SELECTIVE TARGETING OF GARP-LTGFβ AXIS IN THE TUMOR MICROENVIRONMENT AUGMENTS PD-1 BLOCKADE VIA ENHANCING CD8+ T CELL ANTI-TUMOR IMMUNITY

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Background Immune checkpoint blockade (ICB) targeting programmed cell death protein 1 (PD-1) and its ligand has revolutionized cancer immunotherapy. Unfortunately, while some cancer patients experience robust and lasting remission following treatment, most fail to respond clinically. Accumulation of transforming growth factor b (TGFβ) in the tumor microenvironment (TME) can induce an immunosuppressive milieu and therapeutic resistance. TGFβ drives cancer immune evasion by inducing regulatory T cells (Tregs) and limiting CD8+ T cell function within the TME. Glycoprotein-A repetitions predominant (GARP; encoded by LRRC32) is a cell surface docking receptor for all isoforms of latent TGFβ (LTGFβ) and is expressed by effector Tregs, cancer cells, and platelets.

Methods We studied the role of LRRC32 expression in human cancer patients by mining the existing bulk transcriptomic databases. Then, we generated, characterized, and humanized an anti-GARP monoclonal antibody (called PIIO-1). Lastly, anti-tumor efficacy and its underline mechanism was investigated by murine tumor models.

Results We found that the overexpression of LRRC32 in human cancers correlates with unfavorable immune TME and poor responsiveness to ICB, indicating that targeting GARP may improve cancer immunotherapy. Therefore, we established our anti-GARP antibody PIIO-1 with a unique characterization that specifically binds to the ligand-interacting domain of free GARP and blocks the recognition by all LTGFβ isoforms. PIIO-1 antibody does not induce thrombocytopenia in our human LRRC32 knock-in mice due to the lack of recognition of GARP-LTGFβ complex on platelets. It obtains the anti-tumor efficacy against both GARP+ and GARP- tumors in a mono- or combo- therapeutic strategies with PD-1 blockade. Mechanistically, PIIO-1 preferentially distributes to the TME and dLNs and inhibits canonical TGFβ pathway in their infiltrating immune cells. In addition, PIIO-1 treatment prevents CD8+ T cell exhaustion and improves its migration into TME in a CXCR3-dependent manner.

Conclusions GARP overexpression in cancer patients contributes to immune suppression as well as ICB resistance. Targeting GARP by using PIIO-1 antibody blocks LTGFβ activation in vivo effectively and safely. PIIO-1 is responsible for the improvement of function and trafficking in tumor-infiltrating CD8+ T cells and synergizing anti-PD-1 efficacy. Therefore, PIIO-1 is potent for the clinical development of cancer immunotherapy.