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T-cell target antigens across major gynecologic cancers

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HIGHLIGHTS

- Gynecologic cancers are immunogenic tumors, becoming candidates to benefit from immunotherapy.
- Antigen-targeted therapies show potential for the successful treatment of gynecologic malignancies.
- Combination of different immunotherapeutic approaches is predicted to impact the patient outcome.

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ABSTRACT

Immunotherapies have achieved remarkable success in treating different forms of cancer including melanoma, non-small cell lung carcinoma, bladder cancer, synovial cell sarcoma, and multiple myeloma using immune checkpoint blockade or gene-engineered T-cells. Although gynecologic cancers have not been historically classified as immunogenic tumors, growing evidence has shown that they are in fact able to elicit endogenous antitumor immune responses suggesting that patients with these cancers may benefit from immunotherapy. Modest clinical success has been accomplished in early trials using immunotherapeutic modalities for major gynecologic cancers including ovarian, cervical, and endometrial cancer. Unlike solid cancers with high mutational burdens, or hematologic malignancies where target antigens are expressed homogenously and exclusively by tumor cells, identifying tumor-restricted antigens has been challenging when designing a T-cell targeted therapy for gynecologic tumors. Nevertheless, mounting preclinical and clinical evidence suggests that targeting shared, viral or patient-specific mutated antigens expressed by gynecologic tumors with T-cells may improve patient outcome. Here we review the strengths and weaknesses of targeting these various antigens, as well as provide insight into the future of immunotherapy for gynecologic cancers.

1. Introduction

The major types of gynecologic malignancies include ovarian (including fallopian tube and primary peritoneal), endometrial, cervical and vulvar/vaginal cancer. Ovarian cancer (OC) is the most lethal gynecologic malignancy and ranks fifth among cancer deaths among women. The underlying difficulty of treating OC is that the majority of patients are diagnosed with advanced stage disease at initial presentation, and despite improvements in surgery and platinum-based chemotherapy, more than 80% will develop a recurrence. This recurrent disease is often refractory to subsequent treatment and ultimately fatal. Endometrial cancer (EC) represents the most frequent cancer of the genital tract, with a 5-year survival rate of 95% for stage I disease which is found in 67% of cases. However, the survival rate reduces to 17% for disseminated disease, and EC has a rising incidence and mortality. Cancers of the cervix have improved 5-year survival rates since most are detected at an early stage. Vulvar and vaginal cancers are less prevalent but have a similar survival rate which is associated with stage of disease. Moreover, since human papillomavirus (HPV)-infection is the major risk factor, implementation of prevention measures and vaccines has shown a dramatic decrease in incidence of vulvar, vaginal and cervical cancer (CC) (https://seer.cancer.gov/statfacts). Still, the prognosis for advanced stage disease remains poor. Taken together, it is clear that new therapies are needed for the treatment of advanced gynecologic cancers.

Although OC has not traditionally been considered an immunogenic cancer, clinical evidence of spontaneous anti-tumor responses, mechanisms of immune evasion, and clinical responses to immunotherapy contradict this notion. In fact, the presence of tumor infiltrating lymphocytes (TILs), especially CD8+ CD3+ T-cells, correlates with better

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survival in OC patients [1]. TILs have also been detected in cervical and endometrial tumors with prognostic significance. These observations suggest the suitability of these malignancies to be targeted with T-cell based immunotherapy, and imply that immune boosting therapies, such as immune checkpoint blockade with anti-PD-1/PD-L1 or CTLA-4 antibodies, will be most effective in tumors with pre-existent T-cell antitumor responses.

Cancer vaccines have the potential to prime naïve T-cell responses against gynecological cancers, as well as activate and expand pre-existent T-cell immunity. Consistent with results in other cancers, vaccines have shown limited efficacy in patients with advanced or recurrent disease. However, the induction of tumor antigen-specific T-cells can be achieved via vaccination with peptide, protein, viral, bacterial, tumor, and dendritic cell (DC)-based or anti-idiotypic vaccines, with some reports of improved survival. As an alternative approach, adoptive cell transfer (ACT) allows for the passive infusion of tumor-antigen specific T-cells to cancer patients, and has emerged as a powerful form of cancer therapy (Fig. 1a). Tumor antigen-specific T-cells for ACT may be derived from various sources. Endogenous autologous T-cells derived from resected tumor (TILs) or the peripheral blood of naive or vaccinated patients may be isolated and expanded ex vivo for subsequent reinfusion. Alternatively, non-reactive autologous T-cells collected from peripheral blood can be endowed with tumor antigen specificity prior to reinfusion into the patient. This can be achieved by tumor antigen-specific stimulation in vitro or by genetically engineering T-cells to express either an exogenous tumor antigen-specific T-cell receptor (TCR) with specificity for a tumor antigen, or a chimeric antigen receptor (CAR). TCRs can recognize both extracellular and intracellular processed antigens in a major histocompatibility complex (MHC) restricted manner. While clinically promising, this strategy is limited by the need for intact antigen

