Cell Based Immunotherapy: As a Promising Futuristic Solution for Effective Cancer Therapy

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Abstract

Cell based therapy is rapidly emerging as an alternative to conventional chemotherapy based treatment for cancer. While chemotherapy, radiation therapy and surgical intervention have been the mainstay treatment regime for vast majority of cancers, they are often associated with unwanted treatment related side-effects. Quite often the side effects dramatically compromise the quality of life for the patients. Therapy related AML (t-AML) is one such consequence of mutation events associated with cytotoxic drugs. In order to make cancer therapy more tumor specific thus sparing the non-cancerous components of the body, cell-based therapy harnessing the body immune system (cancer immunotherapy) is now explored in ever increasing number. This review is focused on the emergence of novel technologies that aim in engineering T lymphocytes to selectively recognize cancer specific markers on transformed cells thus facilitating their elimination without harming the normal cells of the body. Clinical data shows an enormous potential of this approach and is currently followed in several institutions worldwide against wide varieties of cancers with almost complete remission and fewer side effects.

Introduction

Stem cells have the potential to cure various diseases. Stem cells are the body’s natural reservoir – replenishing the various specialized cells that have been used up or damaged. This is essentially due their unlimited plasticity and enormous capacity to differentiate into other cells type in the body. This fact is exploited in the treatment of various diseases as a part of an ever growing field of stem cell therapy and tissue engineering. However the potential of stem cells is restricted depending on where these cells are originated. Cells that can form extra embryonic or placental cells as well as all the cell types in a body, are essentially called Totipotent stem cells. Embryonic cells within the first few cell divisions after fertilization are the only cells that are totipotent. Pluripotent cells can give rise to all of the cell types that make up the body; embryonic stem cells are considered pluripotent. Multipotent cells can develop into more than one cell type, but are more limited than pluripotent cells; adult stem cells and cord blood stem cells are considered multipotent. Hematopoietic stem cells are one of the most studied multipotent cells.

Stem cells hold a lot of promise in the treatment of cancer. Patients with cancer are first treated with high dose of chemotherapy with the aim to destroy the rapidly multiplying cancer cells. This process also results in the collateral damage of the patients own stem cells in bone marrow. Following the chemo regime, the patient is transplanted with fresh stem cells to rebuild the entire hematopoietic system. This is often called engraftment and takes about a few weeks to establish. Depending upon where this new stem cell comes from, the transplant process is called autologous (Auto SCT, patients own stem cells), allogenic (Allo SCT, stem cells from HLA matched or unrelated donors) or syngeneic (SYNSCT, from identical twins). The stem cells could either originate from bone marrow of the donor (BMT, bone marrow transplant), from peripheral blood (PBSC, peripheral blood stem cell transplant) or cord blood (CBT, Cord blood transplant). BMT is far the most common procedure.

While chemotherapy, radiation therapy, surgical intervention and small molecule based drug therapy remain the mainstay for treatment of cancer, a relatively new and emerging area of considerable interest is cancer cell immunotherapy. Cell-based immunotherapy is aimed to trigger a patient’s own immune system against cancer by modulating and enhancing the functions of effector T cells [1]. One such approach is isolating the T cell from the patient or HLA matched donor and in-vitro expanding and activating these cells by mitogenic stimulation. Expanded cells are re-infused back to the patient with results often showing potential anti-tumor properties leading to tumor size shrinkage and tumor dissemination. There are currently several well validated protocols for in-vitro T cells expansion. Following Allo SCT for example, tumor infiltrating lymphocytes (TIL) could be identified and co-stimulated and activated ex-vivo. One such way to activate them is incubating the cells using CD3 CD28 Dynal magnetic beads.

