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Targeting the tumor and its associated stroma: One and one can make three in adoptive T cell therapy of solid tumors

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ABSTRACT

Adoptive T cell therapy (ACT) has become a promising immunotherapeutic option for cancer patients. The proof for ACT therapeutic efficacy was first obtained with allogenic T cells and then reproduced with T cells isolated from patients' tumor samples (i.e. tumor-infiltrating lymphocytes). It is now clear that specificity of ACT products can be educated by genetically engineering T cells with classical T Cell Receptors (TCR) or chimeric antigen receptors (CAR). To date a poor accessibility of the tumor mass and a hostile microenvironment, influenced by genetic and epigenetic instability, mainly limit ACT therapeutic efficacy in the case of solid tumors. Available data indicate that these hurdles might be overcome by combinatorial therapeutic strategies targeting the tumor and its associated stroma. Here we review some of the available dual targeting strategies focusing on given combination of TCR/CAR-redirected T cell products and their association with drugs targeting the tumor-vessel and/or epigenetic modifiers, with the ability to sensitize tumors to T cell recognition. Existing data have proven synergistic effects in combined settings (one and one can indeed make three) and suggest that further benefit might be achieved by additional combinatorial therapeutic approaches (could one + one + one make ten?) in ACT of solid tumor.

1. Introduction

The absence of immune effector cells, and in particular of CD8 T cells, in the tumor mass or their confinement to the adjacent stroma has been defined as one of the negative prognostic values for patients with solid tumors [1]. Recent advances in cell manufacturing and engineering have proven the feasibility of generating defined cell products capable of improving patients' responsiveness to their own tumors in adoptive T cell therapy settings (ACT) [2]. Such attempts can artificially increase the representation of immune cells reactive to patients' tumors, and by that overcome immunological ignorance, one of the mechanisms accounting for initial tumor escape. Although results generated by ACT products in preclinical models, and state-of-the art clinical trials are promising, it is now well recognized that tumors evolve multiple inhibitory mechanisms, which include a dysfunctional vasculature which limit active T cell infiltration into the tumor mass and a complex immune-inhibitory tumor microenvironment enriched in T regulatory (Treg) lymphocytes, myeloid-derived suppressor cells (MDSCs) and tumor-associated macrophages (TAM) which drives T cell exhaustion [3–5]. These are weak propagators of the immune response and actively promote tolerance because of poor expression of co-stimulatory molecules and inflammatory cytokines and chemokines, and expression of inhibiting factors. Furthermore, both genetic and epigenetic instability characterize most solid tumors and contribute to malignant transformation caused by the deregulation of cell cycle control, cell growth, apoptosis, cell adhesion, DNA repair and angiogenesis, and escape from immune surveillance due to the silencing of tumor associated antigens (TAA) or of components of the antigen presenting/processing machinery (Fig. 1).

To overcome these hurdles, combinatorial approaches able to simultaneously target the tumor and various component of its associated stroma have been developed and in some instances validated in preclinical and clinical settings. The intent of this

Abbreviations: ACT, adoptive T cell therapy settings; TAA, tumor associated antigens; TCR, T cell receptors; CAR, chimeric antigen receptors; Treg, T regulatory cells; MDSCs, myeloid-derived suppressor cells; TAM, tumor-associated macrophages; DC, dendritic cells; HSCT, hematopoietic stem cell transplantation; DLI, Delayed Lymphocyte Infusion; TILs, tumor-infiltrating T lymphocytes; VEGF, vascular endothelial growth factor; FAP, fibroblast activation protein; EC, endothelial cells; DNMT, DNA methyl transferases; HDAC, histone deacetylases.

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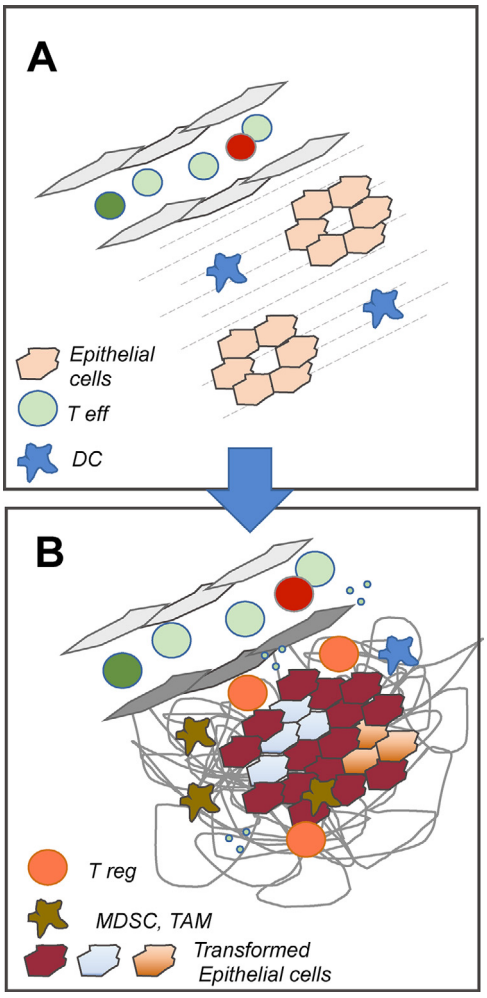

