Microbiome-Driven Precision Medicine in CAR-T Cell Therapy in Hematology

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Large international multicenter cohorts of CD19-CAR-T treated lymphoma patients demonstrate that broad-spectrum antibiotic administration prior to CAR-T infusion is consistently associated with inferior progression-free and overall survival. Antibiotic exposure correlates with increased tumor burden, elevated systemic inflammation, reduced CAR-T expansion, and higher immune checkpoint expression on circulating CAR-T cells. Longitudinal metagenomic analyses reveal that antibiotics induce profound gut microbiome dysbiosis, including loss of microbial diversity, altered functional pathways, and depletion of metabolically active commensal bacteria.

Mechanistic studies in mouse models and in vitro systems establish causality, showing that antibiotic-induced microbiome disruption directly impairs CAR-T antitumor activity. Loss of microbial-derived short-chain fatty acids (SCFAs), including butyrate and propionate, emerges as a central mechanism. SCFAs can enhance CAR-T cytotoxicity, persistence, and metabolic stability probably via signaling through receptors such as GPR109. Diet further modulates these interactions. High cellulose intake combined with antibiotic exposure exacerbates dysbiosis, promotes intestinal *Enterococcus* expansion, and associates with inferior clinical outcomes, underscoring harmful diet-drug-microbiome interactions.

Collectively, these findings position the gut microbiome as both a biomarker and a mechanistic regulator of CAR-T efficacy and support the concept of microbiome stewardship strategies to preserve or restore microbiome fitness to improve outcomes of T-cell based immunotherapies, including emerging CAR-T approaches for solid tumors.