Biomedical Research Foundation

Activin-A in allergic airway inflammation and remodeling

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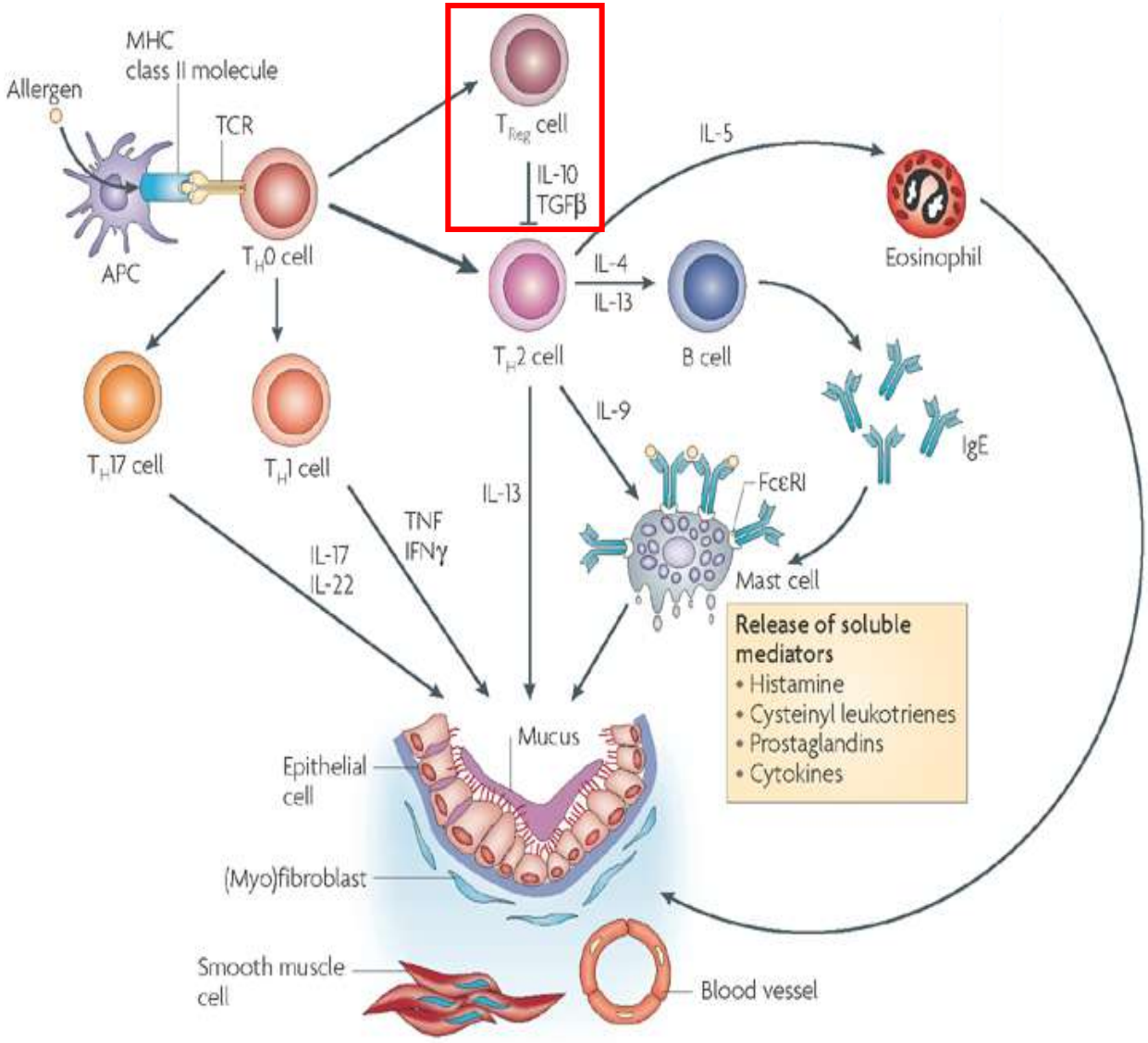
ACADEMY OF ATHENS

Immune-suppressive mechanisms represent important therapeutic targets.



(Holgate et. al., Nat Rev Immunol 2008)

Suppression of allergic immune responses is mediated by:

1. Immunoregulatory cytokines, such as TGF-β1 and IL-10

2. Immunosuppressive cells, such as T regulatory cells (Tregs) and plasmacytoid DCs (pDCs).

- *In vivo* transfer of Tregs and pDCs protects from allergic airway disease *(Kearley et. al., JEM 2007, Kool et. al., JI 2009).*

- *Suppressive mechanisms inhibit allergic responses from asthmatics in vitro (O'Garra NRI 2007).*

However, these mechanisms are not sufficient for suppression of asthma suggesting that other mediators are involved.

Activin-A

A cytokine which belongs to the TGF-β1 superfamily (TGFβ1-5, activins/inhibins, bone morphogenetic proteins , etc.

Activin-A participates in essential and diverse biological activities.

- stimulation of FSH-secretion *(Biochem. Biophys. Res. Commun., 1986)*
- development (mesoderm induction) *(Nature, 1990)*
- haematopoiesis *(Nature, 1987, Proc. Natl. Acad. Sci. USA, 1988)*
- tissue fibrosis and remodeling (*Biochem. Biophys. Res. Commun., 1996, Am. J. Respir. Cell Mol. Biol., 2005, Am. J. Pathol., 2006)*

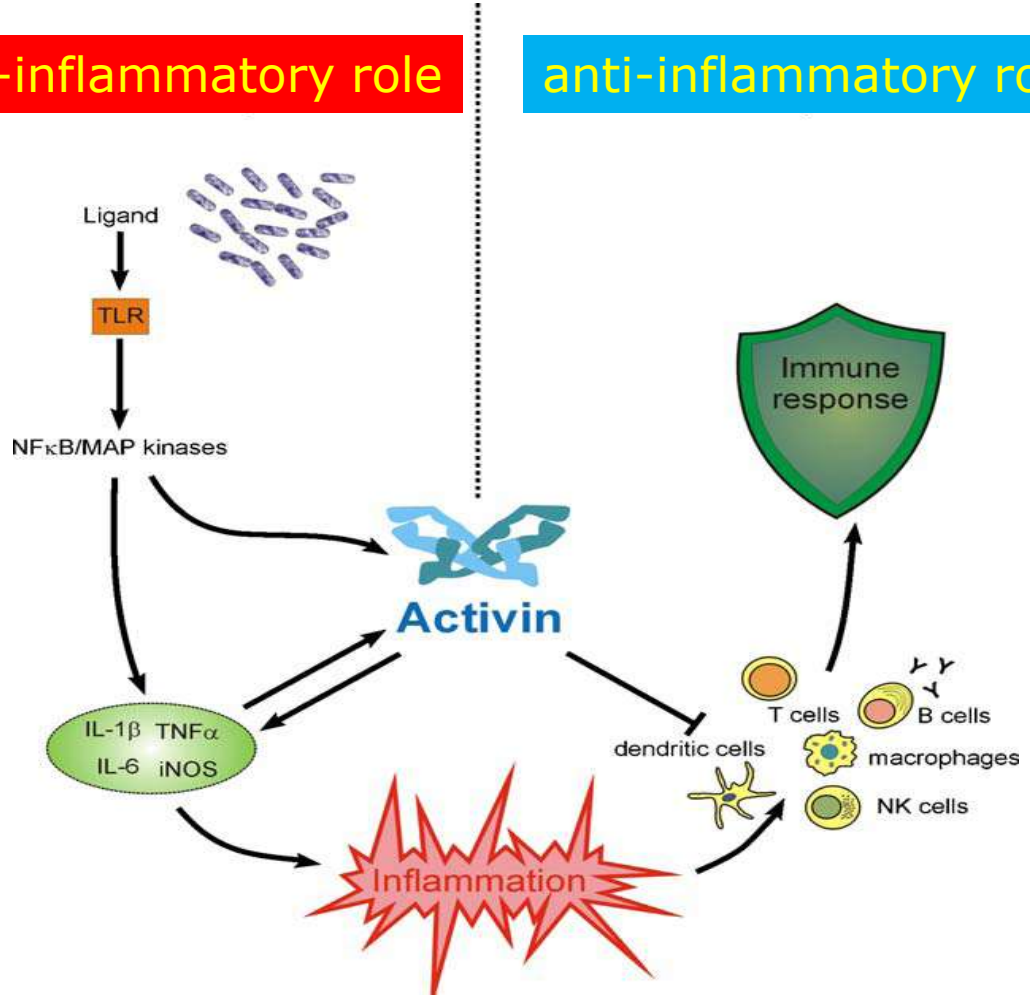
Activin-A expression is increased during allergic diseases:

