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CAR T-Cells for Glioblastoma: Current Concepts, Challenges and Future Perspectives

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Abstract

Glioblastoma is the most common malignant primary brain tumor and associated with a poor prognosis even after multimodal therapy. Chimeric antigen receptor (CAR) T-cells have emerged as a promising therapeutic avenue in glioblastoma. CARs incorporate antigen-recognition moieties that endow autologous T-cells with specificity against antigens expressed on glioblastoma (e.g. IL-13Rα2, EGFRvIII, and HER2). Compelling anti-tumor effects of such therapy have been shown in murine glioblastoma models. In humans, five phase I/II studies on IL-13Rα2-, EGFRvIII-, and HER2-directed CAR T-cells for the treatment of glioblastoma patients have been published suggesting an acceptable safety profile. However, anti-tumor effects fell short of expectations in these initial clinical studies. Tumor heterogeneity, antigen loss, and the immunosuppressive tumor microenvironment are among the most important factors to limit the efficacy of CAR T-cell therapy in glioblastoma. Novel target antigens, modification of CAR T-cell design, the combination of CAR T-cell therapy with other therapeutic approaches, but also the use of CAR NK-cells or CAR macrophages may optimize anti-tumor effects. Numerous clinical trials studying such approaches are ongoing, as well as several preclinical studies. With an increasing understanding of immune-escape mechanisms of glioblastoma and novel manufacturing techniques for CARs, CAR T-cells may provide clinically relevant activity in glioblastoma. This review focuses on the use of CAR T-cells in glioblastoma, but also introduces the basic structure, mechanisms of action, and relevant side effects of CAR T-cells.