ENGINEERING OF T CELLS WITH CCR10 FOR ENHANCED TRAFFICKING OF ADOPTIVE CELL THERAPY

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Background Trafficking T cells into tumor microenvironments is critical to the success of cancer immunotherapy, such as adoptive cell transfer therapy. Chemokines and their receptors play an important role in inducing trafficking and homing of T cells. They activate integrin for T cell adhesion to endothelial cells and help T cells traffic through chemotaxis in microenvironment of cancer. Therefore, the introduction of chemokine receptors that react with tumor-derived chemokines could improve the effectiveness of adoptive T cells. CCR10 is a chemokine receptor for CCL28, which is a high-ranking chemokine secreted from tumor tissue. We engineered T cells with CCR10 to improve trafficking of T cells.

Methods Cloning was performed using vectors containing NY-ESO-1 and HLA-A*02:01 specific (1G4) TCR and CCR10. Transduction of Jurkat cells-NFAT-luciferase (TCR KO) and peripheral blood mononuclear cells (PBMC) was performed after the production of the lentivirus using a lenti-x-293T cell. A375 cell line, which expresses HLA-A*02:01 and NY-ESO-1, was selected as a target. CCL28 was overexpressed in A375 cell line, and transwell migration assay was performed using CCR10-1G4 TCR-T and 1G4 TCR-T. 1G4 TCR reactivity was measured using luciferase after NY-ESO-1 peptide pulsing in T2 cell.

Results Transduction efficiency of the 1G4 TCR and CCR10 on post-transduction day 7 was more than 90% each in Jurkat and 40% each in CD8+ PBMC. However, when we used the vector containing 1G4 TCR and CCR10 together with T2A linker, the expression efficiency of CCR10 was 30% to 40% in Jurkat and 10% to 20% in CD8+ PBMC. Transwell migration assay was performed using mock Jurkat, CCR10-Jurkat, 1G4 TCR-Jurkat, and CCR10 1G4 TCR-Jurkat. Compared to mock or 1G4-Jurkat, CCR10-Jurkat or CCR10-1G4 TCR-Jurkat had increased migration by more than 10% during 4 h migration period. In addition, migration of CCR10 1G4 TCR-Jurkat increased according to incubation time when transwell assays were performed for 4, 8, and 16 hours. The reactivity of CCR10 1G4 TCR-Jurkat was measured using luciferase. The RLU of the T2 cells without pulsing the NY-ESO-1 peptide was below detection level. When reacted with T2 cells pulsed NY-ESO-1 peptide by diluting 10 times from 1ug to 0.001ug, RLU was 3.40E+04, 5.44E+04, 6.16E+04, and 7.24E+04, respectively.

Conclusions CCR10 engineered TCR-T showed increased in vitro trafficking efficacy. Further studies with application of CCR10 to other T cell therapies would improve quality of adoptive T cell therapy.