Abstract

Asthma is characterized by a chronic inflammatory reaction in the airways. Roughly, asthma can be subdivided into atopic asthma involving elevated levels of serum IgE and a less familiar form, non-atopic asthma. Non-atopic asthma is an increasing problem in the developed world. The mechanisms involved in the induction and on-going respiratory impairments associated with non-atopic asthma are unknown and poorly investigated. In the present thesis the involvement of mast cells and nerves in asthma were studied in vitro using primary cultured mast cells and neurons and in vivo, in a murine model for non-atopic asthma. Non-atopic asthma was induced in mice by skin-sensitization with the low molecular weight compound dinitrofluorobenzene (DNFB) followed by intranasal intra-airway challenge with a water-soluble dinitrobenzene derivate, dinitrobenzene sulphonic acid (DNS). Features of this pulmonary reaction included acute bronchoconstriction and mast cell activation shortly after challenge, and tracheal hyperreactivity, mononuclear and neutrophilic cell infiltration and an increase in mucosal exudation in the alveolar lumen 24 to 48 h after challenge. This hypersensitivity reaction was not associated with an increase in hapten specific IgE. The role of the mast cell was established by studying responses in genetically mast cell-deficient and congenic normal mice. Mast cell-deficient strains failed to show any features of the hypersensitivity response. Mast cell reconstitution restored the acute bronchoconstriction, tracheal vascular hyperpermeability, BAL neutrophilia and tracheal hyperreactivity observed after DNFB sensitization and intranasal DNS challenge. These findings clearly demonstrate a key role for mast cells in the regulation of pulmonary hypersensitivity responses associated with non-atopic asthma. TNF-α is a multifunctional proinflammatory cytokine that is produced and released by mast cells. An important role for this mast cell mediator in pulmonary hypersensitivity reactions is demonstrated in chapters 5 and 6. Intra-airway application of TNF-α to non-treated mice resulted in the infiltration of a significant number of neutrophils (chapter 6). Furthermore, neutrophil infiltration and tracheal hyperreactivity induced by DNFB sensitization are both strongly reduced by neutralizing anti-TNF-α antibodies (chapter 5). Sensory nerves in the airways signal to the central nervous system. A subtype of these neurons express tachykinins such as substance P. The neurokinin-1 receptor is the preferred receptor for the ligand substance P. In the employed model for non-atopic asthma, blockade of the NK-1 receptor with a specific antagonist or the genetic absence of the NK-1 receptor prevented the development of tracheal hyperreactivity and cellular (neutrophil) accumulation in the mouse airways (chapter 2). Furthermore, it is shown that intra-airway application of substance P in non-treated mice results in the development of tracheal hyperreactivity (chapter 6). In vitro, substance P is able to activate mast cells. It is demonstrated that NK-1 receptors are significantly expressed on mast cells shortly co-cultured with IL-4 and/or SCF in contrast to non-treated mast cells that barely express NK-1 receptors (chapter 7). The increase in NK-1 receptor expression induced by IL-4 and SCF is time dependent. The number of positive cells increases with the length of co-culture although a plateau level is reached. To directly link substance P release to mast cell activation, the direct communication of BMMC and neurite-sprouting SCG was examined. It is shown that mast cell activation can occur as a direct response to the possible release of substance P from neurites (chapter 8).