

Transforming Growth Factor-beta Signalling Through Smad3 in Allergy: Studies on the Mechanisms of Asthma, Atopic Dermatitis and Allergic Contact Reactions

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Minna Anthoni, MSc, from the Department of Dermatology, Allergology and Venereology, University of Helsinki and the Finnish Institute of Occupational Health, Helsinki, Finland, defended her PhD thesis on 12 December 2008 in Helsinki. The opponent was Professor Ilkka Harvima from the University of Kuopio, Finland, and the custos was Professor Annamari Ranki. The thesis was supervised by docent Harri Alenius and docent Antti Lauerma from the Finnish Institute of Occupational Health. The thesis book is available at: <http://urn.fi/URN:ISBN:978-952-10-5102-9>.

Allergic diseases, such as atopic dermatitis, asthma, and contact dermatitis, are complex diseases influenced by both genetic and environmental factors. It is unclear why allergy and subsequent allergic disease occur in some individuals but not in others.

Transforming growth factor (TGF)- β is an important immunomodulatory and fibrogenic factor that regulates cellular processes in injured and inflamed skin. TGF- β has a significant role in the regulation of the allergen-induced immune response participating in the development of allergic and asthmatic inflammation. TGF- β is known to be an immunomodulatory factor in the progression of delayed-type hypersensitivity reactions and allergic contact dermatitis. TGF- β is crucial in regulating the cellular responses involved in allergy, such as differentiation, proliferation and migration.

TGF- β signals are delivered from the cytoplasm to the nucleus by TGF- β signal transducers called Smads. Smad3 is a major signal transducer in TGF- β -signalling that controls the expression of target genes in the nucleus in a cell-type specific manner. The role of TGF- β -Smad3-signalling in the immunoregulation and pathophysiology of allergic disorders is still poorly understood. In this thesis, the role of TGF- β -Smad -signalling pathway using Smad3-deficient knock-out mice in the murine models of allergic diseases, atopic dermatitis, asthma and allergic contact reactions, was examined.

The Smad3-pathway regulates allergen-induced skin inflammation and systemic IgE antibody production in a murine model atopic dermatitis. The defect in Smad3-signalling decreased Th2 cytokine (IL-13 and IL-5) mRNA expression in the lung, modulated allergen-induced specific IgG1 response, and affected mucus production in the lung in a murine model of asthma. TGF- β / Smad3-signalling contributed to inflammatory hyper-



Fig. 1. Minna Anthoni (left) defended her PhD thesis in Helsinki in December 2008. The opponent was Professor Ilkka Harvima (right) from Kuopio and the custos was Professor Annamari Ranki.

sensitivity reactions and disease progression via modulation of chemokine and cytokine expression and inflammatory cell recruitment, cell proliferation and regulation of the specific antibody response in a murine model of contact hypersensitivity.

TGF- β modulates inflammatory responses, at least partly through the Smad3 pathway, but also through other compensatory, non-Smad-dependent pathways. Understanding the effects of the TGF- β signalling pathway in the immune system and in disease models may help in elucidating the multilevel effects of TGF- β . Unravelling the mechanisms of Smad3 may open new possibilities for treating and preventing allergic responses, which can lead to severe illness and loss of work ability. In the future the Smad3 signalling pathway might be a potential target in the therapy of allergic diseases.