Advancements in Genetic Engineering
ISSN: 2169-0111

Chhabra, Adv Genet Eng 2013, 2:1
DOI: 10.4172/2169-0111.1000104

Commentary Open Access

Engineering Anti-Tumor T Cell Immunity

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Keywords: Cancer; Immunotherapy; TCR engineering; Chimeric antigen receptor

Abbreviations: CCTL: Cytolytic T Lymphocytes; DC: Dendritic Cells; TCR: T Cell Receptor; CAR: Chimeric antigen receptor

T cell immunity is critical for protection against infectious agents as well as cancer. T cell immune response is a well orchestrated process that involves three key components. CD8+ T cells that harbor cytolytic machinery and can target and kill the tumor cells in an antigen specific manner, CD4+ T cells that can either "help" the generation of a productive CD8+ T cell or "regulate/suppress" it, and the Antigen Presenting Cells (APC) that can efficiently process the antigens and present them to the effector T cells in small fragments, termed as the antigenic epitopes. The specificity and efficacy of T cell immune response is evident by the remarkable success of vaccines against infectious agents. However, attempts to develop similar approaches against cancer have not resulted in similar success. The main reason for this is the fact that, most human cancers arise from within and self-reactive immune repertoire is eliminated during developmental process to prevent autoimmunity. As a result, host immune system is somewhat ill-equipped to generate a protective anti-tumor immune response against most cancers.

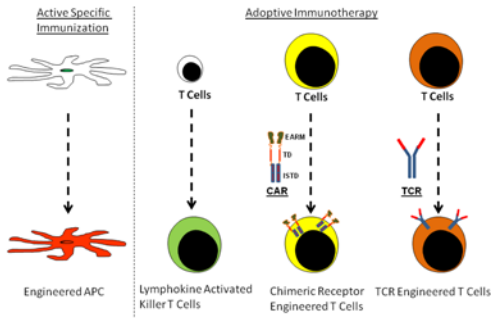

Figure 1: Evolution of Approaches to Engineer Anti-Tumor T Cell Immunity: T cell immunity approaches can be put into two broad categories, the active specific immunization and the adoptive immunotherapy. Active specific immunization approaches administer Antigen Presenting Cells (APC) engineered through different means to the cancer patients to present the tumor associated antigenic epitopes to host anti-tumor CTL precursors for generating a productive anti-tumor T cell response. Adoptive immunotherapy approaches on the other hand administer anti-tumor immune effectors generated *ex-vivo*. Early adoptive immunotherapy approaches utilized non-specific cytolytic effectors, called lymphokine activated killers (LAK), generate by culturing the immune effectors in the presence of high dose cytokines. Recent technological advances have made it feasible to create customized anti-tumor T cells by engineering the normal non-tumor specific T cells with either a Chimeric Antigen Receptors (CAR), comprised of an Extracellular Antigen Recognition Motif (EARM) an Transmembrane Domain (TD) and an Intracellular Signal Transduction Domain (ISTD), or with a tumor antigen specific T Cell Receptor (TCR) isolated from a donor harboring functional anti-tumor T cells.

However, a significant progress has been made in engineering key components of T cell immunity for generating a protective anti-tumor immunity (Figure 1). The identification of human cancer associated antigens and characterization of antigenic epitopes within these antigens [1,2], and technological advancement in generating sufficient professional antigen presenting cells [3], led to the development of active specific immunization approaches [4-6]. Among these includes administration of antigenic peptides specific for specific tumor antigens, administration of APC, either pulsed with the antigenic epitopes or engineered with recombinant viral/non-viral vectors, for an efficient priming of the CD8+ anti-tumor Cytolytic T Lymphocyte (CTL) precursors, for generating a productive anti-tumor immune response. The salient feature of the active specific immunity approaches is that these strategies rely upon the existing host immune repertoire for producing a protective anti-tumor immune response. Although remarkable clinical responses were observed in a few cancer patients, overall success with active specific immunization approaches was low [7].

