Review Article
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Personalized immunotherapy in cancer treatment: a mini review

Abstract

Immunotherapy is an art of exploiting the immune system to dampen or trigger desired molecular pathway for treatment. "Personalized" immunotherapy involves using one's own immune cells especially T- cells and tailoring them to specifically recognize target cells. This field of medicine is now called "Living treatment" as the genetically engineered T-cells infused in patient's body proliferate and alleviate the target tumor.[1]

Conventional treatment of diseases, especially cancer treatment has devastating effect on the human body. No matter how much the medical field has advanced, we have not been able to eliminate the side effects of the conventional drugs. Personalized immunotherapy has the primary advantage of "self" as they are derived from person's own unique molecular profile bypassing the immune surveillance machinery. Using T-cells for cancer treatment was proposed and tested in 1985 by Rosenberg et al.,[2] What was thought a "dead end" before has now become the "living" treatment two decades later. Here we review the current strategies in the development of these immunotherapies and briefly describe how they act providing examples of the immunotherapies that showed improved objectives response in clinical trials.

Keywords: personalized immunotherapy, t-cells, cancer, immune system, pd-1, tumor cells, pd-l1

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Abbreviations: PD-L1, programmed death ligand-1; ACT, adoptive cell transfer; TILs, tumor infiltrated lymphocytes; PBLs, peripheral blood lymphocytes; CARs, chimeric antigen receptors; TAAs, tumor associate antigens; PAP, prostatic acid phosphatase

Introduction

Most promising immunotherapy concepts

Antibody based immunotherapy: Antibodies are unique molecule that recognizes very specific peptides and proteins. They can block signaling pathways by binding to crucial molecules. This property is being used in several immunotherapeutic approaches.[3] For example activation of T lymphocytes is triggered by binding of antigenic peptides and co-stimulatory molecules to the T-cell receptor, and the IL-2 mediated signaling. The antigenic peptides bound to major-histocompatibility complex of antigen presenting cells present them to the T-cells, which triggers the downstream events. Thus, a complex interplay between the antigen presenting cells, T- lymphocytes and target cells is necessary for an antigen specific immune response.[4] Upon T-cell activation, CTLA-4 is expressed on the surface competes with CD28 to bind to CD80 and CD86. Thus, the T-cells are inactivated by CTLA-4 by competing against the activation of the stimulatory molecules such as CD28. The ability to block CTLA-4 with an antibody to potentiate T cell activation and response against tumor cells provided the scientific foundation for the development of mAbs for cancer treatment (eg., ipilimumab).[5]

Tumor cells can exploit the immune regulatory mechanism to shield themselves from immune components that are able to fight cancer. One example is premature inactivation of the activated T-cells. T-cells once activated increase the expression of inhibitory PD-1 receptors to prevent from over-activation. However, tumor cells express programmed death ligand-1 (PD-L1) that interacts with the PD-1 receptor and shuts the T-cells prematurely. Universities such as John Hopkins and many others Pharmaceutical Companies are designing monoclonal antibodies that will prevent the PD-1 receptors from binding to PD-L1. One such example is the MDX-1106 antibody, which blocks PD-1 receptors on activated T cells from interacting with PD-L1 and PD-L2 proteins on tumor cells. When this interaction occurs it hinders the body's immune system from attacking cancer cells.[6–8]

Adoptive cell transfer: Adoptive cell transfer (ACT) is an innovative approach where the person's own immune cells are used to target the tumor.[1,9] Adoptive cell transfer can be achieved by using patient Tumor Infiltrated Lymphocytes (TILs) or Peripheral Blood Lymphocytes (PBLs).

For ACT, tumors resected from a patient are cultured in-vitro in the presence of IL-2. Within 2weeks, the tumor infiltrated Lymphocytes (TILs) proliferate and destroy the tumor cells, creating pure cultures of the lymphocytes. These anti-tumor lymphocytes are then selected for high avidity recognition of the tumor and are programed to proliferate and destroy the tumor inside the patients. About 1011 lymphocytes are infused into patient's blood for effectively fighting the cancer. ACT seems to be substantially beneficial in patients who received lymph depleting conditioning before infusion of the lymphocytes.