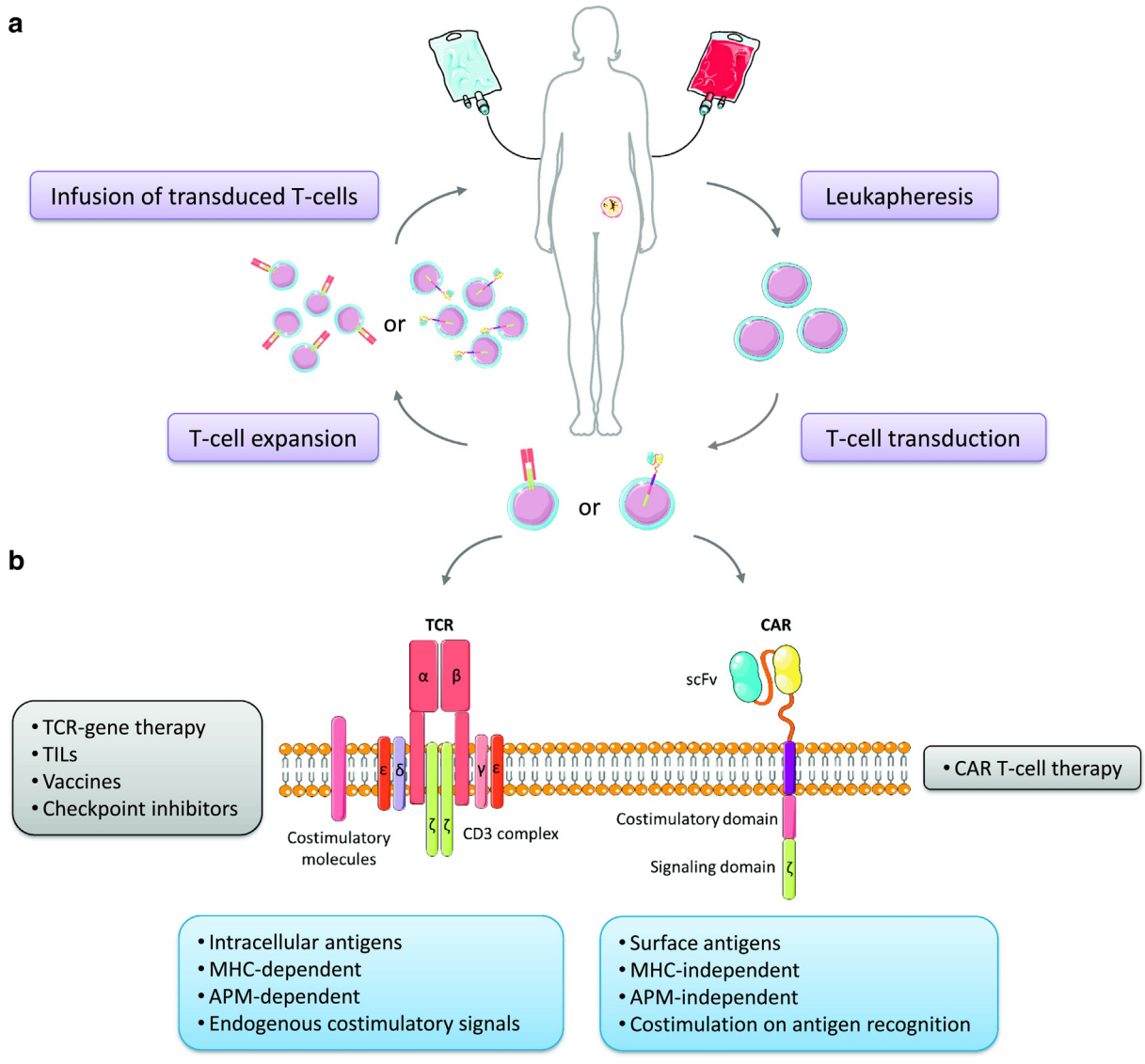

Fig. 1. Immunotherapies targeting tumor antigens. (a) Overview of adoptive T-cell transfer therapy. Peripheral blood from patients is harvested and T-cells are obtained through leukapheresis and activated ex vivo. After activation, T-cells can be genetically modified by transducing with constructs encoding for either T-cell receptors (TCRs) or chimeric antigen receptors (CARs) targeting the desired tumor antigen, and then engineered T-cells are expanded ex vivo and reinfused to the patient. (b) TCRs are made of α and β chains specific for a certain antigen and can be isolated from tumor-specific T-cells. Those chains associate with CD3 complex, composed of γ, δ, ε, and ζ chains. CARs are comprised of an extracellular antibody single-chain variable fragment (scFv) domain linked through a transmembrane motif to intracellular signaling domains derived from CD3ζ. Generally it also includes one or more costimulatory domains. Both intracellular and extracellular antigens can be recognized by TCRs as long as they are processed by antigen processing machinery (APM) and presented in the context of major histocompatibility complex (MHC) class I molecules, pathways that are frequently downregulated in tumor cells. For this approach, endogenous costimulatory signals are also needed. In contrast, antigen recognition by CARs does not rely on APM or MHC class I presentation, and costimulation is built in to antigen recognition. However, only surface antigens are eligible to be targeted by CAR T cells. Other immunotherapeutic approaches non-based on gene engineering but also relying on T-cells bearing tumor-specific TCRs are TILs, vaccines, and checkpoint inhibitors.

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