a) the sera of individuals with allergic asthma *(JACI 2006)*.

b) the lung and BAL of mice during acute and chronic allergic airway inflammation *(CEA 2006, AJRCMB 2001, JI 2007)*.

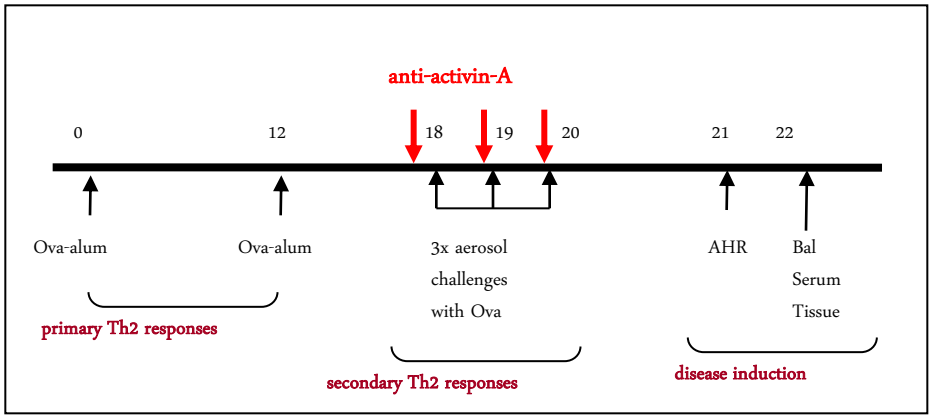
c) human and mouse Th2 lymphocytes, key players in allergic responses *(JACI 2006, JI 2006)*.

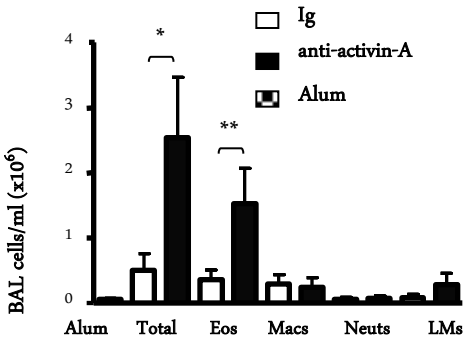
Contradictory data regarding activin-A's effects on immune responses

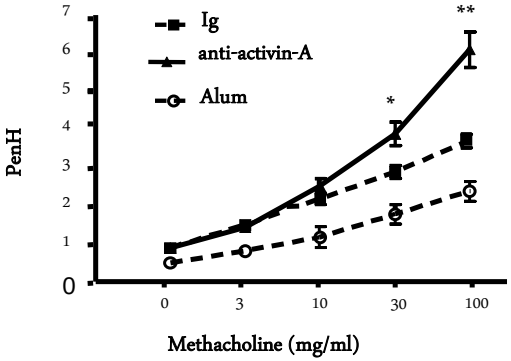


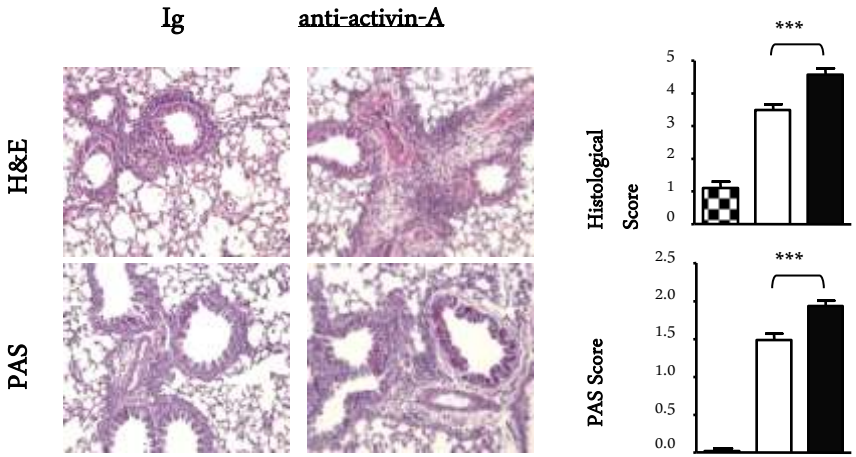
The role of activin-A in Th2-mediated allergic responses and associated disease remains unclear.

We hypothesized that activin-A is an immunosuppressive cytokine during allergic responses.



