Targeting the epidermal growth factor receptor (HER) family by T cell receptor gene-modified T lymphocytes.

Abstract:
Human epidermal growth factor receptor 2 (HER2) has been successfully targeted as a breast cancer-associated antigen by various strategies. HER2 is also overexpressed in other solid tumors such as stomach cancer, as well as in hematological malignancies such as acute lymphoblastic leukemia. HER2-targeted therapies are currently under clinical investigation for a panel of malignancies. In this study, we isolated the T cell receptor (TCR) genes of a HER2-reactive allo-human leukocyte antigen-A2-restricted CTL clone and introduced the TCR- and -chain genes into the retrovirus vector MP71. Murinization and codon optimization of the HER2-reactive TCR was required for efficient TCR expression in primary human T cells. The tumor recognition efficiency of HER2-TCR gene-modified T cells was similar to the parental CTL clone from which the TCR genes were isolated. The known cross-reactivity of the HER2-reactive TCR with HER3 and HER4 was retained when the TCR was transduced into primary T cells. Our results could contribute to the development of a TCR-based approach for the treatment of HER2-positive breast cancer, as well as of other malignancies expressing HER2, HER3, and/or HER4.