Harnessing the Mechanistic Similarities Between Natural Killer (NK) Cells and CAR T-cells to Reveal Apolipoprotein B Receptor's Hidden Role of Low-Density Lipoprotein (LDL) Uptake on NK Cell Cytotoxicity and Functionality

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Although CAR T-cell therapy has significantly improved treatment outcomes for hematologic B-cell malignancies, challenges such as relapse and mortality rates (35-50% within 6-12 months post-treatment) persist. Natural killer (NK) cells, having a similar mechanism/conditional for attack as CAR T-cells, are not widely studied due to MHC-1 immune evasion by adapted malignant B-cells. This research aims to investigate the role of APOBR (Apolipoprotein B Receptor), a lipid metabolism-related gene, in NK cell-mediated cytotoxicity and its implications for CAR T-cell therapy. Using RNA transcriptomics from 16 patients (8 responders, 8 non-responders (CAR T)) and computational modeling, this study examines how the impact of reduced LDL uptake via reduced APOBR expression leads to limiting metabolic stress and immune exhaustion; while exploring HDL uptake/regulation probes the discussion of long-term NK cell adaptation. siRNA knockdown of APOBR in NK-92 cells co-incubated with K-562 leukemia cells was conducted to evaluate changes in IFN-y production and tumor cell lysis. Flow cytometry, ELISA assays, and computational sequencing revealed that reduced APOBR expression led to increased NK cytotoxicity and cytokine production, supporting the hypothesis that modulating lipid metabolism can enhance immune persistence in CAR T-cell therapy. scRNA-sequencing reveals APOBR’s specificity in NK cells, revealing a pivotal NK cell limitation that has dodged researchers for decades. While the similar mechanisms between CAR T-cells and NK cells fueled this research, apoB-containing lipoproteins or apoB-100 tests are most commonly applied in the world of Cardiovascular Disease (CVD). NK cells also regulate cardiac fibrosis and inflammation, highlighting a critical recent pivot in my research.

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