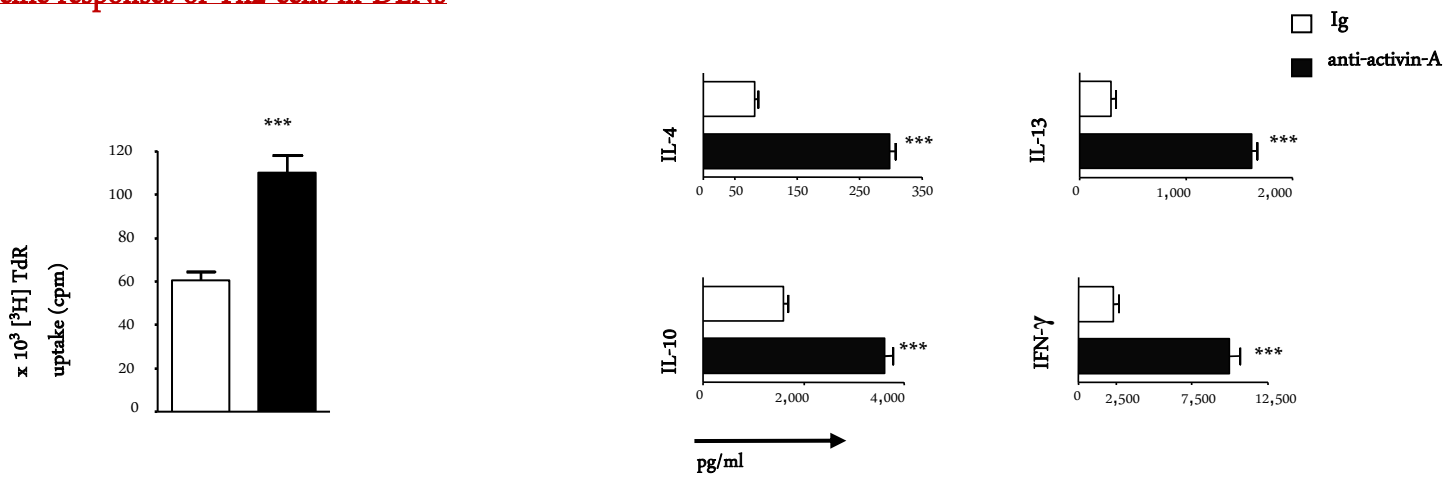




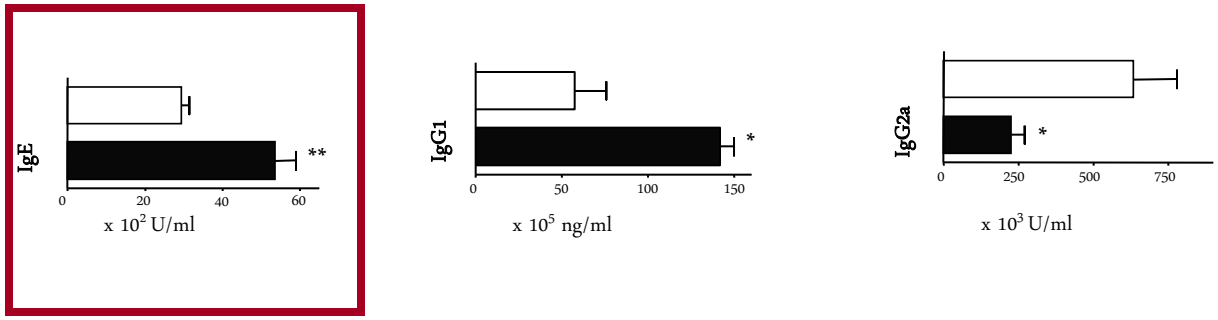


Semitekolou et al, Journal of Experimental Medicine 2009

OVA-specific responses of Th2 cells in DLNs

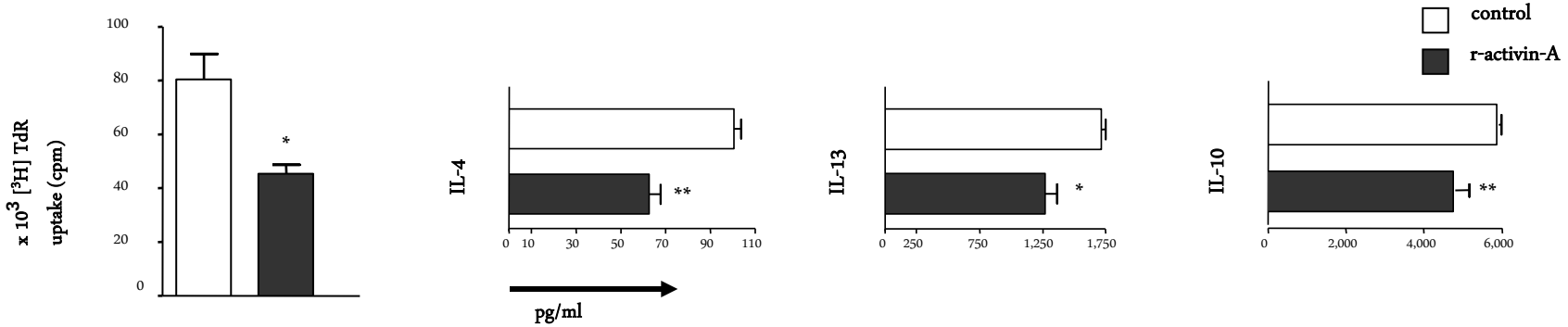


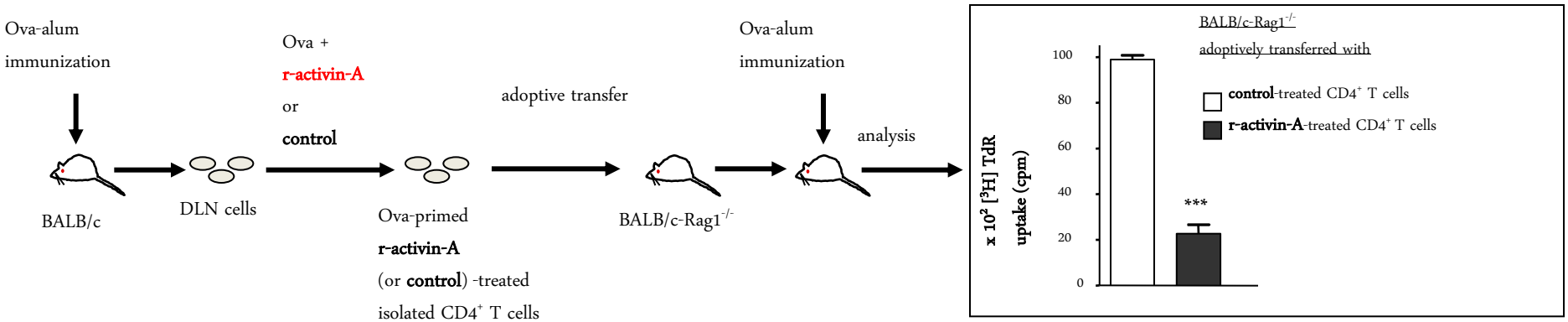
OVA-specific Ig responses

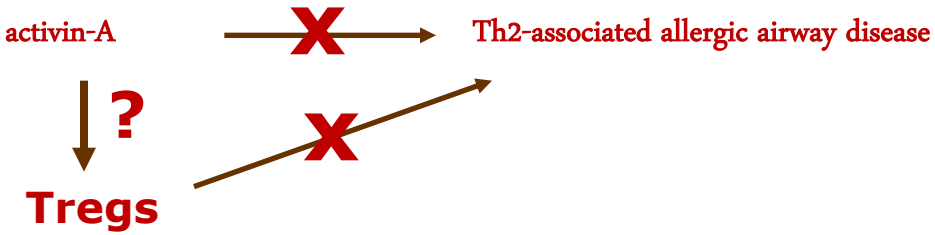


Depletion of activin-A during allergen challenge in the airways enhances Th2 allergic responses and exacerbates asthmatic disease.

Activin-A suppresses allergic Th2 responses *in vitro* and *in vivo*.