Another approach is to isolate T cells from cancer patients and re-engineer them to express anti-tumor molecules or tumor recognizing killer receptors on the cell surface (Chimeric antigen receptor; CAR). CARs are engineered fusion proteins comprising of a non-HLA restricted antigen recognition and binding domain (i.e., the antigen-binding domain of an antibody) and T-cell intracellular signaling domains. These CAR-expressing T-cells are transplanted back to the patients which then home to tumor sites that express the target antigen, destroying such tumors and conferring long-term, anti-tumor immunity [2,3]. Patient’s own T cells were modified ex-vivo in the laboratory to create a type of CAR cell called a CTL019 cell. These cells are designed to attack a protein called CD19 that occurs on the surface of B cells. This is a novel technology aimed to enhance the tumor killing power of the body’s own T cells [4]. Chimeric antigen receptor expressing T cells were found to be effective against CD19

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expressing B cells in chronic lymphocytic leukemia (CLL) as well as acute lymphoblastic leukemia (ALL). CTL019 CARs engrafted to the patients with leukemia multiply numerous times thus producing a pool of guided anti-tumor CARs that persist for several months protecting against tumor relapse. CARs have evolved over past one decade, initially starting as the simplest first generation CAR that have the intracellular domain of CD3 to second generation CARs that in addition also expresses co-stimulatory receptors (CD24, 41BB etc). Third generation CARs are complex sophisticated vehicles comprising of several receptors and co-receptor on T cell surface to enhance their anti-tumor properties several fold. CARs are already approved for Phase I clinical trials to use the T cells for adoptive cell transfer. New CARs are designed to recognize different tumor cell antigens targeting a whole range of cancer. CAR based techniques are thus the new hope to cancer treatment without the toxicity and side effects of conventional chemotherapy. However the process employing CARs needs deeper understanding into the pros and cons of T cell therapy due to the reported risk of release of large amount of inflammatory cytokines and other factors that could potentially be dangerous.

Work from a team of scientist [5] has discovered a novel way to generate CARs from IPs (induced pluripotent cells) opening further new possibilities for immunotherapy.

Zakaria et al. [6] recently reported in Molecular Therapy Nucleic acid that targeting multiple cancer-specific markers simultaneously could result in better therapeutic efficacy. They created a functional chimeric antigen receptor-the TanCAR, a novel artificial molecule that mediates bispecific activation and targeting of T cells. Bispecific TanCAR can initiate simultaneous targeting of tumor cells and the components of tumor microenvironment thereby augmenting T cell activation and response. This approach boosted the avidity and broadened the therapeutic applications of CAR in general and TanCAR in particular (Figure 1).

**Areas of Application of CAR (from clinical trials.gov)**

2.1. Adoptive immunotherapy for eradication of tumors expressing a tumor-specific antigen:

2.1.1. B-cell malignancies (CD19-targeted CARs):

2.2. Leukemias (CLL, ALL)

2.3. Lymphomas (NHL)

2.3.1. Prostate Cancer (PSMA-targeted CARs)

2.3.2. Mesothelioma, Pancreatic Cancer, Lung Cancer (Mesothelin-targeted CARs)

2.3.3. Ovarian Cancer (Muc16-targeted CARs)

2.3.4. Neuroblastoma (GD2-targeted CARs)

2.3.5. Myeloma (CD56-targeted CARs)

2.4 Applicable to adoptive immunotherapy in other indications, such as auto-immune disease and HIV-infection

**Development Status**

**Participating institutes**

Fred Hutchinson Cancer Research Center/University of Washington Cancer Consortium NCI

- Phase I clinical trial successfully completed in CD19+ chronic lymphocytic leukemia (CLL);
- Phase II clinical trial planned in CD19+ chronic lymphocytic leukemia (CLL);
- Phase I clinical trials ongoing in CD19+ acute lymphoblastic leukemia (ALL) and PSMA+ metastatic prostate cancer;

Abramson Cancer Center of the University of Pennsylvania

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**Figure 1:** Workflow for CAR based immunotherapy.
- Pre-clinical and pre-IND work currently underway with CARs targeting Mesothelin (Mesothelioma) and Muc 16 (Ovarian Cancer);
- Fully optimized, scalable, closed-system manufacturing process for production and expansion of clinical-grade, autologous T-cells expressing CARs sufficient for supply of phase II clinical trials;

Scalable gamma-retroviral vector production system utilizing packaging cell lines grown in suspension with serum-free media under development for phase II clinical trials.

References
5. Induced pluripotent stem (iPS) cell-derived, chimeric antigen receptor (CAR)-expressing T cells for immunotherapy (2013). Science-Business eXchange 6