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CD19 Chimeric Antigen Receptor (CAR) modified cytokine killer cells compared to classical CD19 CAR-T: advantages and disadvantages

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Abstract

Chimeric antigen receptor (CAR) T-cell therapy has demonstrated remarkable efficacy and unique long-term outcomes in treating relapsed/refractory hematological malignancies in both pediatric and adult patients. However, a subset of patients remains unresponsive, with disease progression continuing despite treatment. Moreover, CAR-T therapy has shown limited success in treating solid tumors.

Accumulating evidence on the role of various lymphocyte subpopulations in antitumor immunity suggests that cytokine-induced killer (CIKs) cells represent a promising alternative for adoptive cell therapy. A key advantage of CIKs is their low toxicity and the presence of unrestricted MHC cytotoxicity against both hematological and solid malignancies.

In our study, we hypothesize that modifying CIKs with CARs would enhance their antitumor efficacy compared to unmodified CIKs. Using a unique retroviral vector containing the CD34 or CD14 marker gene, we successfully generated CD19 CAR-expressing lymphocyte populations, including both classically activated T lymphocytes and CIKs. We then compared their functional properties by analyzing lymphocyte subpopulations based on markers such as CD3, CD4, CD8, CD56, CD62L, and CD45RA, as well as their ability to specifically recognize CD19-positive targets. Additionally, we assessed cytokine production, including IFN-γ (via ELISA and intracellular staining), IL-2, TNF-α, and IL-10 (via intracellular staining).

Our findings indicate that CIKs can be efficiently modified using a retroviral vector while maintaining functional activity. CD19 CAR-CIK populations contained higher numbers of NKT ($CD3^+CD56^+$) and $CD3^+CD8^+$ lymphocytes compared to CD19 CAR-T cells. However, the proportion of naïve-like T cells ($CD62L^+CD45RA^+$) and effector memory RA^+ T cells ($CD62L^-CD45RA^+$) remained similar in both CAR-modified populations. Additionally, CD19 CAR-CIKs exhibited a slightly increased ability to produce IFN-γ and TNF-α in response to $CD19^+$ tumor cells. Despite that, key questions remain regarding the functionality of CD19 CAR-CIKs in an immunosuppressive tumor microenvironment, particularly in the presence of high levels of TGF-β, IL-10, and PD-L1, which may inhibit their activity or lead to exhaustion. Our future research will focus on overcoming these challenges to enhance the therapeutic potential of CAR-CIKs.

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