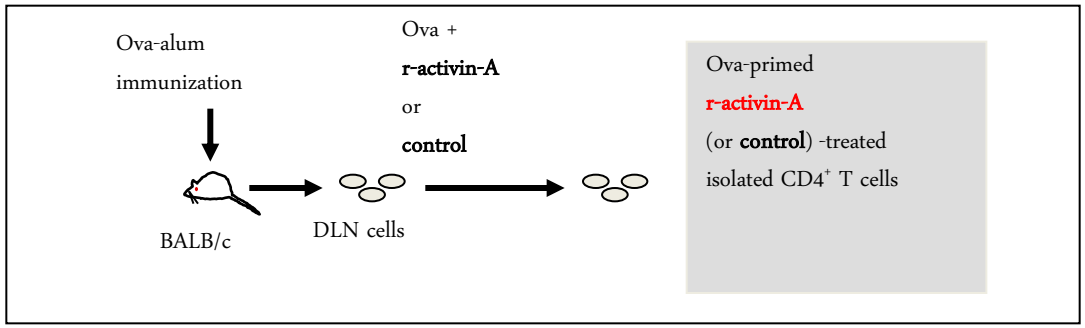


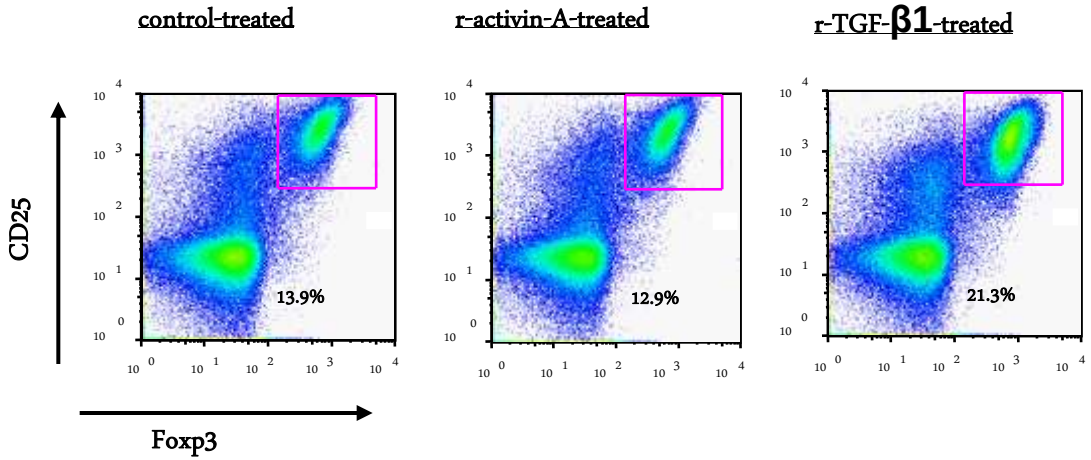


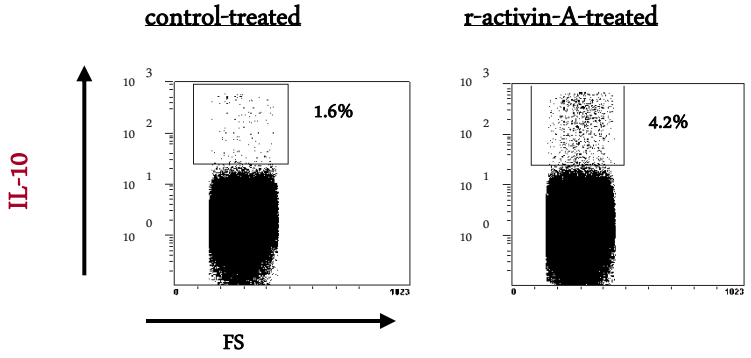


Is activin-A-mediated Th suppression associated with induction of Tregs?

Activin-A induces $CD4^{+}CD25^{-}Foxp3^{-}IL\text{-}10^{+}$ regulatory T cells

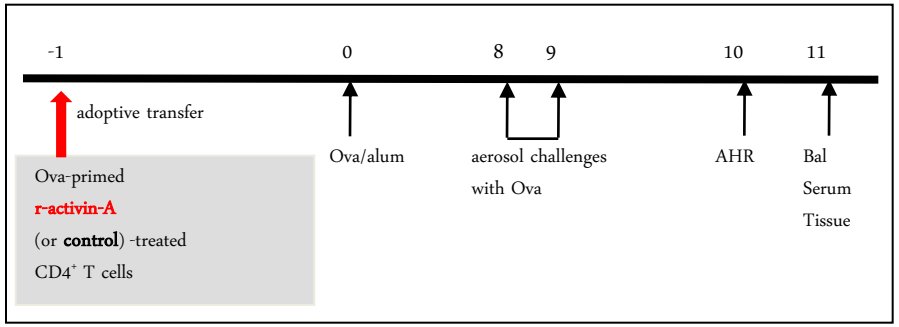


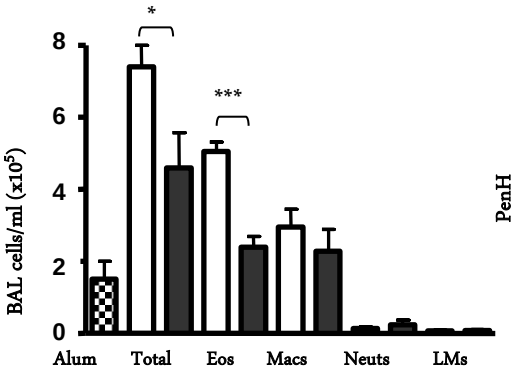


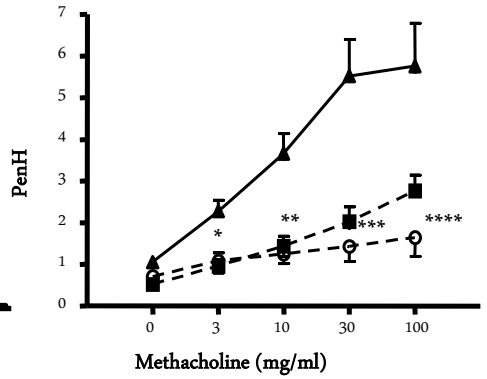


can activin-A-induced Tregs suppress allergic airway disease?

