Bioresponsive hydrogel enhances adoptive T cell therapy against head and neck squamous cell carcinoma

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Surgery remains one of the primary modalities for treating head and neck squamous cell carcinoma (HNSCC) and is effective in most patients. However, surgery can also be highly morbid and is less effective once a tumor spreads to lymph nodes or distant sites. Surgery also results in local and systemic immunosuppression and removal of relevant tumor antigens that could limit post-operative immunemediated tumor control. Therefore, a postsurgical treatment that suppresses tumor recurrence and helps maintain the anticancer immune activity is highly desired. T cells recognizing tumor antigens can be found in hosts with progressively growing cancer. Thus, adoptive T cell therapy using the tumor antigen-specific T cells isolated from the original tumor tissue for solid malignancies holds the promise of responses and potential cures in advanced cancer patients. We recently discovered a subset of human CD8 tumor infiltrating lymphocytes (TILs) using two activation markers, CD39 and CD103. This subset of CD8 TIL within progressively growing solid tumors appeared to be chronically stimulated and was enriched for T cell receptors that recognized tumor antigens in situ. Furthermore, these CD8 TIL had a resident memory signature that kept these cells sequestered within the tumor, which potentially led to chronic T cell activation by tumor antigens. While this subset of CD8 TIL appeared to be capable of recognizing cancer cells in situ, they could not suppress tumor growth completely, which might be caused by limited cell number, reduced cell function, and/or immune editing by the tumor microenvironment. Recently, high-affinity antigen has been reported to promote T cell retention in tumor through the downregulation of CXCR4-CXCL12 axis after antigen encounter, whereas large portion of functional tumor-specific CD8 T cells exit the tumor. Thus, CXCR4 inhibition has the potential to limit the T cell egress and thereby promote the efficacy of adoptive T cell therapy. In this application, we propose to develop a tumor-responsive hydrogel formulated by a CXCR4 antagonist as the crosslinker for in situ delivery of tumor-specific T cells. The high reactive oxygen species (ROS) in tumor can facilitate the tumor-specific degradation of hydrogel associated with the release of the CXCR4 antagonist, which boosts the retention of the tumor-specific T cells and thereby enhances tumor control. Meanwhile, some anti-cancer cytokines, such as IL-2, will be co-delivered by hydrogel to support the proliferation and survival of the tumor specific T cells. Two animal models, including mouse HNSCC cell linebased immunocompetent model and patient-derived HNSCC cell line-based NOD scid gamma (NSG) mouse model, will be involved to evaluate the therapeutic efficacy of our T cell encapsulated hydrogel. We will form a multidisciplinary team and pursue three interconnected aims. Aim 1. Isolation and characterization of the tumor specific T cells in mouse HNSCC model. We will isolate the tumor-specific T cells from the mouse MOC2 and MOC22 HNSCC model and compare their gene expression with the human CD39 and CD103 double positive TILs. Aim 2. Formulation of the hydrogel and evaluation of the encapsulated T cell activity. WZ811 will be selected as the CXCR4 antagonist for hydrogel formulation. We will characterize the drug loading and ROSresponsive release profile of the hydrogel. The tumor-specific T cells will be encapsulated into the hydrogel and the growth and viability will be evaluated. Aim 3. Investigation of the therapeutic efficacy of T cell encapsulated hydrogel. We will first determine the safety dosage for further animal studies. The hydrogels will be intratumorally administrated in mouse and human HNSCC models and the tumor growth will be monitored to evaluate the therapeutic efficacy.