

How can animal models lead to improved specific immunotherapy (SIT)?

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Over the past few years, the immunopathogenesis of immediate-type hypersensitivity responses of the respiratory tract has been delineated to a great extent. It is now generally accepted that the inflammatory component of allergic conditions is largely controlled by activated CD4-positive T cells which secrete a unique cytokine profile termed TH-2. These T cells control many events of early- and late-phase allergic reactions including IgE synthesis, mast-cell and eosinophil activity, and survival and recruitment of inflammatory cells into lesions. With regard to bronchial asthma, several of these events can be closely mimicked in murine animal models.

Several groups have contributed to this field of research by developing useful mouse models of respiratory allergy. Our models have the following features:

- 1) Development of allergen-specific IgE/IgG₁ antibody titres after systemic or local immunization.
- 2) Development of airway inflammation after allergen aerosol challenges in sensitized mice. This type of airway inflammation is characterized by an influx of eosinophils and T cells into the airways and is associated with enhanced IL-4 and IL-5 production.
- 3) Development of increased airway responsiveness represents a hallmark in these models. In our laboratory, we have the facilities to assess airway responsiveness by head-out body-plethysmography as well as by *in vitro* electric stimulation of tracheal segments.
- 4) Altered innervation and neuropeptide release has been observed in these models. These changes are related to enhanced production of the neuropeptides NGF and BDNF.

Therefore, these models mirror several key features of human bronchial asthma.

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Such models can now be used to assess novel strategies for immunointervention. Questions of prevention as well as therapeutic intervention can be studied. We have analysed immunointervention on the level of cytokine inhibition, using, for example, soluble IL-4 receptor molecules as well as IFN- γ administration. Results from these studies have provided evidence that intranasal (local) administration of mediators, soluble receptors, and monoclonal antibodies represents an important route of administration with many advantages for bioactivity and bioavailability. In addition, it is of great advantage in the animal models to study the

underlying mechanism of such therapeutic strategies. Furthermore, environmental conditions can be controlled, including nutrition, infections, and stress; the genetic background is defined; and allergen exposure is well controlled.

In summary, mouse models have an established place in the development of novel intervention strategies. They are placed between bench and bedside. A number of novel approaches are currently being discussed and developed in basic science, and they can be easily screened in such model systems.

References

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