HARNESSING ANTI-TUMOR METABOLIC SENSING SWITCH GPR84 ON MACROPHAGES FOR CANCER IMMUNOTHERAPY

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Background Immune checkpoint blockade (ICB) has shown tremendous clinical success, but this clinical response is limited to a small proportion of patients, and one of the major resistance mechanisms is the macrophage enriched in the immuno-suppressive tumor microenvironment (TME).1-3 Majorities of tumor-associated macrophages (TAMs) are associated with enhanced pro-tumorigenesis activity, significantly impairing T cell function and facilitating tumor escape from immune checkpoint blockade therapy.4-6 Due to the plasticity of macrophages, excitement has been growing for the possibility of reshaping these pro-tumorigenic TAMs toward the anti-tumorigenic phenotype to enhance immunity against cancer.7, 8 Emerging evidence reveals that free fatty acids (FFAs) accumulated in TME are critical in determining macrophage function. Though a majority of studies highlight the impact of metabolic processes, fatty acids also serve as vital signaling molecules for regulating immune response, however the molecular mechanism remains elusive.

Methods By an unbiased analysis of single-cell transcriptome data from multiple tumor models, we discovered that anti-tumorigenic TAMs uniquely express elevated levels of a fatty acid receptor, G-protein-coupled receptor 84 (GPR84). To determine the role of GPR84 in TAM-mediated immunity against cancer, we have established new mice with myeloid-specific deletion of GPR84 (Gpr84<sup>fl/fl</sup> LysM<sup>Cre</sup>) and evaluated the GPR84 agonist 6-OAU using the MC38 tumor model.

Results Herein, the bioinformatics analysis of the clinical patient sample finds that GPR84 enriched TAM is associated with enhanced anti-tumor function. Furthermore, genetic ablation of GPR84 will impair the pro-inflammatory phenotype and enhance the anti-inflammatory phenotype. In contrast, GPR84 activation by 6-OAU subverts TAM-mediated immunosuppression via enhanced NF-kB activity. Moreover, 6-OAU treatment significantly retards tumor growth and increases the anti-tumor efficacy of anti-PD-1 therapy.

Conclusions Overall, we identify a previously unappreciated fatty acid receptor, GPR84, as an important metabolic sensing switch for orchestrating anti-tumorigenic macrophage polarization. Pharmacological agonists of GPR84 hold great promise to reshape and reverse the immunosuppressive TME, and thereby restore responsiveness of cancer to overcome resistance to immune checkpoint blockade. Overall, GPR84, a not fully understood fatty acid receptor, can repolarize the TAM towards the antitumor phenotype and enhance the anti-PD1 response, which is a promising potential therapeutic target.

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