**Immunology**

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# Linking obesity, immune dysfunction and cancer risk



Obesity increases the risk of many cancer types, but the underlying mechanisms remain unclear. A new study published in *Nature Communications* shows that obesity elicits immune-cell dysfunction, which compromises immune surveillance and increases the risk of cancer in mice.

Previous reports have identified several potential links between obesity and cancer risk, including increased levels of growth hormones and adipokines, which can directly contribute to tumor formation and progression. Recent studies suggest that obesity might also contribute indirectly to tumorigenesis by suppressing anti-tumor immunity and, more specially, T-cell function.

To further investigate this possibility, Piening and colleagues (Saint Louis University School of Medicine) compared $CD8^+$ T cell responses in lean and diet-induced obese mice carrying B16 melanoma tumors. Tumor infiltration by $CD8^+$ T cells was equivalent in lean and obese mice, but single-cell RNA sequencing analysis revealed functional defects in $CD8^+$ tumor-infiltrating lymphocytes (TIL) from obese mice, as well as metabolic differences between $CD8^+$ TIL from lean and obese mice.

Further experiments revealed that obese mice on a western diet (WD) challenged with B16 melanoma showed no therapeutic response when treated with immune checkpoint blockade (ICB), whereas lean mice on a normal diet showed resistance to tumor progression. Switching obese mice on WD to a healthier, low-fat diet, improved the responses to ICB immunotherapy when compared to obese mice maintained on WD. By contrast, obese mice treated with glucagon-like-peptide-1 (GLP-1) receptor agonist semaglutide — an FDA-approved drug used for the treatment of type-2 diabetes, now shown to be effective for weight loss — still experienced $CD8^+$ TIL dysfunction and poor responses to ICB.

All together, these results indicate that in obese mice, metabolic alterations might lower the effector activity of $CD8^+$ TIL, resulting in poor tumor control. Although weight loss may be an avenue to improve anti-tumor immunity and treatment outcomes in cancer patients with obesity, different weight loss strategies might have different impacts on the immune responses to cancer.

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