PLT012, A MONOCLONAL ANTIBODY TARGETING CD36, UNLEASHES ANTI-TUMOR IMMUNITY VIA METABOLIC REPROGRAMMING IN TUMOR MICROENVIRONMENT

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Background Accumulation of lipid metabolic products in tumor microenvironment (TME) has been documented to augment the malignancy of cancer by dampening anti-tumor immunity, including increased immunosuppressive features in various immune cells and development of exhausted phenotypes in T cells, which further orchestrates hurdles for immunotherapies. Previously, CD36, a fatty acid transporter, has been reported to be up-regulated in both malignant cells and tumor-associated immune cells, including regulatory T cells, tumor-associated macrophages and CD8+ T cells, to adjust the metabolic preference, which allow the cells to adapt in the lipid-enriched TME. This CD36-mediated adaption not only alters metabolic regulations, but also impacts the immune cell properties to construct an immunosuppressive TME. It has been suggested that blocking CD36-mediated fatty acid uptake rewires host anti-tumor immunity within the TME, including reducing abundance of tumor-infiltrating Treg and restoring survival and functions in CD8 T cells, highlighting the therapeutic potential of anti-CD36 antibodies.

Methods PLT012, a humanized anti-CD36 antibody, was developed via phage display, followed by the affinity maturation and developability optimization. Binding epitope of PLT012 was revealed by CryoEM structural analysis. Biological analyses of fatty acid blockade were validated in macrophages and isolated tumor-infiltrating T cells. The efficacy of PLT012 was assessed in genetically-induced melanoma and hydrodynamic injection-mediated hepatocellular carcinoma (HCC) murine model. Mechanism of action (MOA) of PLT012 was confirmed in human HCC samples on an ex vivo culture platform.

Results Firstly, PLT012 was generated with no concerns on ADCC/CDC effects and possessed the cross-reactivity among species, including murine, non-human primates and human. We found that PLT012 recognizes the lipid binding domain of CD36 without interfering TSP-1 binding site by CryoEM analysis. Administration with PLT012 significantly reduced M2 macrophage differentiation and fatty acid uptake in CD8+ TILs. Importantly, HCC-bearing mice treated with PLT012 exhibited a significant reduction in tumor growth with increased CD8/Treg ratio, which was in lines with the ex vivo observations of PLT012 treatments in human HCC samples.

Conclusions These results demonstrate that blocking CD36-mediated metabolic alterations in Treg and CD8+ TILs with PLT012 treatment can elicit a robust tumor growth inhibition and shift the immunosuppressive nature within the TME toward an immunosupportive one. This study further provides the pillar for harnessing immunometabolic targeting in cancer immunotherapy.

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