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Identification of plausible target as an inter-organ target to mitigate cachexia while enhancing tumor suppression by anti-PD-L1

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Immune checkpoint inhibitors (ICIs) are associated with immune-related adverse events (irAEs) due to overactivation of the immune system, despite their potent anti-cancer effects. In this study, we investigated the association between ICI treatment and weight loss in cancer patients. Using a systematic transcriptome analysis of multiple tissues from a cancer cachexia mouse model treated with anti-PD-L1 therapy, we identified significant dysregulation in pathways linked to muscle wasting, notably in extracellular matrix and collagen fibril organization. Strikingly, anti-PD-L1 treatment was found to exacerbate immune cell infiltration into muscle tissue, accelerating muscle wasting. Single-cell RNA sequencing further revealed an accumulation of CD8⁺ T-like cells in the gastrocnemius muscle of CAC mice, indicating a direct link between immune infiltration and muscle degradation. To uncover potential therapeutic targets capable of mitigating both cancer and cachexia, we performed a gene interaction network analysis. The clinical relevance of the identified target was supported by correlations between its expression and cancer incidence across TCGA and HPA datasets. Collectively, our findings propose a promising therapeutic target that addresses both cancer and cachexia, offering a promising approach to prevent muscle-related irAEs when combined with ICIs.

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