

Chapter 15

Pharmacology of Different Immunity Cell Components and Growth Factors: Approaches for Cancer Immunotherapy

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ABSTRACT

Tumor-associated macrophages are immune cells that regulate various factors in the tumor microenvironment and play an important role in connecting cancer with various immune cells in the tumor microenvironment. Recently, these tumor-associated macrophages have also been recognized as biomarkers for the treatment of cancer, and anti-cancer drugs have been developed targeting them. This new therapeutic approach is to achieve the effect of reprogramming immune cells to attack cancer cells by combination therapy with immune checkpoint inhibitors and a next-generation immuno-oncology drugs developed based on tumor-associated macrophages. These Chapter elaborates therapeutic strategy and development of drug targeting tumor-associated macrophages to date is limited to inhibiting the recruitment of them. Thus, in order to develop a novel development of Pharmaceutical drug delivery system like nanoparticles, etc. that encompasses the whole tumor microenvironment, particularly Evasion methodology is essentially needed with mechanisms in which macrophages regulate immunity.

1. INTRODUCTION TO NOVEL IMMUNOTHERAPEUTIC APPROACHES TOWARD CANCER

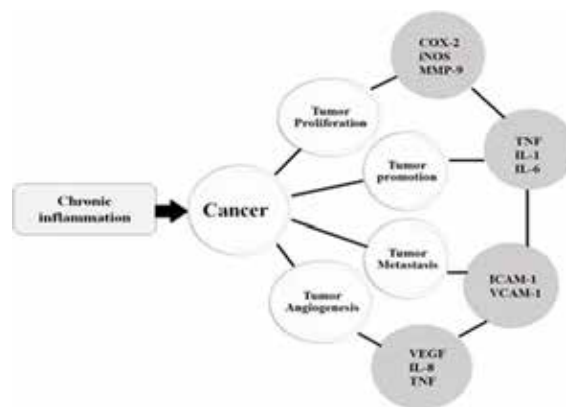
Immune therapeutic-based current approaches comprise vaccines, chimeric antigen receptor (CAR)-expressing T cells, immune checkpoint inhibitors, and bispecific antibodies. The basic aims of all these therapies are to amplify the “killing power” of various immune cells and to target the malignantly transformed cells.

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1.1 Immune Cell-Mediated Immunostimulatory Approaches toward Cancer

The basic focus of the immunotherapeutic approach is to amplify the immune response specifically against tumor cells. Various immune cells such as macrophages, neutrophils, and microglial cells have been tried for drug delivery to treat tumors. Similarly, T cells secreting IL-2 have been used to treat tumors in the past. Recently, adoptive cell transfer (ACT) has utilized tumor-infiltrating lymphocytes (TILs) obtained from the tumor microenvironment or from circulating peripheral T cells. ACT is infused back into lymphodepleted patients after *ex vivo* expansion. However, TILs expressing a T-cell receptor (TCR) population of a heterogeneous nature have been directed against various antigens. To overcome this problem and improve TIL tumor targeting, T cells are modified by genetic engineering to express α/β -TCR or CARs along with native TCRs. CARs have two domains, including an extracellular domain specific for antigen binding plus one or two intracellular T cell signaling domains. These artificial recombinant CARs cause the production of reactive T cells directed against the tumor antigen. Furthermore, these artificial CARs do not require MHC molecule and T cell interaction, instead acting directly against cells expressing tumor antigens. However, this therapy has certain limitations such as to produce CAR cells in higher amounts *ex vivo*, which may compromise its *in vivo* activity and endurance. Finally, α/β -TCR and CARs can also bind target protein on normal (non-tumor) cells and exhibit toxicity. (Yang Z., 2016)

Figure 1. Novel Immunotherapeutic Approaches toward Cancer



Furthermore, the current regimen using autologous ACT is quite time-consuming, expensive, and very difficult to obtain sufficient CAR-T cell with appropriate quality for the elder and newborn patients. Thus, to ensure the easy availability of CAR-T therapy, the development of allogeneic adoptive transfer approach is highly desirable, which utilizes the universal CAR-T obtained from the healthy donor derived T cells to exploit against multiple diseases. To make this approach workable, the $\alpha\beta$ TCR on allogeneic CAR-T cells should be removed to inhibit the graft-versus-host responses and human leukocyte antigens class I (HLA-Is) should be eliminated to render their immunogenicity minimized. It was previously reported that TCR α subunit constant (TRAC) mutation trigger the loss of $\alpha\beta$ TCR on T-cell surface and beta-2 microglobulin (B2M) is necessary for the HLA-I heterodimers expression on cell surface. Thus, to develop the most potent and universal CAR-T cells, multiple genes elimination will be

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