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Activation and Propagation of Tumor-infiltrating Lymphocytes from Malignant Pleural Effusion and Ascites with Engineered Cells for Costimulatory Enhancement

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Abstract

Adoptive cell therapy (ACT) of autologous tumor-infiltrating lymphocytes (TILs) has shown an effect on mediating tumor regression in some patients with highly advanced, refractory metastatic malignancy. Here, the *in vitro* generation of TILs isolated from malignant pleural effusion and ascites was compared with which using engineered cells for costimulatory enhancement (ECCE) and 3 common γ-chain cytokines, interleukin (IL)-2, IL-7, and IL-15, alone or in combination. We showed the robust clinical-scale production of TILs with a less differentiated 'young' phenotype by expansion in the presence of ECCE combined with IL-2/7/15. Furthermore, a major fraction of the TILs generated in this fashion was shown to produce much more IFN-γ and TNF-α, and displayed cytolytic activity against target cells expressing the relevant antigens. To our knowledge, this is the first time that the combination of ECCE and IL-2/7/15 has been applied for the generation of TILs isolated from malignant pleural effusion and ascites.

Keywords

adoptive cell therapy, tumor-infiltrating lymphocytes, malignant pleural effusion and ascites, 4-1BBL, IL-7, IL-15

Introduction

The term tumor-infiltrating lymphocyte (TIL) was originally mentioned by Wallace Clark in 1969 and later defined operationally as a lymphocyte that has left the bloodstream and has gained direct contact with tumor cells. More recently, the term TIL has been used to describe a variety of tumor infiltrating cells including T cells, T regulatory (Treg) cells, natural killer (NK) cells, and B cells, as well as macrophages, dendritic cells (DC), and myeloid-derived suppressor cells (MDSCs)[1]. Cancer immunotherapy based on ACT using autologous TIL has been shown to mediate durable complete responses in refractory metastatic melanoma[2, 3]. TILs are naturally occurring T cells which are able to recognize tumor-associated antigens (Ags), including neo-Ags[4]. This can explain the highly specific antitumor responses and the low toxicity of TILs in comparison with genetically modified T cells expressing transgenic T-cell receptors (TCRs) or chimeric antigen receptors (CARs)[5]. This is in particular noteworthy, as TIL ACT is mainly applied to highly advanced patients, who have often failed numerous prior treatments and have multiple