Evolving strategies for tumor immunotherapy: enhancing the enhancer and suppressing the suppressor

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Cancers develop complex and dynamic tissue microenvironments to support their sustained growth, invasion and metastasis. For decades, rapid progress has been made in the cross talk between tumor cells and the surrounding microenvironment, especially the local immune system [1]. In response to growing tumors, multiple immune cells and cytokines may act as ‘enhancers’ of the immune system to maintain powerful defenses against tumor cells. However, tumors can subvert various microenvironmental elements including the immune system itself as a ‘suppressor’ to counteract antitumor immune responses. Re-educating the disabled immune system within the tumor microenvironment and also reactivating the compromised immune response systemically, such as enhancing the ‘enhancer’ and suppressing the ‘suppressor’, have proven to be effective strategies for treating cancers (Figure 1). Notably, the development of immune checkpoint inhibitors and chimeric antigen receptor-T cells (CAR-T) has been the most exciting breakthrough in tumor immunotherapy recently. Therefore, more innovative research on the regulation and intervention of immune responses in tumor microenvironments may provide multiple new immunotherapeutic strategies for cancers.

ENHANCE THE ENHANCER

Exogenous administration of nonspecific immunopotentiators, such as Toll-like receptor (TLR) ligands and cytokines, was an earlier strategy to improve antitumor immunity, which is now applied as adjunctive therapies. To induce tumor antigen-specific immunity, various types of tumor vaccines have been developed using the tumor itself or those that are neoantigen-identified [2]. Vaccines prepared from the tumor itself such as AGS-003 are being tested in controlling metastatic renal cell cancer. And rindopepimut, a vaccine targeting EGFRvIII protein in glioblastoma multiforme, has been approved for Phase III clinical trials. Additionally, tumor-secreted extracellular vesicles (EVs) packaging tumor elements are taken as natural tumor vaccines [3].

Efficient antigen presentation by dendritic cells (DCs) in vivo is indispensable for these therapeutic vaccines. Therefore, DC-based vaccination has been applied in the clinic and proven to be effective. Ex vivo-generated DCs from monocytes or CD34+ cells are pulsed with tumor antigens, activated by immune adjuvants and cytokines, and then injected back into the patients as vaccines [4]. Now we are heading a multi-center Phase III clinical trial of autologous DC-based chemotherapy and radiotherapy, DC vaccines combined with checkpoint inhibitors are conducted to reverse immune suppression in the tumor microenvironment.

SUPPRESS THE SUPPRESSOR

Antigen-specific T-cell responses against tumors are critical in tumor immune surveillance. To overcome tumor-induced T-cell exhaustion, the adoptive transfer of engineered T cells using the genetically modified T cell receptor (TCR) or synthetic receptors named CARs has met with great success in cancer treatment recently. The CAR-T therapy shows impressive clinical outcomes in patients with hematologic malignancies, especially B-cell malignancies. However, limited therapeutic effects have been achieved in solid tumors, partly owing to tumor heterogeneity and difficulty in acquiring specific neoantigens as targets. Several CARs targeting HER2, mesothelin, cMet, MUC1, GD2, EGF and CD133 for solid tumor therapy are currently in clinical trials. A recent exciting study reported that IL13Rα2-targeted CAR-T cells used in a patient with recurrent multifocal glioblastoma eliminated all intracranial and spinal tumors, indicating a promising future [5]. More recently, the down-regulation of the type I interferon receptor chain IFNAR1 was found in stroma of colorectal cancers, which contributed to the formation of the immune-privileged niche in the tumor microenvironment. Up-regulation and stabilization of IFNAR1 may improve the efficacy of adoptive T-cell therapy [6].
enhancement of direct immune attack against tumors, but also the elimination of immunosuppressive factors, such as immune checkpoint blockade. CTLA-4 is a negative regulator of T-cell-mediated immune responses and CTLA-4 blocking can improve T-cell activation against tumor cells. Ipilimumab is a fully human monoclonal IgG1κ antibody against CTLA-4 for the treatment of multiple tumor types (melanoma, renal cell carcinoma, prostate cancer, etc.). PD-1 is also an inhibitory receptor with sustained expression in dysfunctional T cells. Blocking PD-1 or its ligand PD-L1 is effective in reversing the function of exhausted T cells. Currently, there are several anti-PD-1/PD-L1 antibodies including Nivolumab approved by the Food and Drug Administration (FDA), which have shown significant anti-cancer effects. Combined therapies using these two checkpoint inhibitors or with other tumor therapies and finding more checkpoint targets are current trends in drug development.

The myeloid-derived suppressor cells (MDSCs) were defined as a heterogeneous population of immature myeloid cells to suppress immune response against tumors and promote tumor progression. Now, several strategies have been developed for snipping the immunosuppressive MDSCs in the tumor microenvironment. Promoting the differentiation of immature MDSCs and inhibiting the expansion, recruitment or functions of MDSCs might be a promising approach. For instance, anti-CXCR2 antibody therapy prevented MDSC trafficking to the tumor, leading to inhibition of tumor growth. COX2 inhibitor celecoxib could suppress MDSC expansion. Recent studies showed that neutrophils, a major myeloid subset, contributed to tumor progression and metastasis, suggesting another potential therapeutic target [7].

OUTLOOK AND CHALLENGE

Cancer immunotherapies have been proved to be curative for patients with various types of cancers. There are many ongoing efforts to make intense adjustment on biomedical research and clinical explorations to maximize the efficacy of cancer immunotherapy.

**Figure 1.** Strategies for developing immunotherapies against cancers by enhancing the ‘enhancer’ and suppressing the ‘suppressor’. Enhancing-the-‘enhancer’ approaches include tumor vaccines, adoptive cellular therapies, etc.; suppressing-the-‘suppressor’ approaches include checkpoint inhibitors, inhibition of immunosuppressive cells, etc. APC, antigen-presenting cell; Breg, regulatory B cell; CAR, chimeric antigen receptor; DC, dendritic cell; MDSC, myeloid-derived suppressor cell; NKT cell, natural killer T cell; NK cell, natural killer cell; TAM, tumor-associated macrophage; TAN, tumor-associated neutrophil; TCR, T-cell receptor; Treg, regulatory T cell; TIL, tumor-infiltrating lymphocyte.
Prospects of fuel cell technologies

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Fuel cells (FCs) are efficient and clean devices to electrochemically convert the chemical energy of fuels such as hydrogen, natural gas (NG), methanol, ethanol and hydrocarbons to electric energy with significantly high efficiency and much lower greenhouse-gas emission as compared to well-established internal combustion engine (ICE) technologies. Thus, FCs are regarded as the most promising energy-conversion strategies for the sustainable energy development. FC technologies can be categorized according to the nature of the electrolytes, including low-temperature proton-exchange membrane fuel cells (PEMFCs), alkaline fuel cells (AFCs), phosphoric acid fuel cells (PAFCs) to high-temperature molten-carbonate fuel cells (MCFCs) and solid-oxide fuel cells (SOFCs). Operating temperatures and ionic-transfer processes of FCs are determined by the nature of the electrolytes. As shown in Fig. 1, in general,