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Mini-review

MHC class II restricted neoantigen: A promising target in tumor immunotherapy

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ABSTRACT

Neoantigen is a patient-specific tumor antigen resulted from mutations during oncogenesis. Emerging data suggested that immune responsiveness against neoantigens correlated with the success of clinical tumor immunotherapies. Nowadays, the majority of studies on neoantigens have focused on MHC class I restricted antigens recognized by CD8+ T cells. With improved understanding of the underlying principles of tumor biology and immunology, increasing emphasis has been put on CD4+ T cells and MHC class II restricted antigens. MHC class II restricted neoantigen has the potential to be a promising target of tumor immunotherapy, although the limited comprehension and technical difficulties need to be overcome before being applied into clinical practice. This review discussed the immunologic mechanism, screening technique, clinical application, limitations and prospectives of MHC class II restricted neoantigens in tumor immunotherapy.

Introduction

With increased understanding of the underlying principles of tumor biology and immunology, tumor immunotherapy develops rapidly, and plays an increasingly important role in comprehensive tumor therapy. For almost all the immunotherapeutic strategies, such as monoclonal antibody (mAb), bispecific T cell engager (BiTE), adoptive cell transfer (ACT) and tumor vaccine, it is critical to select appropriate tumor antigens (TAs) as the target of immunotherapy.

Since similar on-target but off-tumor toxicities have been observed in immunotherapies targeting shared tumor and tissue differentiation antigens in several studies [1–3], exploiting TAs expressing more exclusively on tumor cells was in urgent need to improve the safety of immunotherapies. Viral antigen, which exclusively presented in virus-associated tumors, and cancer-testis Ag (CTA), which shared across multiple tumors and typically restricted to non-MHC-bearing germ cells such as testis in adult tissue [4], are both antigens of concern. Besides them, neoantigen, as an immunogenic product of somatic mutation of tumors, also serves as a potential target for immunotherapy. Increasing evidence suggests that some clinical effects of immunotherapy are likely mediated by immune responses against somatic mutations in tumors of patients [5–10].

The development of the next-generation sequencing technology makes it possible to screen personalized neoantigens. Nowadays, much work on neoantigen screening focused on MHC class I restricted peptides. However, with the deepening of understanding on tumor immunology and the accumulation of experimental and clinical evidences, increasing emphasis has been placed on MHC class II restricted antigens in antitumor immunology. In 2014, Rosenberg reported that a patient with widely metastatic cholangiocarcinoma received CD4+ T cells adoptive transfer and experienced continuous tumor regression up to 35 months [11–13]. Given that clinical trials on CTA-specific CD8+ TCR-T cells mostly ended in failure due to severe toxicity, the result presented at the 2016 AACR Annual Meeting appeared to be encouraging. This phase I clinical study demonstrated that

Abbreviations: mAb, monoclonal antibody; BiTE, bispecific T cell engager; ACT, adoptive cell transfer; TAs, tumor antigens; CTA, cancer-testis Ag; TILs, tumor-infiltrating lymphocytes; CTL, cytotoxic T cell; IL-2, interleukin 2; CD40L, CD40 ligand; ROS, reactive oxygen species; GTE, genetic targeting expression system; WES, whole-exome sequencing; TMG, tandem minigene; IVT, *in vitro* transcribed; CTCs, circulating tumor cells; ERBB2IP, erbb2 interacting protein; IDH1, isocitrate dehydrogenase type 1; MERIT, mutanome engineered RNA immunotherapy; PR, partial regression; TCR-T cell, T-cell receptor T cell; CAR-T cell, chimeric antigen receptor T cell; EMT, epithelial–mesenchymal transition.

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intervention with genetically engineered CD4+ TCR-T cells targeted MAGE-A3 was well tolerant and effective, with 3 of 14 (21.4%) objective responses observed in patients with various metastatic tumors [14]. Here, we introduce the background of MHC class II restricted neoantigen, screening technique, its clinical application and provide an overview of current challenges and future prospectives of this immunotherapy.

The advantages of MHC class II restricted neoantigens and CD4+ T cell responses in antitumor immunity

Adoptive transfer of autologous tumor-infiltrating lymphocytes (TILs) along with interleukin 2 (IL-2) to patients with melanoma achieved objective tumor regression, suggesting that T cells play a significant role in antitumor immunity [15]. Because cytotoxic T cell (CTL) can kill tumor cells directly and destroy tumor masses *in vivo*, and tumor cells constitutively express MHC class I rather than MHC class II moleculars [16,17], much attention has been placed on CD8+ T cells, with a series of MHC class I restricted TAs been identified. Immunotherapies based on MHC class I restricted TAs have shown some evidences of therapeutic effects in clinical trials, however, the overall immune responses were still transient and too weak to eradicate tumor cells in the majority of patients [18]. One of the reasons of this limitation may be the lacking of CD4+ T cell responses. Spontaneous CD4+ T cell responses against tumor antigens have been detected in tumor patients, and high density of tumor-infiltrating CD4+ Th1 cells was strongly correlated with good prognosis for almost all tumor types [19–22]. In fact, increasing evidence suggested that CD4+ T cells play major role in antitumor immunity.

