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Increased Cytolytic Activity of Effector T-Cells against Cholangiocarcinoma Cells by Self-Differentiated Dendritic Cells with Down-Regulation of Interleukin-10 and Transforming Growth Factor-β Receptors

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Abstract : Cholangiocarcinoma (CCA) is an aggressive malignancy of bile duct epithelial cells in which the standard treatments, including surgery, radiotherapy, chemotherapy, and targeted therapy are partially effective. Many solid tumors including CCA escape host immune responses by creating tumor microenvironment and generating immunosuppressive cytokines such as interleukin-10 (IL-10) and transforming growth factor-β (TGF-β). These cytokines can inhibit dendritic cell (DC) differentiation and function, leading to decreased activation and response of effector CD4+ and CD8+ T cells for cancer cell elimination. To overcome the effects of these immunosuppressive cytokines and to increase ability of DC to activate effector CD4+ and CD8+ T cells, we generated self-differentiated DCs (SD-DCs) with down-regulation of IL-10 and TGF-β receptors for activation of effector CD4+ and CD8+ T cells. Human peripheral blood monocytes were initially transduced with lentiviral particles containing the genes encoding GM-CSF and IL-4 and then secondly transduced with lentiviral particles containing short-hairpin RNAs (shRNAs) to knock-down mRNAs of IL-10 and TGF-β receptors. The generated SD-DCs showed up-regulation of MHC class II (HLA-DR) and co-stimulatory molecules (CD40 and CD86), comparable to those of DCs generated by convention method. Suppression of IL-10 and TGF-β receptors on SD-DCs by specific shRNAs significantly increased levels of IFN-γ and also increased cytolytic activity of DC-activated effector T cells against CCA cell lines (KKU-213 and KKU-100), but it had little effect to immortalized cholangiocytes (MMNK-1). Thus, SD-DCs with down-regulation of IL-10 and TGF-β receptors increased activation of effector T cells, which is a recommended method to improve DC function for the preparation of DC-activated effector T cells for adoptive T-cell therapy.

Keywords : cholangiocarcinoma, IL-10 receptor, self-differentiated dendritic cells, TGF-β receptor
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