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Title: Activin-A induces human regulatory T cells that control allergic asthma

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Body: Activin-A is a cytokine involved in essential biological processes.Our previous studies have uncovered activin-A as a controller of experimental asthma through the induction of mouse regulatory T cells (Tregs).Here, we studied the role of activin-A in the induction of human Tregs suppressive against allergic responses in asthmatics.Peripheral blood CD4+ T cells were stimulated with a clinically-relevant allergen in the presence of activin-A (or control).The phenotype of activin-A-treated T cells and their suppressive function on human T cell responses and in asthma protection in a humanized mouse model were investigated.Our data reveal that activin-A greatly inhibits human T cell proliferation and Th2 cytokine release.Activin-A-treated T cells remain hyporesponsive after allergen restimulation and do not express effector cytokines. Still, they express significantly increased amounts of immunosuppressive IL-10.Notably, activin-A-treated T cells are suppressive against allergic responses of atopics and asthmatics, pointing to the generation of a Treg subset (act-A-iTregs). Act-A-iTregs also restrain Th2 responses in the bronchoalveolar lavage (BAL) of severe asthmatics.Using a humanized model of asthma, we show that, co-transfer of act-A-iTregs with human T effectors confers protection against asthma in vivo, as shown by greatly decreased airway hyperresponsiveness, BAL, lung inflammation and Th2 responses in the lungs and draining lymph nodes.Our data reveal that activin-A generates IL-10-producing Tregs that suppress human allergen-driven responses and protect against asthma.Our findings may facilitate the use of act-A-iTregs in adoptive-transfer therapies aiming to re-establish tolerance in asthma.