According to the secretion of cytokines, CD4+ T cells can be classified into different subsets such as Th1, Th2, Treg and Th17 cells [23–25]. Th1 cells, which secret IFN-γ, TNF-α and IL-2, have been shown to mediate definite anticancer effects through multiple mechanisms (Fig. 1A). Through the CD40–CD40 ligand (CD40L) interactions between CD4+ Th1 cells and APCs, Th1 cells help to prime CD8+ T cells and initiate immune responses [26–28]. Th1 also help to maintain function of CD8+ T cells through the secretion of cytokines, such as IL-2, which is essential for the growth and proliferation of CD8+ T-cell (Fig. 1B) [29,30]. Moreover, activated CD4+ Th1 cells promote the recruitment and infiltration of CD8+ T cells and other immune cells such as macrophages, granulocytes, eosinophils and NK cells to the site of tumor through the secretion of IFN-γ or IFN-γ inducing chemokines, such as CXCL10 and CXCL 9 (Fig. 1C) [30–34].

Besides that, several studies showed that CD4+ Th1 cells upregulate the expression of MHC class II molecules on the surface of tumor cells by secreting IFN-γ and acquire cytotoxicity *in vivo*. Thus CD4+ T cells are capable of recognizing and killing MHC class II expressing target cells directly through a MHC class II – CD4 restricted way, independent of B, NK or other T cells in the host (Fig. 1D) [35–37]. A recent study suggested that IFN-γ, synergistically with TNF-α, directly induced senescence-defining permanent growth arrest in tumors (Fig. 1E) [38].

Continuous loss of CD8+T cells was observed in the absence of CD4+ T cells, resulting in failure to resist following viral challenge,

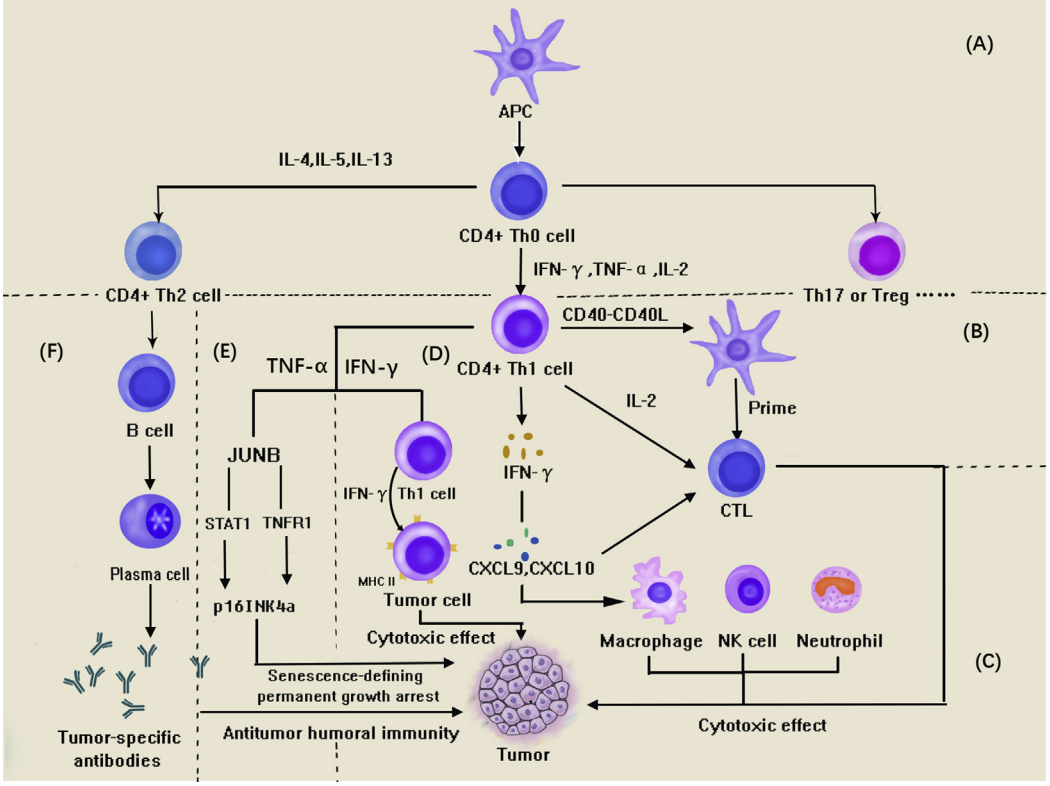

Fig. 1. (A) According to the secretion of cytokines, CD4+ T cells can be classified into different subsets such as Th1(IFN-γ, TNF-α,IL-2), Th2 (IL-4, IL-5 and IL-13), Treg and Th17 cells. (B) CD4+ Th1 cells provide help to prime CD8+ T-cell through CD40–CD40L interactions between CD4+ Th1 cells and APCs, and maintain function of CD8+ T cells through the secretion of cytokines, such as IL-2. (C) Activated CD4+ Th1 cells promote the recruitment and infiltration of CD8+ T cells and other immune cells such as macrophages, granulocytes, eosinophils and NK cells to the site of tumor through the secretion of IFN-γ or IFN-γ inducing chemokines, such as CXCL10 and CXCL 9 (D) CD4+ Th1 cells may upregulate the expression of MHC class II molecules on the surface of tumor cells by secreting IFN-γ, and acquire cytotoxicity *in vivo*. (E) IFN-γ, combined with TNF-α can activate the JUNB downstream target p16INK4a through STAT1 and TNFR1 signaling pathway, inducing senescence-defining permanent growth arrest in tumors. (F) CD4+ Th2 cells help the activation of B cells and the production of the specific antibodies.