The Role of Chemokines in the Pathogenesis of Atopic Eczema (Chemokines -Atopy)

Objectives

Atopic disorders are a group of increasingly common multifactorial chronic diseases, which cause inflammatory and degenerative changes in the skin and mucosal surfaces. Chemokines are small secreted proteins which critically regulate leukocyte trafficking. This research project will identify and characterize chemokines and their receptors mediating the initiation, maintenance and progression of atopic diseases. Specific aims of the study are to investigate:

I. Comprehensive overview of the expression of all known chemokines and chemokine receptors in human AD and a murine model of AD. a) Disease-associated chemokines and their receptors in skin will be characterized and their cellular origin determined. b) Chemokine receptor expression and chemotactic response of skin-homing T cells and dendritic cells of AD will be explored.

II. Role of chemokines and chemokine receptors in skin inflammation in a murine model of AD. Effects of a) chemokine/receptor neutralization and responses of b) chemokine receptor-deficient mice will be explored.

III. Regulation of chemokine/receptor expression by external and intrinsic factors in AD. a) Effects of typical trigger factors of AD on chemokine/receptor expression in normal human and murine skin will be investigated. b) Effect of in vitro stimulation of pathologically relevant cells by cytokines, pathogens, superantigens and specific IgE will be explored.

Scientific approach

The Chemokines-Atopy project is divided to six workpackages:

WP-1 (Human atopic dermatitis) will characterize the expression of chemokines and their receptors in human atopic dermatitis skin. Additionally, the effect of topically applied allergens and bacterial toxins on the expression will be studied.

WP-2 (Murine atopic dermatitis) will characterize the expression of chemokines and their receptors in murine model of atopic dermatitis. Additionally, the effect of topically applied bacterial toxins on the expression will be studied.

WP-3 (Skin-homing T-cells and DC) will characterize chemokine receptor expression on the surface of skin-homing T cells and dendritic cells. Also, chemotactic response of skin-homing T cells and dendritic cells to pathologically relevant chemokines will be investigated.

WP-4 (In vivo role of chemokines) will characterize in vivo role of chemokines and their receptors in a murine model of atopic dermatitis by (1) blocking chemokines or receptors with antibodies or small receptor antagonists or (2) by using chemokine receptor gene deficient mice.

WP-5 (Extrenal triggering factors) will characterize the effects of external triggering factors of atopic dermatitis to chemokine/receptor expression on human and murine normal skin. The effects of mechanical skin injury and topical bacterial toxin application will be studied.

WP-6 (Regulation of DC and cutaneous cells) will investigate the regulation of atopic dermatitis-associated chemokines in relevant cells, i.e. in vitro-derived dendritic cells, human primary keratinocytes, dermal fibroblasts and dermal microvascular endothelial cells.
Results

I. Comprehensive study of the expression of chemokines in human AD has been started. A computer patient database containing clinical data and information of chemokines and their receptors has been set up. Human skin samples have been collected with the clinical data. Laboratory techniques including immunohistochemistry have been established for analysis of chemokines. The animal model for AD has been refined and analysis of chemokine/receptor expression in the model started. Dendritic cell and T cell cultures have been started to analyse immune cell function in AD in relation to chemokines.

II. Role of chemokines and chemokine receptors in skin inflammation in a murine model of atopic eczema has been started. The effect of CCL27/CCR10 chemokine-receptor interaction in AD has been shown to be crucial in pathogenesis of skin inflammation of AD.

III. Regulation of chemokine/receptor expression by external and intrinsic factors in atopic eczema has been studied by murine models and in vitro cell cultures. Tape-stripping of murine skin causes concerted regulation of chemokine/receptor expression. Both dendritic cells and human skin epidermal keratinocytes have chemokine-related regulated responses to microbial antigen stimulation in vitro.