Activin-A-induced Tregs protect against allergic airway disease *in vivo*

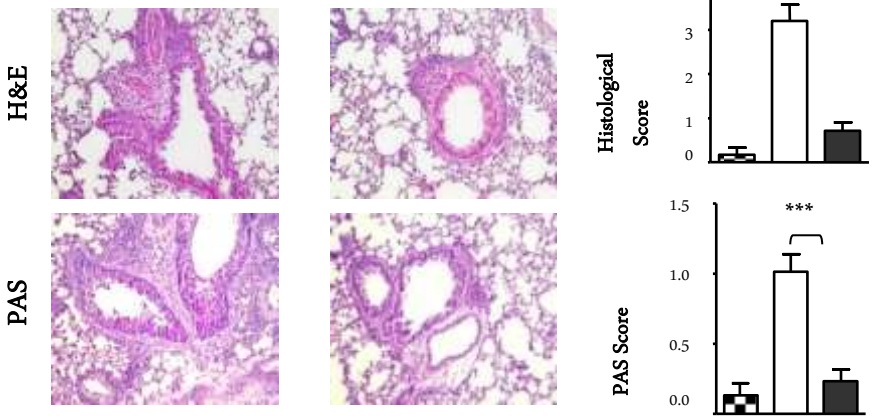




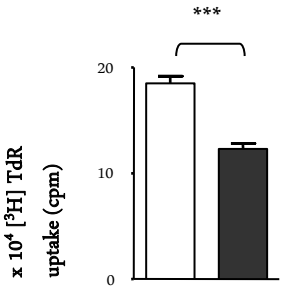


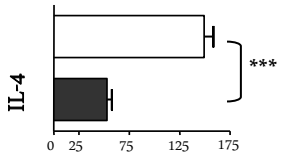
control-treated CD4+ T cells

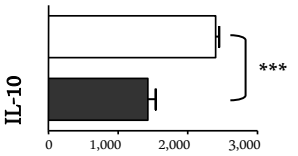
r-activin-A-treated CD4+ T cells

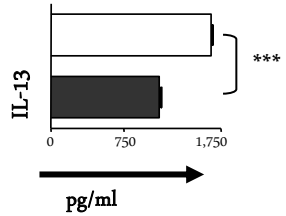


DLN / OVA response

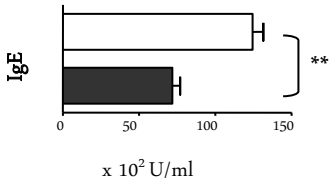


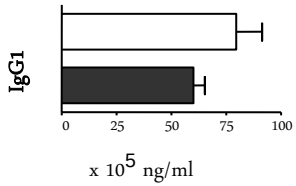


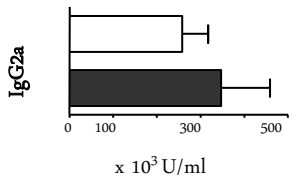




OVA-specific Ig responses

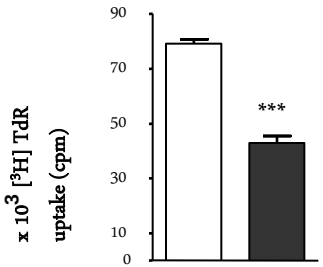


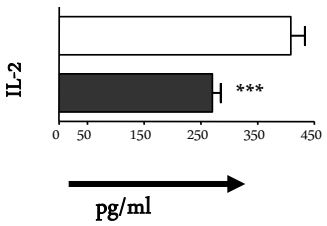


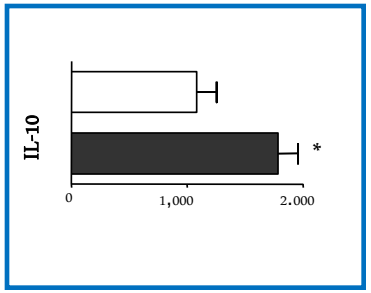


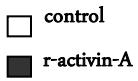
Activin-A-induced Th suppression is mediated by IL-10 and TGF-β1

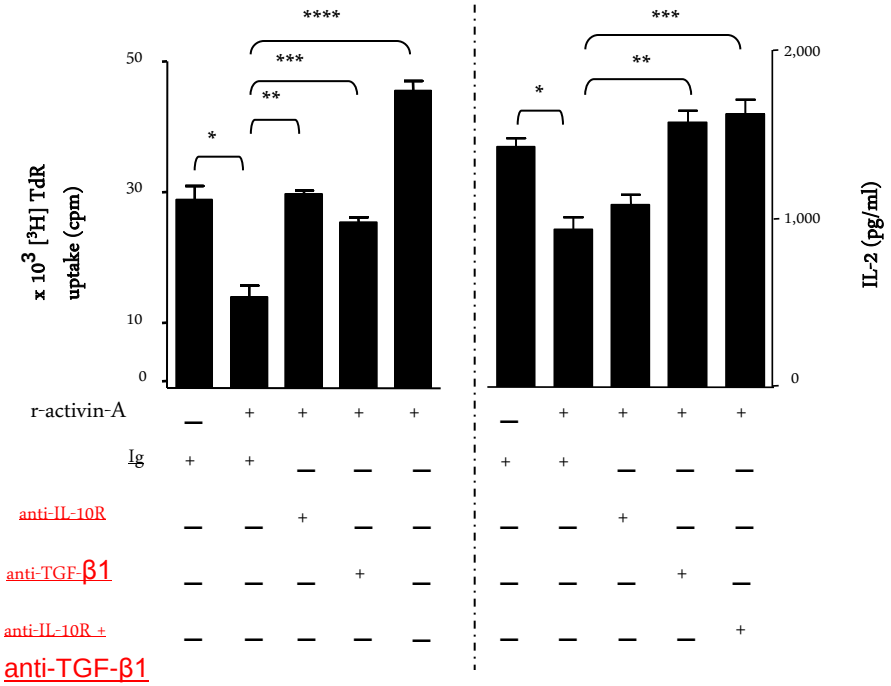
anti-CD3 Th responses





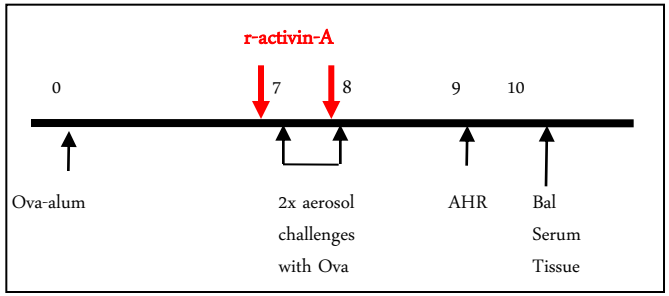


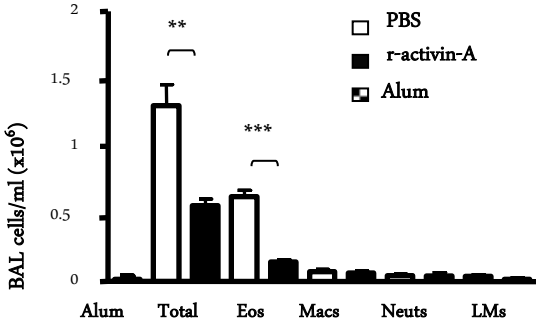


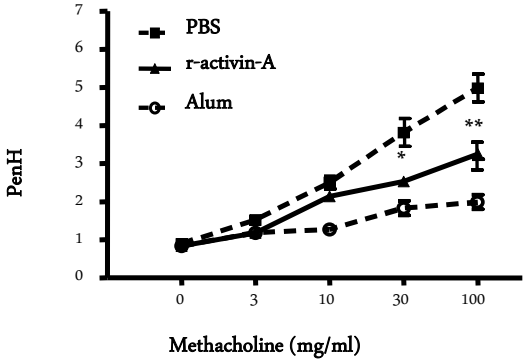


Can activin-A protect from allergic airway disease induction?

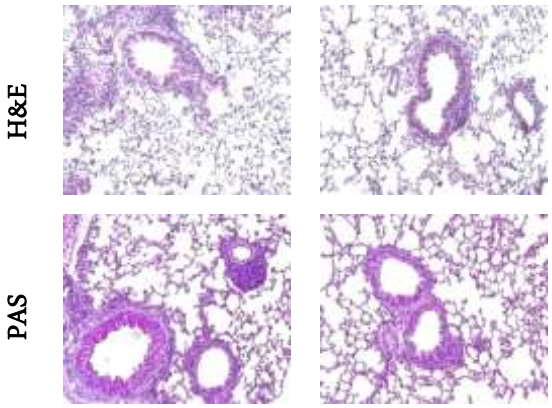
Therapeutic administration of activin-A suppresses experimental asthma.