Fig. 1. Solid Tumors and their complexity. The complexity of tumor transformation within the prostatic tissue is schematically depicted as representative. (A) A normal prostate with well-defined acini and a well-organized stroma is shown. (B) The process of tumorigenesis subverts the structure of the organ. Transformed cells are packed within a disorganized stroma enriched for Treg, MDSC, and a dysfunctional endothelium, which is ignored by poorly represented TAA-specific T cells. Epigenetic silencing drives additional cell transformation and contributes to immune-escape.

review is to highlight some of such therapies, specifically focusing on the combination of ACT –targeting the tumor and the tumor stroma- with tumor-vessel targeting or epigenetic drugs, capable of improving intratumoral infiltration and tumor immunogenicity (Fig. 2).

2. Adoptive T cell therapy: overcoming ignorance to the tumor and its associated stroma

Central and peripheral tolerance dampen T cell responsiveness, and synergize with anti-inflammatory events in preventing both innate and adaptive immunity to transformed cells. To date, ACT mainly relies on autologous or allogeneic T cell products, respectively harvested directly from the patient or from healthy donors. In the case of allogenic T cells, immune-mediated graft-versus-tumor (GVT) effects are based on the ability of a consistent fraction of donor-derived T cells to recognize patient-specific HLA molecules (in the case of haploidentical, or half-matched, transplantation [6]) or the so-called minor histocompatibility antigens (in the case of fully HLA-matched donors) [7]. These can be expressed by the tumor and its surrounding stroma, providing the opportunity for a dual recognition. As of now, allogeneic hematopoietic stem cell transplantation (HSCT), alone or in combination with donor lymphocyte infusions (DLI) remains one of the most potent form of cellular immune therapy for haematological malignancies [8]. Although results have been somehow disappointing with circumstantial evidence of GVT and occurrence of transplant-related toxicities mostly graft-versus-host disease (GVHD), in patients with various solid tumors [9], long-term survival effects were observed in a fraction of renal cell cancer patients [10,11]. To date, allograft for solid tumors as adoptive immunotherapy is still being used and efforts are aimed at minimizing GVHD and promoting GVT [12]. Among these the adoption of non myeloablative conditioning which favors mixed bone marrow chimerism and donor T cell engraftment and reduce the occurrence of GVHD, and the implementation of post-transplant tumor and in some instanced minor H antigen specific vaccination [13], which ultimately boosts protective anti-tumor immunity [8,14].

We also exploited allogenic HSCT/DLI for the treatment of advanced autochthonous mouse prostate carcinoma [15], mostly refractory to conventional active and adoptive immunotherapy. We found that vaccination with dendritic cells pulsed with a TAA peptide was instrumental to instruct tumor-T cell immunity and it granted efficacy to otherwise inefficacious minor histocompatibility antigen mismatched allogeneic HSCT and DLI [16,17]. We also found that in this setting acute prostate cancer debulking and prolonged mouse survival specifically relied on the concomitance and the synergy of T cell responses directed to a TAA- and a minor H antigen-derived peptide. Results indicated that T-cell-mediated recognition of minor H antigens, not exclusively expressed by the tumor but possibly expressed also by tumor-associated stroma components (such as vessel endothelial cells, discussed below) favored tumor infiltration by TAA-specific T cells. This suggested that ACT formulations able to simultaneously target the tumor and its associated stroma provide a therapeutic advantage over mono-targeting ones.

The possibility to manipulate ACT products and confer them desired specificity/ies has been validated in the setting of autologous T cell therapy. The group of Steve Rosenberg first defined the opportunity to isolate tumor-infiltrating T lymphocytes (TILs) from tumor lesions and expand them in vitro to sufficiently high numbers for their re-infusion into patients [18,19]. This strategy allowed the separation of tumor-reactive lymphocytes from putative suppressive mechanisms present within the tumor microenvironment and opened the way to the identification of tumor-reactive T cell clones and of T-cell receptors (TCR), and the era of engineered T cells [20]. To date, only a limited number of normal self-antigens, not expressed by the most common solid tumors, have been safely and successfully exploited in patients. Attempts are now directed towards the identification of tumor-specific mutated antigens, and corresponding TCR [21,22]. Chimeric antigen receptors (CAR) are also being exploited to redirect autologous T cells to tumor surface antigens. These are synthetic receptors which mediate MHC-independent TAA recognition, via an extracellular binding domain, consisting of the light and heavy chain regions derived from an antibody to form a single chain variable fragment, a transmembrane domain and an intracellular signaling/activation domain, generally composed of CD3-zeta CD28/41-BB domains [2]. Results of clinical trials show that the genetic engineering of peripheral blood T cells with tumor-reactive TCR or CAR can result in durable objective regression in patients with a variety of cancer types including metastatic melanoma, sarcomas, lymphomas, and neuroblastoma [20,23].

Given that the tumor-associated stroma has also been recognized as a relevant immunotherapeutic target [24,25], in addition