OC12 & P04 - **Effect of IL-33 targeting in fungal microbiota--induced asthma**

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Background: *Alternaria alternata* spores are a very common potent aeroallergen source that is found in environmental samples. A consequence of human exposure to fungal aeroallergens, sensitization to *A. alternata*, has been unequivocally associated with increased asthma severity. *A. alternata*-specific serine protease activity causes rapid IL-33 release, which underlies the development of a robust Th2 inflammation and exacerbation of allergic airway disease. Targeting of IL-33 is therefore believed to be a potential novel strategy for the treatment of asthma.
Objective: In this study, we describe a novel treatment for allergic asthma targeting IL-33, which is known to play a key role in asthma-related immune responses. Namely, we show that a fusion protein consisting of the extracellular domains of mouse ST2 and IL-1RAcP, further referred to as IL-33 trap, is able to neutralize IL-33 released in response to *A. alternata* and ameliorate the inflammatory responses.
Methodology: An exacerbation model of allergic asthma was established where C57BL/6 J mice were sensitized and subsequently challenged by intratracheal administration of *A. alternata* extract. The IL-33 trap was co-administered during the challenge phase. 24 hours after the final challenge, airway inflammation and lung function were evaluated. Eosinophil infiltration in the airways was quantified by Flow Cytometry. In vitro IL-5 and IL-13 production by cells isolated from mediastinal lymph nodes upon re-stimulation with *A. alternata*, and Th2 cytokines levels in lung homogenate were measured by ELISA. Airway hyperresponsiveness (AHR) was assessed using increasing concentrations of methacholine and broadband forced oscillations (flexiVent, SCIREQ, Montreal, Qc, Canada).
Results: IL-33 trap delivery at the challenge phase strongly attenuated allergic responses in sensitized mice challenged with *A. alternata*. This was reflected by the significant reduction of lung eosinophilia and lymphocytosis. Likewise, increased production of Th2 cytokines associated with asthma, such as IL-5, IL-13 and IL-4, in the lung and mediastinal lymph nodes was also blunted by IL-33 trap. Furthermore, IL-33 trap treatment attenuated *A. alternate*-induced AHR.
Conclusions / Implications for practice: Repetitive administration of *A. alternata* resulted in Th2 driven airway inflammation where the IL-33/ST2 axis plays a crucial role. Together, our data demonstrate the great potential of IL-33 trap as an antagonist of IL-33 for the therapeutic use in allergic asthma.

References

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