Targeting glycosylated PD-1 induces potent anti-tumor immunity

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Abstract

Immunotherapy targeting programmed cell death protein 1 (PD-1) is an inhibitory receptor expressed on the surface of activated T cells that dampens T-cell receptor (TCR)/CD28 signaling by engaging with its ligand programmed cell death 1 ligand 1 (PD-L1) expressed on cancer cells. PD-1 and PD-L1 immune checkpoints represents a major breakthrough in cancer treatment. Despite the clinical success of PD-1 blockade using monoclonal antibodies, most patients do not show promising results, and the underlying regulatory mechanisms of PD-1 remain incompletely defined. Here, we showed that PD-1 is extensively N-glycosylated in T cells, and the intensities of its specific glycoforms are altered upon TCR activation. Glycosylation is critical for maintaining PD-1 protein stability and cell surface localization. Importantly, the glycosylation of PD-1, especially at the N58 site, is essential for mediating the interaction with PD-L1. A monoclonal antibody that specifically targets glycosylated PD-1, STM418, exhibits higher binding affinity to PD-1 than FDA-approved PD-1 antibodies, potently inhibits PD-L1/PD-1 binding, and enhances anti-tumor immunity.

Fig. 1 PD-1 is heavily glycosylated in T cells.

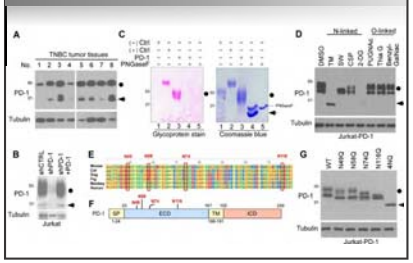


Fig. 2 The specific glycoforms of PD-1 are altered upon T cell activation.

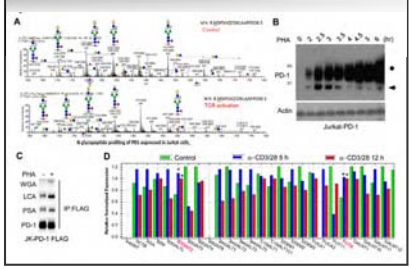


Fig. 3 PD-1 glycosylation is critical for maintaining its stability and membrane expression.

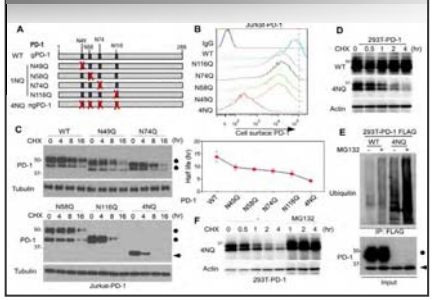


Fig. 4 The glycosylation of PD-1 is essential for its interaction with PD-L1.

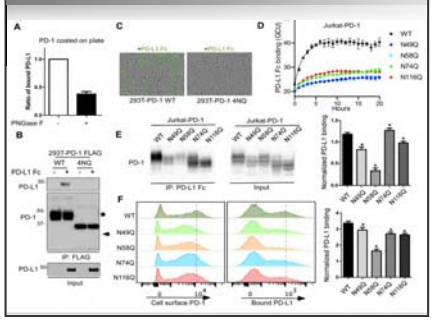


Fig. 5 Production and characterization of antibodies targeting glycosylated PD-1.

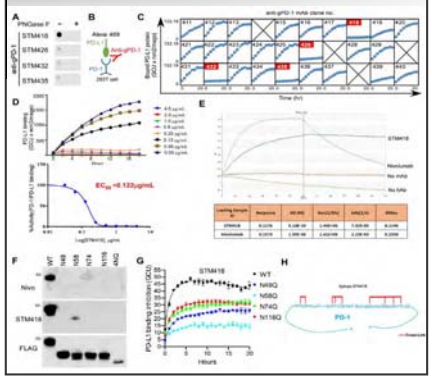


Fig. 6 STM418 enhancesT-cell proliferation and activation in vitro.

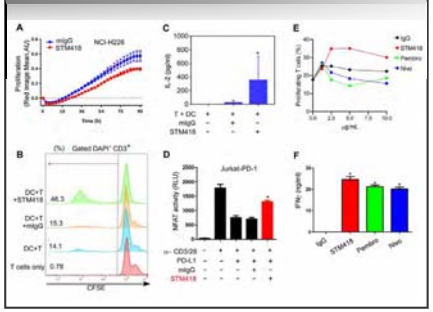
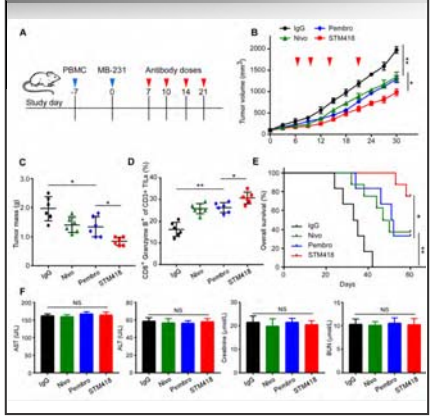


Fig. 7 STM418 induces potent anti-tumor immunity in a humanized TNBC animal model.



Conclusions

Our findings provide novel insights into the functional significance of PD-1 post-translational modification, specifically glycosylation and offer a rationale for targeting glycosylated PD-1 as a potential strategy for immunotherapy.

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