

# Immunotherapeutic Approaches to Target Cancer Stem Cell: Progress and Challenges

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## Editorial

Immunotherapy referred to biological therapy that uses the potential of individual's own immune system to fight cancer. Immunotherapeutic approaches include the use of cytokines, chemokines, monoclonal antibodies, cancer vaccines and immune cells. Immunotherapy is considered one of the most promising and exciting areas for the treatment of cancer.

The success of immunotherapeutic approaches for melanoma and non-small cell lung cancer raised hope for the treatment of other malignancies as well. However, resistance to the cancer therapies developed by tumor cells is the biggest challenge in the cancer treatment. Due to the heterogeneous nature of cancer, the bulk tumor consists of diverse cells having distinct molecular, morphological and phenotypic signatures with differential levels of sensitivity to treatment [1,2]. The cancer stem cells (CSCs) that are rare immortal cells of bulk tumor have the capability to self-renew by dividing and give rise to many cell types that constitute the tumor. CSCs are increasingly identified as the source of tumor progression, metastasis, and cancer therapy resistance and relapse [2,3]. Treatment strategies that can eliminate CSCs and non-CSCs suggested improving the long-term clinical outcome for cancer patients. Since immunotherapy directly utilizes the immune cells and works in the distinct principle from chemotherapy or small molecule therapy, it can be an alternative therapeutic approach to target CSCs.

Identification and validation of target specific to CSCs are crucial for successful execution of immunotherapy. EGFRvIII, a truncated version of EGFR expressed in glioblastoma (GBM) CSCs suggested being a good target for immune interventions [4]. EGFRvIII variants are expressed across the various other tumor types and their expression is often correlated with poor clinical outcome. Peptide CDX-110, derived from EGFRvIII showed high immunogenicity to anti-EGFRvIII monoclonal antibodies (MAbs). Moreover, EGFRvIII-specific dendritic cell vaccine and CDX-110-KLH peptide vaccine demonstrated potential in preclinical and clinical studies for GBM treatment [5]. In addition, chimeric antigen receptor (CAR) T cell redirected to the EGFRvIII is in the process of development for the treatment of GBM patients [6]. Acute Myeloid Leukemia (AML) CSCs expressed Cyclin A1 and WT-1 is recognized as the target of the immunotherapeutic approach. T cell targeting Cyclin A1 and WT-1 are generated and expected to be tested in preclinical models soon [7]. Natural killer cell (NK) immunotherapy is the other immune cell-based therapy that has been explored to target CSCs. Colorectal cancer CSCs demonstrated susceptibility to NK killing due to the upregulation of the ligands for the activating natural cytotoxicity receptors NKp30 and NKp44 [8]. The breast cancer CSCs showed sensitivity to IL-15 and IL-2 activated NK cells. The activity of NK cells was suggested to mediate by elevated expression of the NKG2D ligands ULBP1, ULBP2, and MICA on breast CSCs [9]. Further, melanoma CSCs showed sensitivity to IL-2 activated NK cell cytotoxicity which suggested to mediated by the DNAM-1 ligands Nestin-2 and PVR [10].

The tumor microenvironment (TME) which consists of cancer cells, CSCs, fibroblast, resident and recruited immune cells is a critical barrier to overcome in order to target CSCs. The efficacy of immunotherapeutic can be improved by targeting specific and appropriate antigen, inducing superior immune cell response and facilitating the infiltration of tumor-reactive T cells and NK cells within the TME. Efficacy of T cell can be

improved by substituting amino acid residues within the complementary determining region 3 (CDR3) of the T cell receptor (TCR) chains for avoiding the possibilities of toxicities due to cross-reactivity against unintended targets. Similarly, NK cell immunotherapeutic approaches can be improved by promoting NK cells longevity *in vivo*, increasing the homing of NK cells to tumor sites and inducing hyperresponsiveness. Other strategies that can enhance the effectiveness of immunotherapy using a combination approach by integrating monoclonal antibody, cytokines, vaccines, T cells and NK cells therapy. As our understanding of immunotherapy and CSCs biology improved in recent years, certainly this will lead us to target CSCs with better therapeutic strategies to improve the clinical outcomes for cancer patients.

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