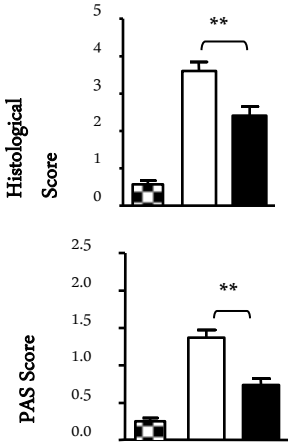






PBS r-activin-A





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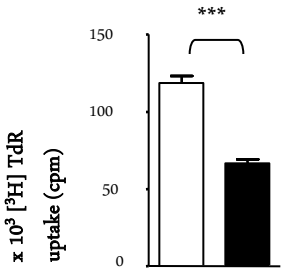
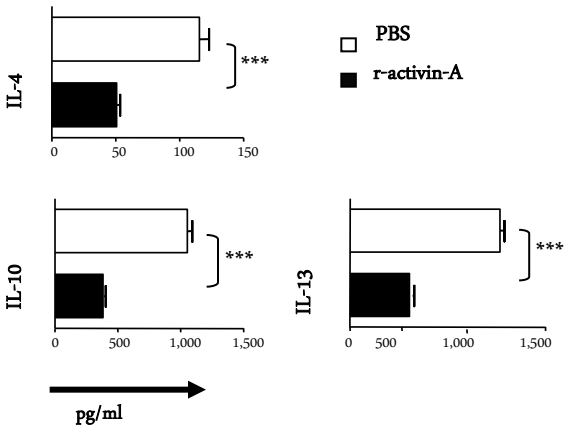
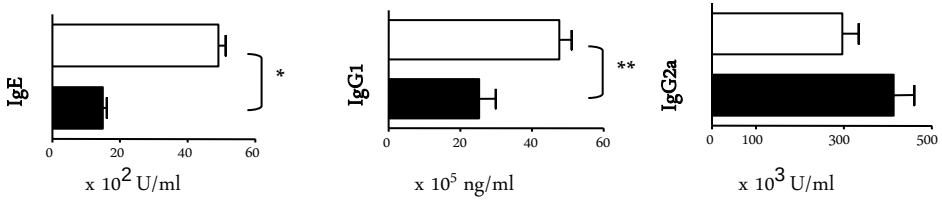


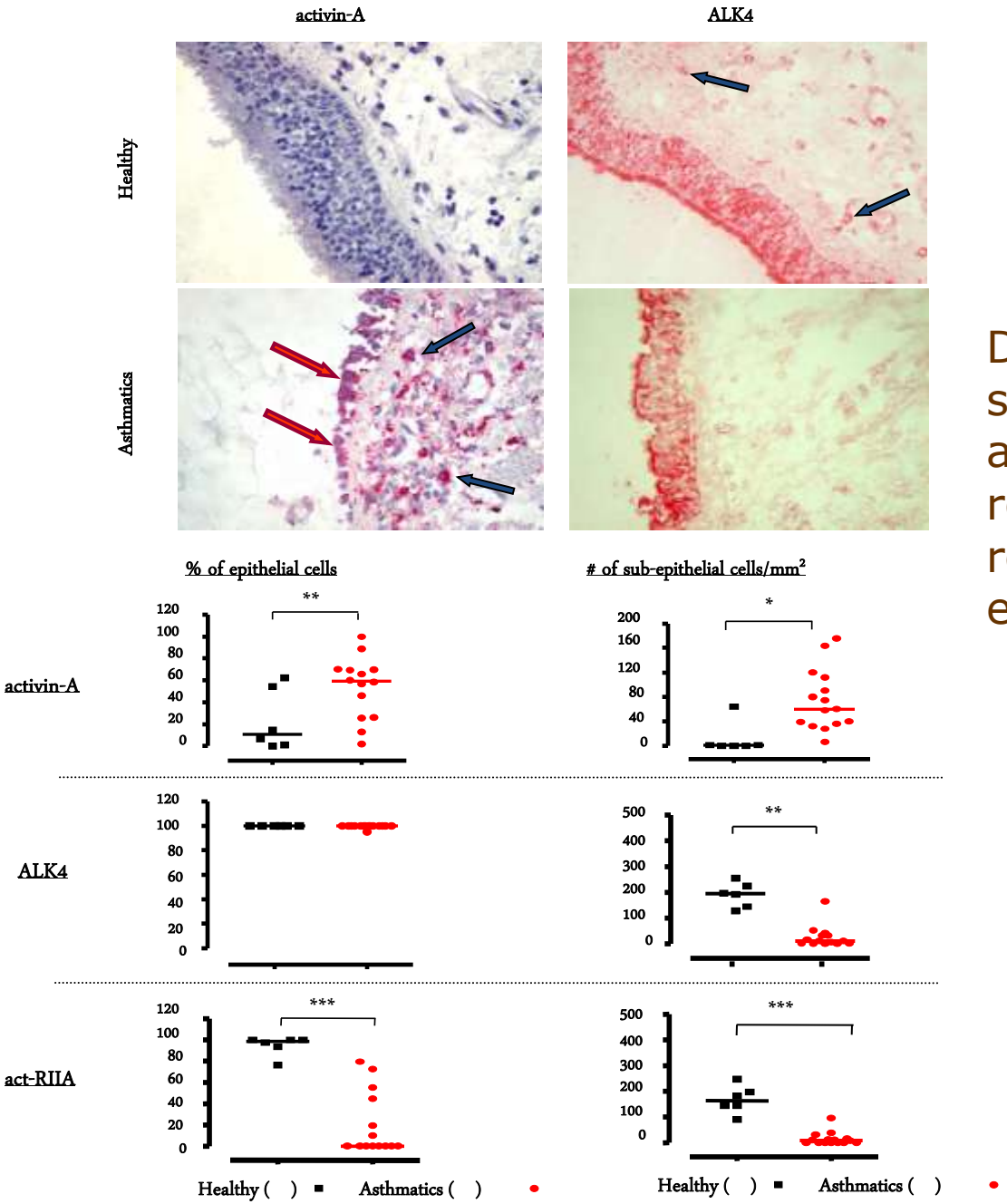


OVA-specific Ig



Semitekolou et al, JEM 2009

Decreased expression of activin-A signaling components in allergic asthma



Decreased activin-A signalling in lungs of asthmatics points to reduced immune regulation and enhanced inflammation.

Activin and transforming growth factor-beta signaling pathways are activated after allergen challenge in mild asthma

Kariyawasam HH, Pegorier S, Barkans J, Xanthou G, Aizen M, Ying S, Kay AB, Lloyd CM, Robinson DS

Journal of Allergy and Clinical Immunology 2009

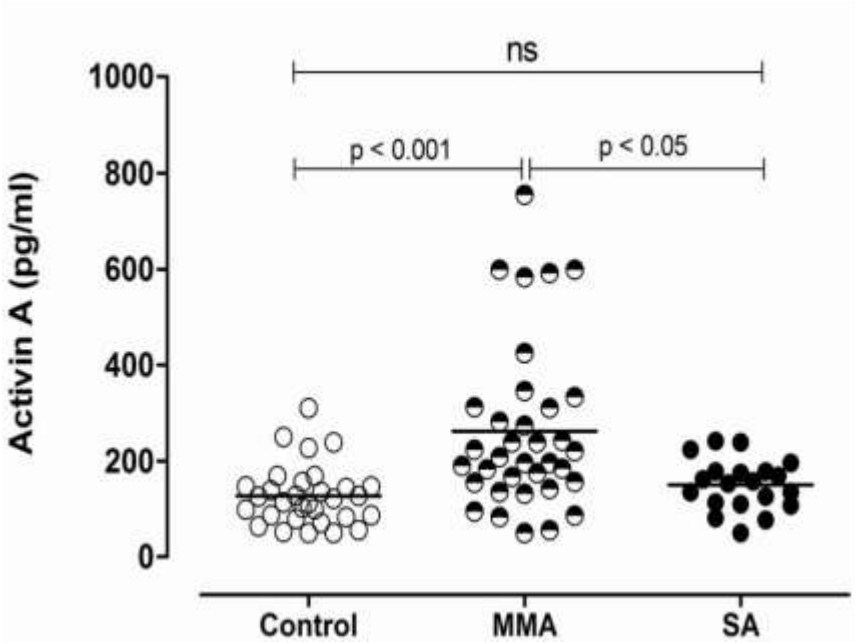
- activin-A's receptor, ALK-4, is significantly increased in sub-epithelial cells of mild asthmatics following pulmonary allergen challenge.

