

List of original publications

1. Enerbäck C, Martinsson T, Inerot A, Wahlström J, Enlund F, Yhr M, Swanbeck G. Evidence that HLA-Cw6 determines early onset of psoriasis obtained using sequence-specific-primers (PCR-SSP). *Acta Derm Venereol* 1997; 77: 273-276.
2. Enerbäck C, Martinsson T, Inerot A, Wahlström J, Enlund F, Yhr M, Samuelsson L, Swanbeck G. Significantly earlier age at onset for the HLA-Cw6 positive than for the Cw6 negative psoriatic sibling. *J Invest Dermatol* 1997; 22: 695-696.
3. Enlund F, Samuelsson L, Enerbäck C, Inerot A, Wahlström J, Yhr M, Torinsson Å, Martinsson T, Swanbeck G. Analysis of three suggested psoriasis susceptibility loci in a large Swedish set of families; confirmation of linkage to chromosome 6p (HLA-region), and to 17q, but not to 4q. *Human Heredity* 1999; 49: 2-8.
4. Enerbäck C, Enlund F, Inerot A, Samuelsson L, Wahlström J, Swanbeck G, Martinsson T. S gene (corneodesmosin) diversity and its relationship to psoriasis; high content of cSNPs in the HLA-linked S gene. *J Invest Dermatol* 2000; 114: 1158-1163.
5. Enerbäck C, Nilsson S, Enlund F, Inerot A, Samuelsson L, Wahlström J, Swanbeck G, Martinsson T. Stronger association with HLA-Cw6 than with corneodesmosin (S-gene) polymorphisms in Swedish psoriasis patients. *Arch Dermatol Res* 2000; 292: 525-530.
6. Enerbäck C, Holmqvist D, Inerot A, Enlund F, Samuelsson L, Torinsson Å, Wahlström J, Swanbeck G, Martinsson T. Cytogenetic analysis of 477 psoriatics revealed an increased frequency of aberrations involving chromosome region 11q. *Eur J Hum Genet* 1999; 7: 339-344.

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Pityrosporum ovale (*Malassezia furfur*) and Atopic Dermatitis Annales Universitatis Turkuensis, Painosalama Oy, Turku, Finland 2000

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ABSTRACT

Allergy to a saprophytic yeast of the human skin, *Pityrosporum ovale* (*P. ovale*), an oval form of *Malassezia furfur*, has been suspected to play a role in atopic dermatitis (AD), especially in patients with head, neck and shoulder dermatitis. The aim of this study was to investigate the importance of *P. ovale* as a source of allergens in adult patients with AD.



Dr Päivi Lintu (*centre*) defended her thesis at the Department of Dermatology, University of Turku. Faculty opponent was Associate Professor Kristiina Turjanmaa from Tampere (*left*) and Chairman was Professor Christer Jansén from the Department of Dermatology, University of Turku (*right*). Associate Professor Kirsti Kalimo (Department of Dermatology, University of Turku) and Associate Professor Johannes Savolainen (Department of Pulmonary Diseases and Clinical Allergology, University of Turku) supervised the Thesis.

To establish standardized extracts for diagnostic work we characterized the allergen extract of *P. ovale*. In immunoblotting we found a total of 39 IgE-binding protein bands. Two of the protein bands were regarded as major allergens: 9 kDa (73% of patients reacting) and 96 kDa (65% of patients reacting) bands. The RAST index levels measured against *P. ovale* mannan, a polysaccharide, and analysed by nitrocellulose RAST, were elevated in 77% of the patients with AD. According to these results, the *P. ovale* allergen extracts used to establish the IgE response in patients with AD should contain at least the major allergens, including mannan. The stability of allergens in *P. ovale* extracts during storage is also important from the clinical point of view and it was analysed with immunoblotting and densitometry. It appeared that the proteins of *P. ovale* were poorly preserved at +20°C even when stored in 50% glycerol. The extract stored at +4°C was better preserved, but completely only for one month. In general the 9 kDa band was the most stable protein allergen. The reliability of negative skin prick test results should be questioned with currently used commercial *P. ovale* extracts.

Hypersensitivity to yeasts appears to cluster. Therefore cross-reactivity between yeasts (*P. ovale*, *Candida albicans*, *Saccharomyces cerevisiae*, *Rhodotorula rubra* and *Cryptococcus albidus*) was examined with RAST and ELISA inhibition assays. The cross-

reactivity between yeast mannans was observed, but the cross-reactivity was also seen between *P. ovale* mannan and *C. albicans*, *S. cerevisiae* and *C. albidus* crude extracts, but to a lower degree. This cross-reactivity of yeasts may be misleading in clinical practice, if a patient have simultaneous positive yeast RASTs.

Both Th1 and Th2 type cytokines appear to be involved in the pathogenesis of AD. Therefore the *P. ovale* and *C. albicans* specific lymphoproliferative and cytokine (IL-2, 4, 5 and IFN- γ -ELISA) responses were evaluated in patients with AD. *C. albicans* induced IFN- γ production and IL-5 production. IL-4/IFN- γ ratio induced by *P. ovale* was higher than that induced by *C. albicans*. *P. ovale* was associated with IgE production. *C. albicans* was also associated to IgE production, but also strongly to IgG production. Our findings suggest that *P. ovale* induces predominantly a Th2-like immune response and *C. albicans* a Th1-like response.

To establish the role of yeasts in the pathogenesis of AD, the effect of yeast eradication by antifungal medication was studied. In a double-blind placebo controlled study with systemic ketoconazole, a significant improvement was seen on clinical SCORAD scale with patients in the ketoconazole group only. Also the number of positive *P. ovale* cultures from skin decreased only during ketoconazole treatment.

As a whole, the results of this study suggest that *P. ovale* is an important source of allergens and can trigger cutaneous inflammation in patients with head, neck and shoulder-type dermatitis. Systemic antifungal medication is useful for patients with elevated IgE antibodies to *P. ovale* and positive yeast culture results.

Key words: *allergy, atopic dermatitis, Malassezia furfur, Pityrosporum ovale, yeast, ketoconazole.*

List of original articles

- I Lintu P, Savolainen J, Kalimo K. IgE antibodies to protein and mannan antigens of *Pityrosporum ovale* in atopic dermatitis. Clin Exp Allergy 1997; 27: 87-95.
- II Lintu P, Savolainen J, Kalimo K, Terho EO. Stability of *Pityrosporum ovale* allergens during storage. Clin Exp Allergy 1998; 28: 486-490.
- III Lintu P, Savolainen J, Kalimo K, Kortekangas-Savolainen O, Nermes M, Terho EO. Cross-reacting IgE and IgG antibodies to *Pityrosporum ovale* mannan and other yeasts in atopic dermatitis. Allergy 1999; 54: 1067-1073.
- IV Savolainen J, Lintu P, Kosonen J, Kortekangas-Savolainen O, Viander M, Pene J, Kalimo K, Terho EO, Bousquet J. *Pityrosporum* and *Candida* specific and non-specific humoral, cellular and cytokine responses in atopic dermatitis. Clin Exp Allergy (in press)
- V Lintu P, Savolainen J, Kortekangas-Savolainen O, Kalimo K. Systemic ketoconazole is effective treatment of atopic dermatitis with IgE-mediated hypersensitivity to yeasts. Submitted.