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Identification of a beneficial allo-PRAME specific immune response within a detrimental immunological war

Abstract:

In HLA matched stem cell transplantation (SCT) it has been demonstrated that beneficial immune response mediating graft versus tumor (GVT) responses can be separated from graft versus host disease (GVHD) immune responses. In this study we investigated whether it would be possible to dissect the beneficial immune response of allo-HLA reactive T cells with potent anti-tumor reactivity from GVHD inducing T cells present in the detrimental immune response after HLA mismatched SCT. To this purpose the presence of specific tumor reactive T cells in the allo-HLA repertoire was analyzed at the time of severe GVHD after HLA-mismatched SCT using tetramers composed of different tumor associated selfantigens (TAA).

Since allo-HLA reactive T cells specific for TAA will not be tolerized for the allo-HLA expressing over-expressed self-antigens, these T cells may express high affinity TAA specific TCRs potentially useful for adoptive T cell therapy. High avidity PRAME specific allo-HLA restricted T cells were identified that exerted highly specific PRAME reactivity. The T cells recognized multiple different tumor cell-lines and leukemic cells, whereas no reactivity against a large panel of non-malignant cells was observed. T cells however exerted also low reactivity against mature DCs and kidney epithelial cells, which was demonstrated to be due to low PRAME expression. Based on potential beneficial specificity and high reactivity, the TCRs of these PRAME specific T-cells may be effective tools for adoptive T-cell therapy. Clinical studies have to determine the significance of the reactivity observed against mature DCs and kidney epithelial cells.