A limitation of this approach is the requirement that patients have preexisting tumor-reactive cells that can be expanded ex vivo. Although lymphocytes could be derived from any tumor tissue, only melonoma seemed to yield reproducible lymphocyte cultures, therefore, alternatively, peripheral blood lymphocytes are now genetically modified to express T-cell receptors that specifically bind to tumor associate antigens (TAAs). Efforts have been made to transfect the CD8+PBLs with the genes encoding TCRs that specifically recognize TAAs including MART-1 and gp100 melanoma/melanocyte differentiation antigens, the NY-ESO-1 cancer-testis antigen, and an epitope from the p53 molecule, which are expressed on many common epithelial cancers.[10–12] These primed PBLs are now

infused into the patient blood where they bind the HLA-A2–matched tumors, including melanoma, lung cancer, and breast cancer.[13–14]

Chimeric Antigen Receptor expressing T Cells (CAR-T): Genetic engineering has made it possible to help cells express Chimeric Antigen Receptors (CARs) or anti-tumor receptors. Primary advantage of CARs over TCRs is that with CAR the T-cells can recognize the tumor cells without the restriction of MHC regulated expression of cell flags. For a T-cell to recognize a target cells, the cells should present the antigenic peptides bound to MHC for recognition by TCRs. Genetic modification of a T cell with a CAR successfully re-directs the T cell towards the target of the CAR. Tumor cell recognition occurs when a CAR on a T cell ligates its antigen on the tumor. Signaling and activation is mediated by the intra-cytoplasmic signaling domains within the CAR.

Most successful clinical outcomes were achieved with B cell acute lymphoblastic leukemia (B-all) with CD19 infused CAR T Cells developed by author of the publication. Using body's own T cells to target and kill tumor cells is certainly a clever approach however; there are important considerations for using Adoptive Cell Transfer for treating cancers. Some of which include selection of appropriate antigenic targets that specifically recognize tumor cells, the effectiveness of T-cells in killing the tumors, and the persistence of the introduced T-cells in the body for years.

Cancer vaccines

Cancer vaccines have proven to be much more challenging than previously thought and are several are in clinical trials. The first cancer treatment vaccine, Sipuleucel-T was approved by FDA in Apr 2010 for use in certain men with metastatic prostate cancer. The prostate Acid phosphatase (PAP) is an antigen that is released from most prostate cancer cells and is used to stimulate antigenic responses towards cancer cells. The Antigen Presenting Cells (APCs) from a metastatic prostate cancer patient are collected and cultured in the presence of prostatic acid phosphatase (PAP) to generate a tumor specific response. PAP linked to Granulocyte macrophage colony stimulating factor (GM-CSF) is presented to APCs to enhance immune response and antigen presentation. These stimulated APCs are then injected back into the patient to achieve an autologous cellular response to recognize and kill the cancer cells.

In a randomized-double blind placebo controlled multicenter clinical trial, the sipuleucel-T increased the overall survival of patients by 4months. Since approved by FDA, Dandreon, the company that manufactures the vaccines claims that 38% of the patients treated with the sipuleucel-T show an overall survival advantage of 3years compared to control group.

Economic considerations of the personalized immunotherapy and what are Pharma Giants up to?

The first antibody based immunotherapy clinical trials using CTAL-4 antibody were conducted by Bristol-Myers Squibbs (BMS). In 2009, (BMS) acquired Medarex, a company that was developing immunotherapy drug for skin cancer. Now, the drug, ipilimumab (a human monoclonal CTAL-4 antibody), is sold in the market under the trade name YERVOY→ Since its launch in 2011, YERVOY→ has brought in $ 706million in the first year and is continuing to gain sales for BMS. BMS is now developing other immune-oncology drugs known as nivolumab and BMS-936559. Other companies such as MERCK, AstraZeneca and Roche also have immunotherapy drugs in their research pipeline.

