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Experimentell Astma- och Allergiforskning

INTERACTIONS BETWEEN MAST CELLS AND SMOOTH MUSCLE IN ASTHMA MODELS

AKADEMISK AVHANDLING
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ABSTRACT

Allergic asthma is the major phenotype of asthma and is characterized by specific responses to allergens as well as airway hyperresponsiveness (AHR), inflammation and remodelling. Mast cells and airway smooth muscle cells (ASM) play an important role in the allergic airway response and there are several indications that a cross-talk exists between these two cell types contributing to asthma pathogenesis. However, these interactions and the mechanisms behind them are not fully understood. The overall aim of this thesis was to further elucidate the interactions between mast cells and ASM in different animal models of allergic asthma.

When responses between wild-type and mast cell-deficient mice, with and without mast cell engraftment were compared, we found that AHR was both mast cell dependent and independent using the same chronic mouse model of asthma. Although pulmonary mast cell number, distribution and possibly prostanoid secretion influenced the severity and localisation of AHR and levels of specific-IgE, inflammatory cell infiltration and remodelling was unaffected. However, the mere presence of mast cells had an effect on the levels of interleukin 17 and 33 (IL-17 and IL-33), two cytokines that are associated with asthma.

By studying airway responses in a guinea pig model of allergic asthma, we found that the early allergic reaction caused an altered airway resistance more similar to the response in humans than that seen in mice. This could be explained by the greater number and different distribution of mast cells, as well as the secretion of histamine and cysteinyl-leukotrienes from mast cells, suggesting that there are advantages to using guinea pigs compared to mice in asthma research.

We continued by studying how IL-33 affected the early allergic reaction in a mouse model of allergic sensitisation. We found that intranasal IL-33 in sensitised mice increased the smooth muscle contraction in isolated airways from these mice when challenged with allergen ex vivo. The increase was mast cell and IL1RL1 (the receptor for IL-33) dependent and was mediated via an enhanced secretion of serotonin. The direct effects of IL-33 on mast cells to increase their production, storage and mediator release were confirmed in mast cell cultures. Finally, we observed that IL-33 increased airway resistance, in a mast cell- and serotonin-dependent fashion following allergen challenge in vivo.

To further investigate how IL-33 influenced other features of allergic asthma, we studied the effects of IL-33 combined with an allergenic antigen on AHR, inflammation and remodelling in two different mouse models of asthma. No differences were observed when using a mast cell-independent protocol of sensitisation and challenge. However, using a protocol that has been shown to induce mast cell-dependent AHR and inflammation in sensitised and challenged mice, IL-33 combined with antigen elicited synergistic deleterious effects on AHR, inflammation and remodelling.

The studies in this thesis emphasise the importance of choosing the appropriate animal model when studying allergic asthma. The findings herein support that pulmonary mast cell number and distribution affects lung function in the disease state. Finally, we have shown that release of IL-33 is increased during allergic inflammatory conditions, and the level of the increase is affected by mast cells. IL-33 worsens several characteristic features of allergic asthma including the early allergic reaction, AHR, inflammation and remodelling, for some features in a mast cell-dependent manner. In conclusion, we have highlighted the importance of IL-33 in conjunction with mast cells for asthma development and severity and have identified a potential new target for asthma therapy.

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