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TGF-β2 mediated secretion of sCTLA-4 from regulatory T cells

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Cytotoxic T lymphocyte antigen-4 (CTLA-4), a membrane bound inhibitory receptor whose expression is induced on activated T cells, has been established as an important regulator of T cell responses and serves to maintain peripheral tolerance. Additionally, recent characterization of a novel mechanism of extrinsic suppression mediated by the soluble isoform of CTLA-4 (sCTLA-4) has served to further establish the importance of CTLA-4 in maintaining homeostasis of the immune system. Previously, we have shown that selective blockade of sCTLA-4 in patients with metastatic melanoma enhances immune responses including increased antigen-specific proliferation of both CD4+ and CD8+ T cells, compared with an isotype antibody control or pan CTLA-4 blockade. Selective blockade also enhanced T cell effector cytokine responses, notably IFN-γ and IL-17. In this study, we demonstrate a protocol for generating a regulatory T cell population, which is characterised by the production of high levels of sCTLA-4. Treatment of naïve human T cells with TGF-β2 together with an anti-CD3 mAb/IL-2 T cell stimulus increased their capacity to produce high levels of sCTLA-4, while decreasing production of effector cytokines - IFN-γ, IL-17 and IL-10. Furthermore, analysis of these sCTLA-4 producing T cells has shown that they express the T regulatory cell transcription factor – FoxP3. Taken together, our data show that TGF-β2 could serve as an attractive therapeutic tool to alleviate symptoms of autoimmunity through the induction of regulatory T cell populations that secrete immunosuppressive sCTLA-4; while on the other hand, neutralizing the effects of TGF-β2 could also prove beneficial to patients with cancer.

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