Hypoxia in the Tumor Microenvironment Impairs CAR T-Cell Cytotoxicity via Metabolic Constraints

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Introduction

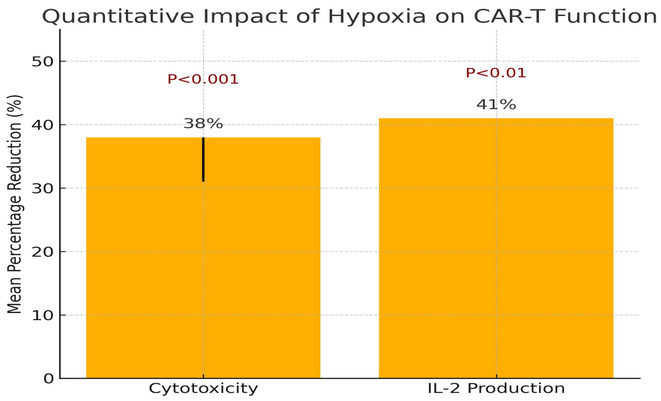
•. CAR-T therapy is effective in hematologic malignancies but limited in solid tumors.
•Hypoxic tumor microenvironment (TME) imposes metabolic stress on CAR-T cells.
•Metabolic stress compromises CAR-T cytotoxicity and persistence.
•Identifying TME hypoxia as a key barrier is vital to improving CAR-T efficacy.

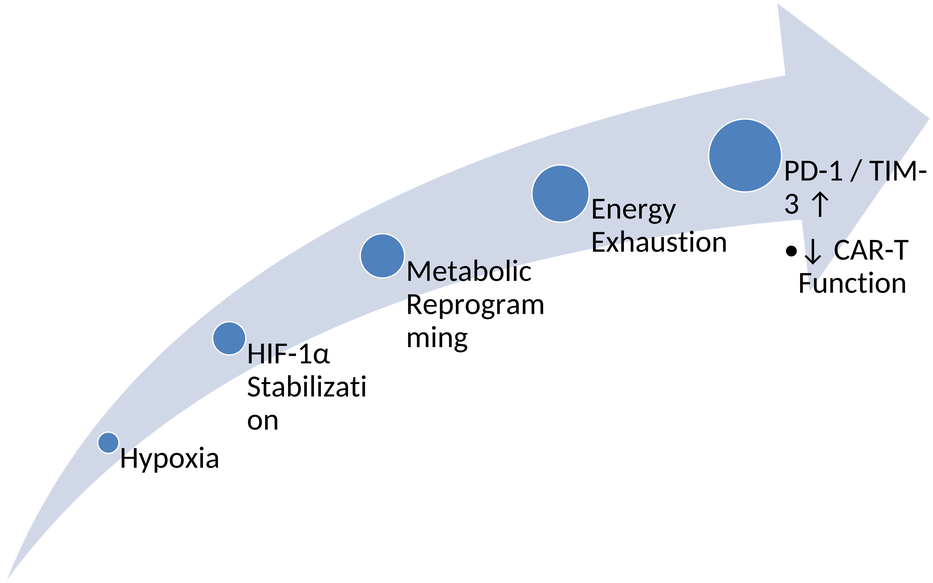
Objectives

•Assess hypoxia's impact on CAR-T function and efficacy.
•Use systematic review and meta-analysis of preclinical and translational studies.
•Establish comprehensive evidence through synthesis of multiple studies.
•Quantify effects of hypoxia and propose mechanistic insights.

Methods

Systematic search of PubMed, EMBASE, and Web of Science (2012–2024).
Included in vitro and in vivo studies of human/murine CAR-T models.
Measured cytotoxicity, cytokine release, proliferation, and persistence under hypoxia.
Analyzed HIF-1α expression, metabolic shifts, and exhaustion markers (PD-1, TIM-3).





Results

•Hypoxia reduced CAR-T cytotoxicity by 38% and IL-2 production by 41%.
•Findings are mechanistically linked to HIF-1α stabilization and a shift toward glycolytic dependency.
•Engineered CAR-T cells (with AKT/PGC-1α modifications) maintained function under hypoxia ($P<0.05$).
•In vivo models confirmed reduced tumor clearance under hypoxic conditions.

Conclusion

Hypoxia significantly impairs CAR-T function via metabolic reprogramming.
Targeting metabolic resilience is a promising therapeutic strategy.
The findings support engineering CAR-T cells to resist hypoxic stress.
The implications extend to a broad spectrum of hypoxic malignancies, not just solid tumors.

References

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