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The Gut Microbiome-Derived Metabolite TMAO as a Modulator of Immune Checkpoint Inhibitor Efficacy in Non-Small Cell Lung Cancer

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Abstract

Gut microbiome composition influences immunotherapy responses, yet specific metabolite mediators remain unidentified. We show that trimethylamine N-oxide (TMAO), produced by gut microbiota from dietary choline, directly impairs CD8+ T-cell effector function through mTORC1 pathway inhibition and mitochondrial dysfunction. Elevated plasma TMAO levels (>6.5 µM) correlated with poor progression-free survival (PFS) in 240 NSCLC patients receiving pembrolizumab. Conversely, pharmacological blockade of TMAO synthesis using iodomethylcholine (IMC) or fecal microbiota transplantation from low-TMAO donors restored anti-tumor immunity and enhanced anti-PD-1 efficacy in murine models. Dietary intervention and microbial modulation represent actionable strategies to optimize immunotherapy outcomes.

Keywords: gut microbiome, TMAO, immune checkpoint inhibitors, non-small cell lung cancer, metabolites, mTORC1 signaling

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