- activin-A inhibits TNF-α and IL-13-induced chemokine production by human bronchial epithelial cells.

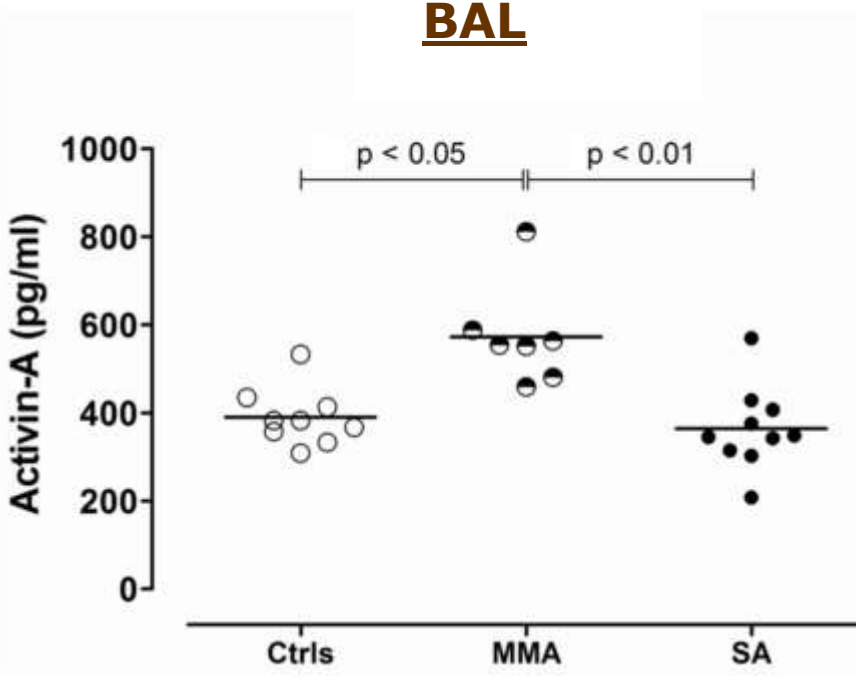
Key role of activin-A in airway inflammation and, possibly, remodeling in humans

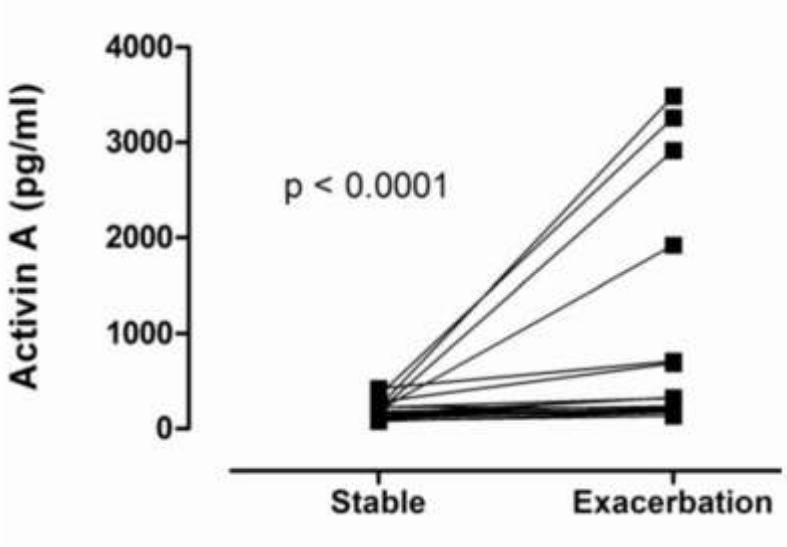
Increased levels of activin-A in individuals with severe asthma

