Expression of a TIM peptide reduces alloreactivity of T cells facilitating an allogeneic NKG2D Chimeric Antigen Receptor T cell therapy approach

Alexandre Michaux1, Eyten Breman1, Sebastian Maun1, Jennifer Bolles1, Laura Saaren1, Benjamin Volki, Fanny Huberty1, Jérôme Marjolais1, Céline Jacques-Hospes1, Carlène Marchand1, Nancy Ramelot1, Thuy Nguyen1, Julien Houssau1, Charles L. Sentman1, David Gilham1, Sophie Aguagué1

1Celyad, Mont-Saint-Germain, Belgium
2Geteil School of Medicine at Dartmouth, Lebanon, NH, USA

BACKGROUND

Chimeric antigen receptor (CAR) T cells have shown impressive clinical results especially in malignancies. Most CAR T cell therapy relies on a single transduction of T cells, which may have limitations in terms of patient T cell manufacturing. T cells derived from an allogeneic healthy donor may immunomodulate some of these issues. However, allogeneic T cells may not show graft-versus-host disease (GVHD). A response in preclinical settings to allogeneic CAR T cell therapy is needed to further transduce healthy T cells for CAR T cell therapy.

In this study, we evaluated the TCR activation using a CAR expressing a TIM peptide (T) in human T cells fused to the TCRαβ chain of the human TCR of PANC-1 cells that were stably expressing NKG2D. NKG2D is a natural killer receptor that recognizes the NKG2D ligands expressed by malignant cells.

RESULTS

TIM and allogeneic T cells process

The expression of TIM is conducted by the association of the various antigen-recognizing TIMαβ chain heterodimer with the CD94/NKG2D signaling machinery (CD94α/CD94β2 and CD94α/CD94β3) divided in TIMαβ heterodimer in the presence of CD163/CD155-coupled ligands to activate TIM in vitro (Figure 8).

T-cell TIM expression in T cells impairs allogeneity in vitro and in vivo by altering TCR activation pathways

Impacts of TIM in T cells 

Impact of TIM in T cells activation was measured in both K562+ and K562− TCRαβ T cells, which were transduced with CAR T cells (Figure 9). Those T cells were incubated in the presence of increasing concentrations of TIM (30–200 ng/mL) for 6 hours and assessed for NKG2D-stimulated T cell activation. Interestingly, an alternative mechanism of the TCR-mediated activation of T cells was observed in the presence of TIM, which may be triggered by the TIMαβ heterodimer. The TIMαβ heterodimer mediated a strong T cell activation which may be triggered by the TIMαβ heterodimer. The TIMαβ heterodimer mediated a strong T cell activation which may be triggered by the TIMαβ heterodimer. The TIMαβ heterodimer mediated a strong T cell activation which may be triggered by the TIMαβ heterodimer. The TIMαβ heterodimer mediated a strong T cell activation which may be triggered by the TIMαβ heterodimer. The TIMαβ heterodimer mediated a strong T cell activation which may be triggered by the TIMαβ heterodimer. The TIMαβ heterodimer mediated a strong T cell activation which may be triggered by the TIMαβ heterodimer. The TIMαβ heterodimer mediated a strong T cell activation which may be triggered by the TIMαβ heterodimer. The TIMαβ heterodimer mediated a strong T cell activation which may be triggered by the TIMαβ heterodimer. The TIMαβ heterodimer mediated a strong T cell activation which may be triggered by the TIMαβ heterodimer. The TIMαβ heterodimer mediated a strong T cell activation which may be triggered by the TIMαβ heterodimer. The TIMαβ heterodimer mediated a strong T cell activation which may be triggered by the TIMαβ heterodimer. The TIMαβ heterodimer mediated a strong T cell activation which may be triggered by the TIMαβ heterodimer. The TIMαβ heterodimer mediated a strong T cell activation which may be triggered by the TIMαβ heterodimer. The TIMαβ heterodimer mediated a strong T cell activation which may be triggered by the TIMαβ heterodimer. The TIMαβ heterodimer mediated a strong T cell activation which may be triggered by the TIMαβ heterodimer. The TIMαβ heterodimer mediated a strong T cell activation which may be triggered by the TIMαβ heterodimer. The TIMαβ heterodimer mediated a strong T cell activation which may be triggered by the TIMαβ heterodimer. The TIMαβ heterodimer mediated a strong T cell activation which may be triggered by the TIMαβ heterodimer. The TIMαβ heterododimer mediated a strong T cell activation which may be triggered by the TIMαβ heterodimer. The TIMαβ heterodimer mediated a strong T cell activation which may be triggered by the TIMαβ heterodimer. The TIMαβ heterodimer mediated a strong T cell activation which may be triggered by the TIMαβ heterodimer. The TIMαβ heterodimer mediated a strong T cell activation which may be triggered by the TIMαβ heterodimer. The TIMαβ heterodimer mediated a strong T cell activation which may be triggered by the TIMαβ heterodimer. The TIMαβ heterodimer mediated a strong T cell activation which may be triggered by the TIMαβ heterodimer. The TIMαβ heterodimer mediated a strong T cell activation which may be triggered by the TIMαβ heterodimer. The TIMαβ heterodimer mediated a strong T cell activation which may be triggered by the TIMαβ heterodimer. The TIMαβ heterodimer mediated a strong T cell activation which may be triggered by the TIMαβ heterodimer. The TIMαβ heterodimer mediated a strong T cell activation which may be triggered by the TIMαβ heterodimer. The TIMαβ heterodimer mediated a strong T cell activation which may be triggered by the TIMαβ heterodimer. The TIMαβ heterodimer mediated a strong T cell activation which may be triggered by the TIMαβ heterodimer. The TIMαβ heterodimer mediated a strong T cell activation which may be triggered by the TIMαβ heterodimer. The TIMαβ heterodimer mediated a strong T cell activation which may be triggered by the TIMαβ heterodimer. The TIMαβ heterodimer mediated a strong T cell activation which may be triggered by the TIMαβ heterodimer. The TIMαβ heterodimer mediated a strong T cell activation which may be triggered by the TIMαβ heterodimer. The TIMαβ heterodimer mediated a strong T cell activation which may be triggered by the TIMαβ heterodimer. The TIMαβ heterodimer mediated a strong T cell activation which may be triggered by the TIMαβ heterodimer. The TIMαβ heterodimer mediated a strong T cell activation which may be triggered by the TIMαβ heterodimer. The TIMαβ heterodimer mediated a strong T cell activation which may be triggered by the TIMαβ heterodimer. The TIMαβ heterodime...