Several adoptive immunotherapy approaches have also been developed with an objective to administer *ex-vivo* expanded anti-tumor immune effectors. Initial adoptive immunotherapy approaches utilized non-tumor antigen specific cytolytic immune effectors, called Lymphokine Activated Killers (LAK), generated by culturing immune effectors in the presence of high dose cytokines [8]. The recent technological advancements such as isolation of T cell receptor, creation of chimeric receptors, characterization of co-stimulatory molecules required for an optimum activation of antigen specific T cell precursors, and the development of novel approaches to primary cells, have made it feasible to create customized T cells with desired antigen specificity [9], including tumor antigen specific T cells, by engrafting human peripheral blood derived T cells with tumor antigenic epitope specific TCRs [10], an approach termed TCR engineering, or by engrafting T cells with chimeric receptors targeting tumor associated antigenic epitopes [11]. Tumor antigen specific TCR engineered T cells have been shown to exhibit potent anti-tumor effector function and early clinical trials with TCR engineered anti-tumor T cells have shown that these cells can produce impressive clinical responses [12]. CAR engineered cells have also been shown to produce remarkable clinical response in Chronic Lymphoid Leukemia (CLL) patients [13].

TCR engineering and chimeric receptors approaches can address one of the key limitations towards developing T cell based cancer immunotherapy, i.e. a lack of potent anti-tumor T cell precursors in majority of cancer patients, however, several concerns still remain towards application of engineered anti-tumor T cell in cancer immunotherapy. On CAR based approaches, although the second generation CAR have addressed the limitations such as lack of co-

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Received October 06, 2012; **Accepted** October 13, 2012; **Published** October 15, 2012

Citation: Chhabra A (2013) Engineering Anti-Tumor T Cell Immunity. Adv Genet Eng. 2:104. doi:10.4172/2169-0111.1000104

stimulatory signals in the first generation CARs and CAR molecules do not have to compete with endogenous TCR chains for expression on engineered cells, identification of tumor specific molecules remains a challenge for applying this technology to other tumor models since most tumor associated molecules are also present on normal cells and this could lead to severe toxicity. Among the limitations on TCR engineered T cells include, identification of high avidity TCRs against tumor associated antigens that will orchestrate a desired anti-tumor effector function in engineered T cells, potential mixing of transgenic TCR chains with endogenous TCR chains of engineered cells that could result in novel TCR combinations with unknown functional specificities with undesired consequences, host immune regulatory mechanisms, immune inhibitory tumor microenvironment making engineered anti-tumor T cells in-effective. Premature activation induced cell death and immune exhaustion of adoptively administered anti-tumor T cells along with immune escape mechanisms employed by a growing tumor pose additional challenges towards developing an effective cancer immunotherapy.

Several approaches are under development to address these limitations. Identification of tumor specific molecules is an ongoing pursuit and approaches are also being developed to modify transgenic TCRs such that it provides them advantage over the endogenous TCR chains for preventing the creation of chimeric TCRs with unknown functional specificities. Antibodies that block inhibitory signals such as CTLA-4, PD-1 have also shown significant promise in clinical trials [14-16]. Natural MHC class II restricted anti-tumor CD4 T cells have also been shown to facilitate epitope spreading in cancer patients and produce protection, making a strong case for incorporation of CD4 T cells in cancer immunotherapy protocols [17]. However, conceptually it is quite challenging to engage MHC class II restricted natural CD4 T cells at the tumor site, especially in an antigen specific manner, since most human cancers are MHC class II negative. Interestingly, MHC class I restricted CD4 T cells generated through TCR engineering approach have been recently shown to not only facilitate "help" towards the generation of robust CTL response, but also to exhibit a direct cytolytic function of their own against human tumor cells [18,19]. Given that CD4 helper T cells have been shown to make CTL less susceptible to Activation induced cell death (AICD), facilitate better tumor infiltration by anti-tumor CTL, helping in generation of CTL responses against multiple tumor epitopes, a phenomenon termed epitope spreading, it will be interesting to see whether these MHC class I restricted TCR engineered CD4 T cells could produce a superior clinical response. A better understanding of the mechanism of AICD in human primary anti-tumor T cells [20] can help create anti-tumor T cells that are less susceptible to premature AICD. In addition, development of methods to maintain the functional profile of anti-tumor effectors in context to the immunosuppressive tumor microenvironment could further improve the clinical efficacy of these approaches.

In summary, recent progress has established that a protective anti-tumor T cell immunity can indeed be engineered that can produce remarkable clinical responses, however, several challenges still remain towards improving the success rate. Combinatorial approaches need to be developed to bring all the technological and intellectual advances together to address the concerns associated with these approaches and turn this enthusiasm into a grand clinical success.

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