serum



BAL



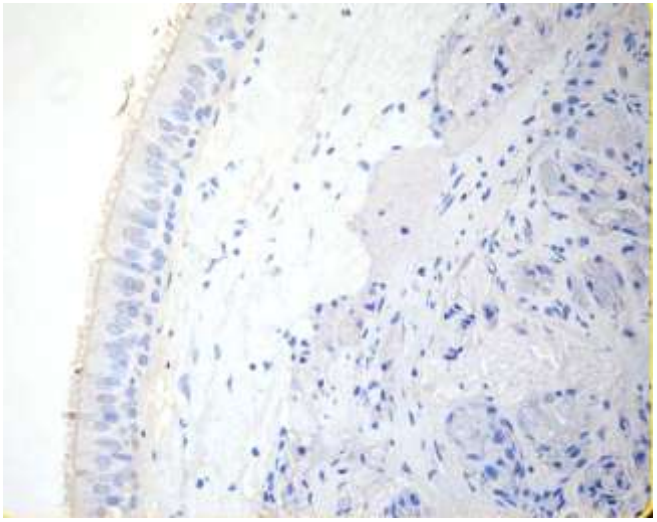


activin-A increases during asthma exacerbations

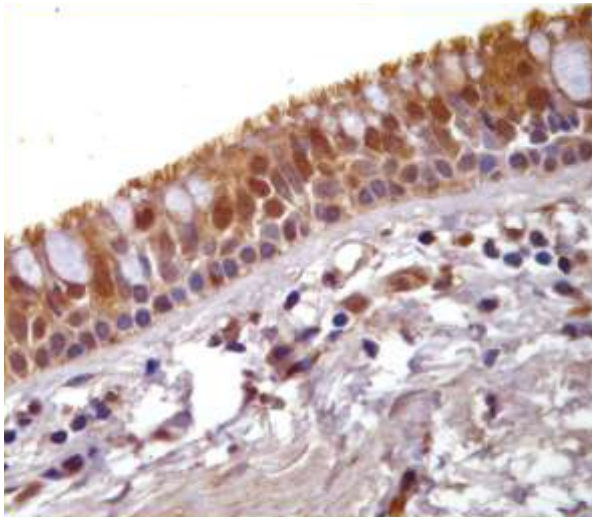
Samitas et. al., in preparation

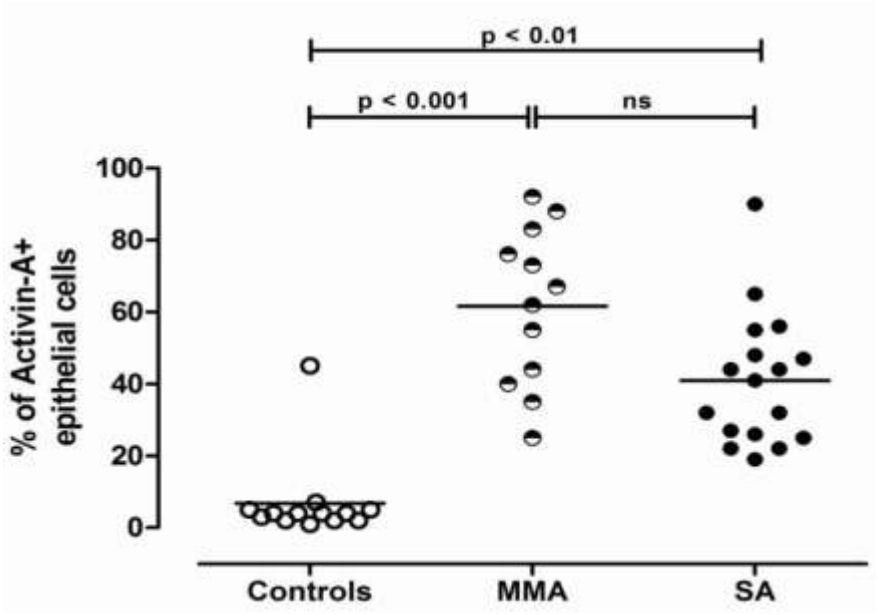
Increased levels of activin-A in individuals with severe asthma

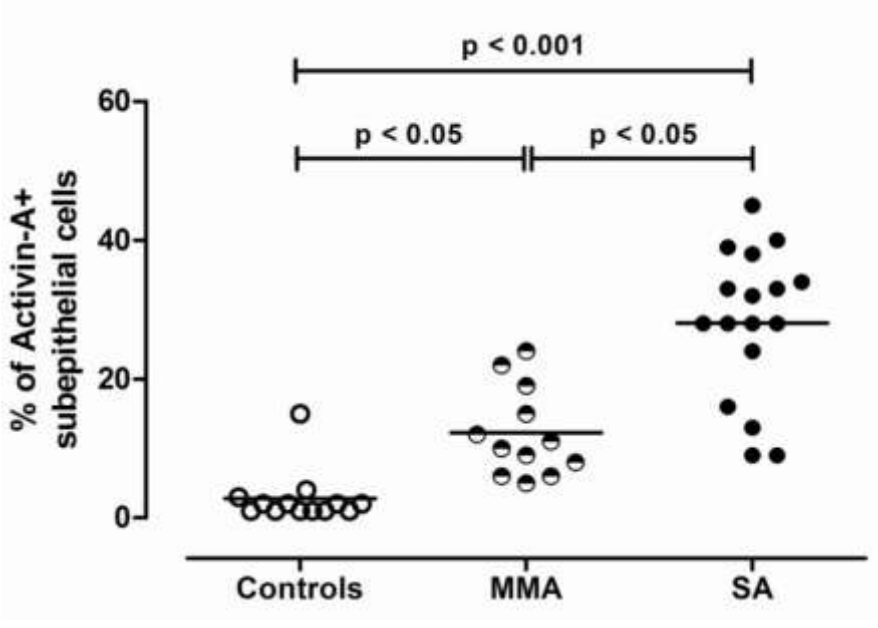
healthy



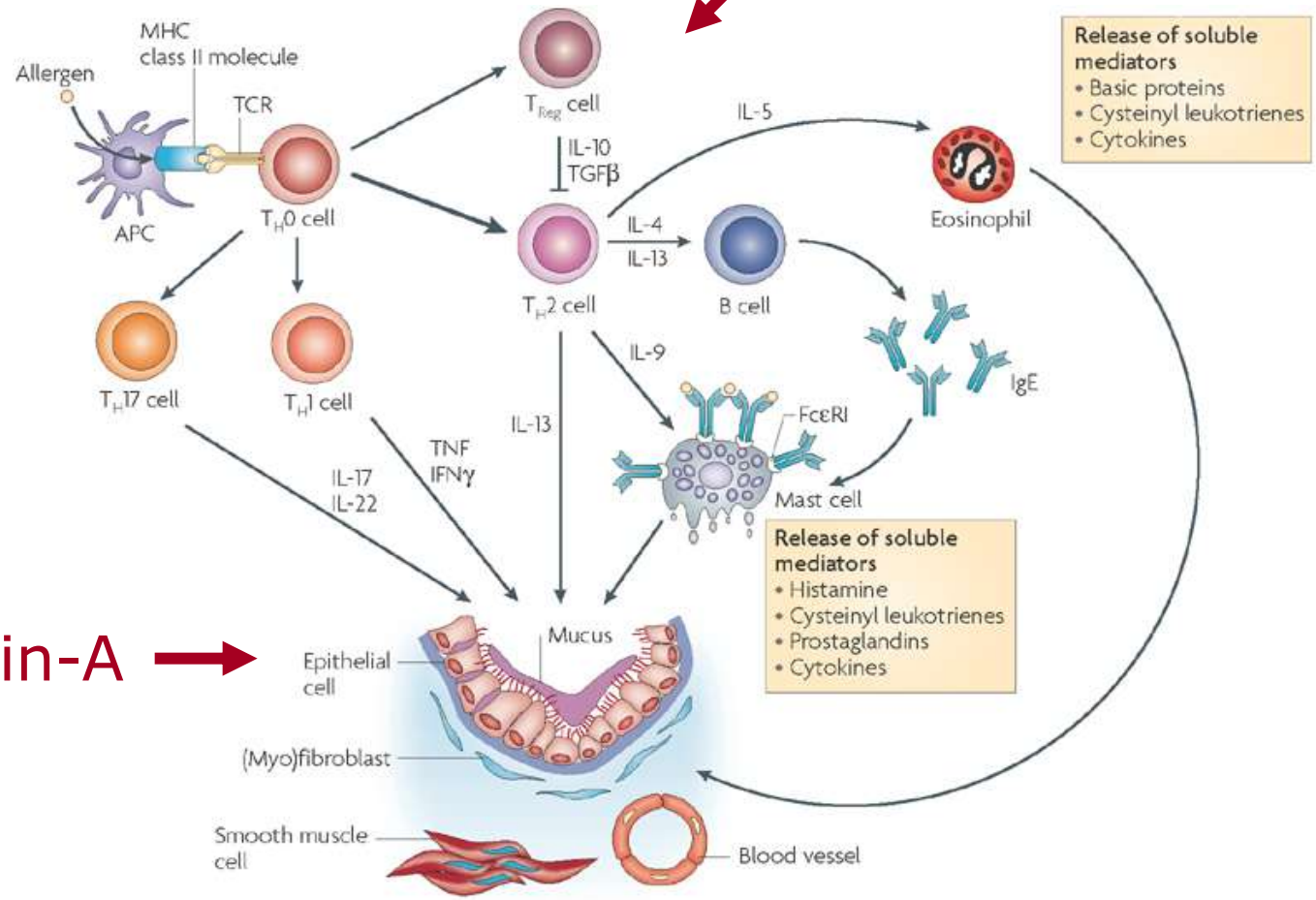
asthmatics







activin-A



activin-A

Future goals

1. generation of human regulatory T cells by activin-A for therapy

2. investigation of the effects of activin-A on airway remodelling (i.e. fibrosis, neo-angiogenesis) in asthmatics

Acknowledgements

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