T cell mediated induction of bronchial hyperreactivity

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Inadequate reactions of the immune system, i.e. allergic or hypersensitivity reactions, can lead to lung tissue injury. We investigated the relationship of type IV hypersensitivity, as an example of IgE independent hypersensitivity, with the induction of airway hyperreactivity. After antigen challenge (picrylsulphonic acid (PSA)) in picrylchloride (PCI) sensitized mice, peribronchial and perivascular accumulation of mononuclear cells was found that was maximal 48 h after challenge. At several time points after challenge, changes in smooth muscle tone of mouse isolated tracheas were measured isometrically. In sensitized mice the response to carbachol was increased, reaching a maximum 48 h after challenge. This hyperreactivity was not found in athymic (nude) mice. We concluded from these data that airway hyperreactivity can be immunologically induced other than by IgE.

Keywords T-cells type IV hypersensitivity (DTH) airway hyperreactivity

Introduction

Asthma can result from an extremely heterogeneous group of disorders. The common denominator of all asthmatics is an increased reactivity of the airway musculature to physical, chemical and pharmacological stimuli. The list of possible agents that induce airway hyperresponsiveness is very long. It includes for example mediators from nearby inflammatory cells. An array of inflammatory cells that produce the mediators was therefore suggested to contribute potentially to airway hyperresponsiveness (Alam *et al.*, 1987; Hargreave *et al.*, 1986; Pauwels *et al.*, 1986).

One important cell type that is involved in asthma is the mast cell. The mediators generated and released by activated mast cells comprise a heterogeneous group of molecules with very diverse and complex functions.

The most well studied example of mast cell release is induced by allergens of IgE sensitized mast cells participating in hypersensitivity reactions of the anaphylactic type. Activation of mast cells by nonimmunological stimuli can also result in release of mediators. Some of these

compounds may well act as so called pseudo-allergens. In addition, there is now substantial evidence that antigen-specific T-cell factors are capable of activating mast cells to release mediators, especially vasoactive amines, in the early and late phases of delayed-type hypersensitivity responses (Meade *et al.*, 1988; Van Loveren *et al.*, 1987). Thus, interaction of T-cells with mast cells via release of mast cell mediators may contribute to bronchoconstrictive responses as are seen in asthma patients.

Delayed-type hypersensitivity in the mouse lung

A role for T-cell dependent reactions in the lungs such as DTH (type IV hypersensitivity) has been studied sporadically. Although DTH skin reactions to pollen antigens are not a general feature of allergic asthma, in the circulation specifically sensitized cells, including T-cells, can be demonstrated either by *in vitro* lymphocyte mitogenesis to pollen allergens or the production of lymphokines such as macrophage

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Figure 1 Inflammatory response to picrylsulphonic acid in picrylchloride sensitized BALB/c mice. Specimen is taken 48 h after intranasal challenge. (HE $\times$ 200).

migration inhibition factor (MIF) (Kay *et al.*, 1987), which is a general *in vitro* parameter of DTH reactions (Geczy, 1984). In some reports T-cell dependent immune responses were suggested to be important in allergic inflammatory lung diseases such as some forms of asthma (Enander *et al.*, 1984; Kay, 1988; Kay *et al.*, 1987; Miyamoto *et al.*, 1971).

Enander *et al.* (1983, 1984) have developed a model to study DTH responses in mouse lungs. We have confirmed and extended these studies (Garssen *et al.*, 1989) and found a pulmonary reaction in PCI skin-sensitized mice that were challenged intranasally with the soluble form of PCI (i.e. PSA). The antigen-specific and T-cell dependent reaction was characterized by peribronchial and perivascular accumulation of lymphocytes and macrophages as well as by increased numbers of alveolar macrophages. The most pronounced inflammatory reaction was found 48 h after challenge (Figure 1).

The lung DTH responses to PSA in PCI sensitized mice were preceded by an increased vasopermeability. This was indicated by the increased content of serum albumin in the extravascular tissue, that originated from the circulation, and probably gained access to the extravascular spaces via gaps between endothelial cells. These gaps were likely induced by 5-hydroxytryptamine (5-HT), released by mast cells or other 5-HT-

containing cells. This event has been suggested to be necessary for the initiation of DTH-like reactions in mice (Van Loveren *et al.*, 1987). Local vascular permeability is thought to facilitate T-cell and eventual leucocyte entrance into the extravascular tissue, and may also activate DTH effector T-cells (Ameisen *et al.*, 1989).

Because there are many routes to interfere in the cascades of processes that lead to DTH responses to PCI in the mouse (Van Loveren *et al.*, 1987), this model is a powerful tool to study a possible relationship of aspects of cellular immunity with the induction of airway hyper-reactivity.

T-cell dependent induction of airway hyperreactivity

We have studied induction of airway hyper-reactivity to carbachol (a cholinergic muscarinic agonist) by lung-DTH, as a model for cellular immune responses.

We found increased tracheal reactivity to carbachol in sensitized mice that was maximal 48 h after challenge. The response was antigen-specific and T-cell dependent since in challenged athymic (nude) mice hyperreactivity to carbachol was not detected. Moreover, hyperreactivity could be observed after challenge of mice that

were passively sensitized by intravenous injection of lymphoid cells from sensitized donor mice. Sensitized lymphoid cells that were depleted of T lymphocytes failed to transfer increased reactivity.

The model that we present here, and that describes an enhanced airway reactivity to carbachol induced by T-cell dependent hyper-

sensitivity, may provide an additional tool for the research of the asthma syndrome, since the majority of all asthmatics show an increased airway reactivity.

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