914 REGULATING NEGATIVE IMMUNE REGULATORS TO ENHANCE IMMUNE CHECKPOINT BLOCKADE ANTITUMOR POTENTIAL

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Background Understanding the exact immunobiology of immune checkpoint blockade (ICB)-related relapse would be essential to augmenting ICB-induced antitumor immunity and overcoming resistance. In response to ICB, a specific and effective immune response is induced. However, the levels of distinct immune cell subsets and the specific signals that draw them into a tumor microenvironment (TME) following broad application of cancer immunotherapies such as immune checkpoint blockade (ICB) remain poorly characterized. We previously showed that lymphocyte function associated antigen-1 (LFA-1) activation is critical for converting CD8 T cell exclusionary tumor microenvironment (TME) and allowing enhanced ICB-induced tumor control.[1,2] Whereas very late antigen-4 (VLA-4) activation did not contribute to anti-CTLA-4 therapy antitumor response. Here, we evaluated the effect of integrin a4b7 blocker as a strategy to overcome immune resistance in the setting of combination immunotherapy (anti-CTLA-4, anti-PD-1 and/or anti-Lag-3).

Methods To evaluate synergy between ICB (anti-CTLA-4 and anti-PD-1 or anti-PD-1 and anti-Lag-3) and VLA-4 integrin blocker, once mice with B16 melanoma, Lewis lung carcinoma (LLC) or pancreatic adenocarcinoma (PAN-02) had developed tumors of approximately 20mm^2, they were treated with either IgG control, VLA-4 blocker, ICB, or combination of both therapies together.

Results We observed no difference in therapeutic benefit between a4b7 blocker and IgG control ($p<0.05$) in all tumor models. Interestingly, we observed that a4b7 integrin blocker demonstrated therapeutic synergy with anti-CTLA-4 and anti-PD-1 but not anti-PD-1 and anti-Lag-3. Likewise, a4b7 integrin blocker in combination with anti-CTLA-4 and anti-PD-1 significantly enhanced antitumor response in PAN-02 ($p<0.001$) and LLC tumor ($p<0.001$) models. Initial immune infiltrates analysis shows improved antitumor response corresponded with increase in CD8+ Teff/Treg, CD4+ Teff/Treg ratios at the TME.

Conclusions Our preliminary results from treatment of mice implanted with tumor and receiving combination checkpoint blockade therapies suggest that a4b7 could potentially enhance intratumoral CD8+ effector T cell/Treg ratios to establish antitumor immunity.

REFERENCES

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