferation ultimately leads to a reduction of telomerase activity and to the shortening of telomeres in normal human T lymphocytes, eventually reaching a critically short