

Dermato-Venereological Research at Aarhus University Hospital

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The Department of Dermatology and Venereology at Aarhus University Hospital has a long-lasting research tradition. Research has focused mainly on translational research in inflammatory dermatoses, such as psoriasis and atopic dermatitis, where molecular biology based work has been integrated with clinical projects. The research facilities are located within the department, which allows close collaboration between cell-based work and the clinic. Within the last decade several new clinical and epidemiological projects have been initiated.

Studies of the pathogenesis of psoriasis

For the last three decades the pathogenesis of psoriasis has been one of the main research areas in the department. Currently, 3 post-doctoral researchers, 6 PhD students and 2 medical students are working on projects related to psoriasis. These projects are all distributed around signal transduction in keratinocytes and lymphocytes and regulation of inflammatory gene expression. More specifically, we are looking at gene regulation at both the transcriptional, translational and post-translational levels. At the transcriptional level projects are exploring the role of Janus Kinase/Signal Transducer and Activator of Transcription (JAK/STAT) and mitogen-activated protein kinase (MAPK) signalling in the pathogenesis of psoriasis, but also as possible treatment targets. At the translational level we are conducting studies of microRNA expression in psoriatic skin and their role in regulation of gene expression. Furthermore, we are also aiming to identify specific microRNAs that can serve as predictors of a treatment response. At the post-translational level a project is studying the role of inflammatory caspases in the pathogenesis of psoriasis, which may involve the activation of pro-IL-1 beta.

These molecular biology-based projects are conducted in cell culture, animal models and tissue samples from patients and involve a wide variety of sophisticated methods.

Atopic dermatitis – from T cells to barrier function – and back

Atopic dermatitis has also been one of the core research subjects in the department over the last 30 years. Primarily, immunology and T-cell function has been the focus of the research and has led to important discoveries, such as the T-cell-attracting capacity of interleukin (IL)-8 (CXCL2). Research into T cells naturally led to questions regarding cytokines, chemokines and chemokine receptors in atopic dermatitis. This work has been carried out in close collaboration with research partners in the USA, Japan and the UK. It spurred an interest in our laboratory in chemokines and led to investigations regarding thymus and activation-regulated chemokine (TARC), cutaneous T-cell-attracting chemokine (CTACK), macrophage-derived chemokine (MDC) and their receptors, using many exciting biochemical methods, such as anti-sense nucleotides and complex flow-cytometry. Animal models were also used for the study of the pruritogenic role of IL-31.

During the last 5 years, one of the most discussed pathophysiological factors in the development of atopic dermatitis has been the skin barrier and the role of filaggrin. We have investigated the

regulation of the expression of filaggrin and upstream regulators of the profilaggrin to filaggrin maturation process, and how these were influenced by inflammatory cytokines, such as IL-4, and IL-13, and typical Th2 cytokines. At the same time we were working with a member of the IL-17 family, IL-25 (IL-17E), a known inducer of the Th2 response. Combining our findings we have found that inflammation of the Th2 type can be induced and perpetuated by IL-25, and that IL-25, in itself, can induce reduced filaggrin expression. Therefore we conclude that atopic dermatitis is both an immunological disorder and caused by barrier dysfunction, and that both inflammation and genetics can influence the barrier. Investigations are ongoing.

Epidemiological research

Epidemiological research is also conducted mainly in collaboration with the Department of Clinical Epidemiology at Aarhus University. The main focus of these epidemiological studies is quality assurance of a given treatment, mainly through the development of clinical registries and databases that include all attending physicians. The main project has been the establishment of such a database to evaluate treatment outcome in non-melanoma skin cancer. In addition, epidemiological studies are conducted in systemic sclerosis, sclerosis-like diseases and primary cutaneous T-cell lymphomas.

Clinical research

The department participates in several clinical phase II, III and IV trials testing new drugs for the treatment of a wide variety of dermato-venereological diseases. In addition, several other innovative and investigator-initiated clinical studies are also being conducted.

Treatment of acne scars with fractionated CO₂ laser

Fractionated carbon dioxide (CO₂) laser is a relatively new, well-documented treatment for reducing acne scars, but the optimal treatment regime has not yet been established. Therefore a new intra-individual randomized clinically controlled study has been started to compare clinical effects and side-effects in patients undergoing symmetrical treatment of acne scars on the face, with 1-month versus 3-month intervals.

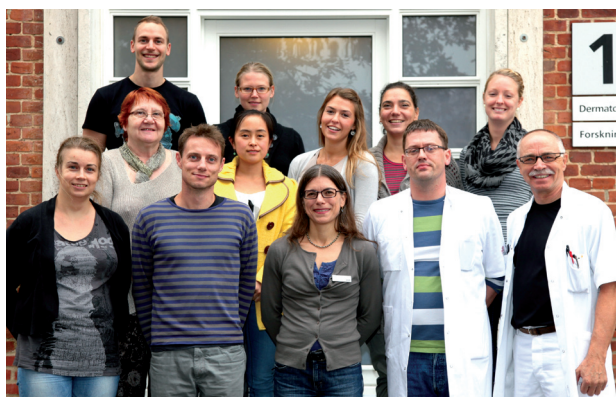
Using infrared laser light, the surface of the skin is removed and the subcutis underneath is heated. An induction of wound healing is induced in microscopic vertical zones of the skin. Further treatments are normally needed. To date it has not been examined whether the intervals between treatments are of importance for the treatment result.