The first CAR-T was experimented on a chronic lymphocytic leukemia patient in 2011 who is free of cancer till date. The CAR-T cells, developed by Carl June, Penn State University aimed at killing CD19 expressing B-Cells and is now with Novartis. A Seattle-based company, Juno Therapeutics was along the same track and was able to raise $310million between December 2013 and August 2014, by showing the results from potential CAR-Ts: JCAR017, JCAR015, and JCAR014 produced promising clinical responses in acute lymphoblastic leukemia and non-Hodgkin's lymphoma. In January 2015, Juno Therapeutics announced that it will have 10 therapeutic candidates for 6 different diseases. Currently, many other biotechnology companies are engaging in cancer immunotherapy and we will just have to wait and see who gets the lion's share in the market.

Overall, the use of T-cell immunotherapy is a radical approach. Now, it is up to the Pharmaceutical companies to work around the logistics and cost involved in developing these therapies. Let's hope that the current momentum of successful clinical trials continues to bring these therapies into market and better the lives of millions of cancer patients.

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Conflicts of interest

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References

1. Rosenberg SA, Restifo NP. Adoptive cell transfer as personalized immunotherapy for human cancer. *Science*. 2015;348(6230):62−68.
2. Rosenberg SA, Mulé JJ, Spiess PJ, et al. Regression of established pulmonary metastases and subcutaneous tumor mediated by the systemic administration of high-dose recombinant interleukin 2. *J Exp Med.* 1985;161(5):1169−1188.
3. Golay J, Introna M. Mechanism of action of therapeutic monoclonal antibodies: promises and pitfalls of in vitro and in vivo assays. *Arch Biochem Biophys*. 2012;526(2):146−153.
4. Scott AM, Wolchok JD, Old LJ. Antibody therapy of cancer. *Nat Rev Cancer*. 2012;12(4):278−287.
5. Leach DR, Krummel MF, Allison JP. Enhancement of antitumor immunity by CTLA-4 blockade. *Science*. 1996;271(5256):1734−1736.
6. Beatty GL, Chiorean EG, Fishman MP, et al. CD40 agonists alter tumor stroma and show efficacy against pancreatic carcinoma in mice and humans. *Science* . 2011;331(6024):1612−1616.
7. Luke JJ, Ott PA. PD-1 pathway inhibitors: the next generation of immunotherapy for advanced melanoma. *Oncotarget*. 2015;6(6):3479−3492.
8. Brahmer JR, Drake CG, Wollner I, et al. Phase I study of single-agent anti-programmed death-1 (MDX-1106) in refractory solid tumors: safety, clinical activity, pharmacodynamics, and immunologic correlates. *J Clin Oncol.* 2010;28(19):3167−3175.
9. Morgan RA, Dudley ME, Wunderlich JR, et al. Cancer regression in patients after transfer of genetically engineered lymphocytes. *Science* . 2006;314(5796):126−129.

10. Cohen CJ, Zheng Z, Bray R, et al. Recognition of fresh human tumor by human peripheral blood lymphocytes transduced with a bicistronic retroviral vector encoding a murine anti-p53 TCR. *J Immunol*. 2005;175(9):5799−5808.

11. Sadelain M, Rivière I, Brentjens R. Targeting tumours with genetically enhanced T lymphocytes. *Nat Rev Cancer.* 2003;3(1):35−45.

12. Zhao Y, Zheng Z, Robbins PF, et al. Primary human lymphocytes transduced with NY-ESO-1 antigen-specific TCR genes recognize and kill diverse human tumor cell lines. *J Immunol.* 2005;174(7):4415−4423.

13. Hughes MS, Yu YY, Dudley ME, et al. Transfer of a TCR gene derived from a patient with a marked antitumor response conveys highly active T-cell effector functions. *Hum Gene Ther* . 2005;16(4):457−472.

14. Morgan RA, Dudley ME, Yu YY, et al. High efficiency TCR gene transfer into primary human lymphocytes affords avid recognition of melanoma tumor antigen glycoprotein 100 and does not alter the recognition of autologous melanoma antigens. *J Immunol* . 2003;171(6):3287−3295.