TARGET THE ACTIVIN RECEPTOR 1C ON CD4+ T CELLS TO ACHIEVE ANTI-TUMOR THERAPEUTIC EFFECTS

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Background Activins, members of the transforming growth factor-β (TGF-β) superfamily, were isolated and identified in endocrine system, and have been widely studied in endocrine-related cancers1, 2 but not substantially in the context of immune system and endocrine-unrelated cancers. 3-5 It has been reported that upon binding to the receptors, activins cause the intracellular recruitment and phosphorylation of smad proteins, which mediate the expression of Foxp3. 6-9 Therefore, we hypothesized that the blockade of the interaction of activins and their receptors will inhibit the activin-mediated Foxp3 induction in CD4+ T cells, thus modify the immune suppressive tumor microenvironment and achieve the goal of cancer immunotherapy.

Methods ELISA (enzyme-linked immunosorbent assay) has been performed to determine the plasma level of Activin A in tumor-bearing mice and cancer patients. In vitro iTreg (induced regulatory T cells) differentiation has been done to naïve CD4+ cells isolated from wild type mice in the presence or absence of Activin A, and the percentage of Foxp3+ cells was demonstrated by flow cytometric analysis. qRT-PCR analysis has been conducted to determine the mRNA level of activin receptor isotypes in the immune subpopulations sorted from Foxp3-YFP mice. In the end, in vivo subcutaneous transplanted tumor studies have been done to evaluate the anti-tumor therapeutic effects of activin-receptor 1c blockade.

Results We show here that tumor-bearing mice had elevated Activin A levels, which correlated directly with tumor burden. Likewise, cancer patients had elevated plasma Activin A compared to healthy controls. Importantly, our in vitro studies suggested that Activin A promoted differentiation of conventional CD4+ cells into Foxp3-expressing induced Tregs, especially when TGF-β was limited. Database and qRT-PCR analysis of sorted major immune cell subsets in mice revealed that activin receptor 1c (Acrv1c) was uniquely expressed on CD4+ cells. Similar phenomena were observed when we treated the mice with anti-Acrv1c antibody after tumor inoculation. This anti-tumor therapeutic effect was more significant when anti-Acrv1c antibody was administrated in combination with anti-PD-1 antibody.

Conclusions Blocking Activin A signaling through its receptor 1c is a promising and disease-specific strategy for preventing the accumulation of immunosuppressive iTregs in cancer. Hence it represents a potential candidate for cancer immunotherapy.

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REFERENCES

Ethics Approval All animal experiments were performed under protocols approved by the Johns Hopkins University Institutional Animal Care and Use Committee (IACUC).

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