Lars Iversen, Professor in Dermatology and Venereology.



Associate Professor Mette Deleuran, Head of the Department of Dermatology.



Members of the research group. *From left, front row:* Ane LN Nielsen, Claus Johansen, Mette Deleuran, Christian Vestergaard, Karsten Fogh. *Middle row:* Borbala Gesser, Zhanyan Kang. *Back row:* Sami Hedegaard Khatib, Stine ML Andersen, Maike Mose, Cecilia Rosada Kjeldsen, Helle Christiansen.

Antioxidants in the treatment of pseudoxanthoma elasticum

PXE is a rare autosomal recessive inherited disease with symptoms from skin, eyes and cardiovascular system. PXE is caused by mutations in the *ABCC6* gene on chromosome 16.p13.1, which codes for a multidrug resistance associated protein (MRP) 6. The function of the transmembrane transporter MRP 6 is unknown. It is assumed that PXE is a metabolic disease and the pathogenesis involves accumulation of calcified and fragmented elastic fibres in the skin, Bruch's membrane of the eye, and medium-sized arteries. Reactive oxygen radicals are thought to be involved in the pathogenesis, and we therefore investigate the effect of high doses of antioxidant vitamin C and E on patients with PXE. In collaboration with ophthalmologists we have examined 25 patients with angioid streaks and patients with known PXE and identified a cohort of 16 patients with PXE willing to participate in the study. The patients are characterized with histology, ophthalmic, cardiovascular and skin examination and treated with antioxidant vitamin C and vitamin E for 2 years. The effect of the antioxidants on skin calcification and fragmentation of elastic fibres, clinical effect on skin and vision are investigated.

Allergic contact dermatitis in Danish children

A PhD project entitled "Allergic contact dermatitis in children" aims to provide detailed knowledge of allergic contact dermatitis

in children in Denmark. Recent studies from all parts of the world have shown that allergic contact dermatitis is also a frequent diagnosis in the paediatric population, and the prevalence of allergic contact dermatitis in children seems to be increasing. The development of contact allergies in childhood has serious consequences for life quality and for future occupation, as acquired allergies are lifelong. The study involves analysis of data from The Danish National Contact Allergy Database, to describe demographics, risk factors, and effect of allergic contact dermatitis on the children's quality of life. Furthermore, the association between filaggrin gene mutations and allergic contact dermatitis in children will be investigated. The project consists of two descriptive studies based on data from The Danish National Contact Allergy Database, a retrospective questionnaire study, and an investigation of the association between filaggrin mutations and allergic contact dermatitis. The study is performed in collaboration between the Department of Dermato-Venerology of Aarhus University Hospital and Odense University Hospital, National Allergy Research Center in Gentofte, and the Danish Contact Dermatitis Group.

Wound healing

The leg ulcer clinic at the Department of Dermatology treats leg ulcers of different aetiology and carries out research to improve treatment modalities. The leg ulcer clinic is involved in clinical trials testing wound healing properties of new wound dressings. In addition, focus is on compression therapy in patients with mixed venous and arterial insufficiency and new technologies with respect to negative pressure wound therapy (NPWT) and intermittent pneumatic compression (IPC).

Comorbidities in psoriasis

A recently established PhD project is conducting a prospective clinical study aiming to improve understanding of the cardiovascular risk associated with psoriasis by comprehensively assessing the risk profile in patients with moderate to severe psoriasis by the use of cardiac CT scanning and biomarkers. The objective of the study is to determine the incidence and severity of coronary atherosclerosis, to determine if severe psoriasis is an independent risk factor for developing coronary atherosclerosis, and to compare coronary atherosclerosis in severe psoriasis with severe atopic dermatitis. In addition, the study will deliver a direct measure of the coronary atherosclerosis before and after a period of effectively treating the skin disease.

The Department of Dermatology, Aarhus University Hospital.



Facts

Aarhus University was founded in 1928. The Department of Dermatology and Venereology appointed its first Professor in 1940, Esbern Lomholt. The Faculty today encompasses 2,000 medical students, 90 professors and 430 teachers and senior researchers, and 400 PhD students.

The group of researchers at the Unit of Dermatology and Venereology at Aarhus University hospital consists of:

- 1 professor
- 6 associate professors
- 3 post-doctoral researchers
- 7 PhD students
- 4 medical students
- 2 technicians are working full-time in the research laboratory

During the past 10 years the group has produced 260 original articles and 10 theses.