

Dermato-Venereological Research at Uppsala University

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Research within our speciality in Uppsala has a history of nearly 60 years and is nowadays concentrated in the university departments of Medical Sciences (to which Dermatology and Venereology belong) and Immunology, Genetics and Pathology. Research in sexually transmitted diseases (STD) will be discussed by Professor Maurius Domeika, WHO collaborating centre, in a forthcoming article in *Forum*. HPV-associated cervical cancer in relation to STD is studied by Anders Strand.

Our dermatological research is focused on inherited skin disorders: genodermatoses, atopic eczema and psoriasis. The aim is to clarify further the pathophysiology of these diseases and to learn more about the molecular function of the human skin barrier, striving to find novel therapies for this group of diseases.

Epidermolysis bullosa and congenital ichthyosis

In collaboration with clinical geneticists, pathologists and a EU network (GeneSkin), we are studying genetic mutations and pathogenetic mechanisms underlying inherited skin barrier defects, such as congenital ichthyosis and epidermolysis bullosa. The Uppsala Genodermatosis Center represents a national referral centre for patients with monogenetic skin diseases. Typically, ichthyosis exhibits generalized hyperkeratosis, whereas epidermolysis bullosa shows skin fragility, but both diseases may be caused by similar keratin mutations disrupting the cytoskeleton (i.e. keratinopathies), says Marie Virtanen. Efficient therapies for these disorders are lacking. Hans Törmä and coworkers have generated immortalized cell lines from patients with keratinopathies to study how cytoskeletal disruption induced by heat stress can be prevented by pre-treatment with various drug candidates (chemical chaperones) with the ability to stabilize the keratin filaments. Promising drugs will soon be tested *in vivo* in collaboration with Prof I. McLean of Dundee University.

Adjuvant therapies for genodermatoses

Patients with keratinopathies and plantar hyperhidrosis often have painful blisters, which we have

found benefit greatly from injections of botulinum toxin (BTX). This goes also for patients with intertriginous Darier and Hailey-Hailey diseases (Swarthling, Vahlquist). The mechanisms of action and new delivery systems for BTX are being studied. We also study the regulation of keratin genes by retinoids and siRNAs, aiming at improving this form of therapy in keratinopathies.

Gene hunting and tailored therapy

Other keratinization disorders, including many types of ichthyosis, are caused by protein or enzyme deficiencies, which negatively affect the horny layer. Finding the causative genes will concurrently reveal essential pathways for barrier homeostasis and give new ideas about therapy. In a collaboration with Swedish and French geneticists we have recently found novel aetiologies for collodion ichthyosis, keratosis linearis with ichthyosis congenita and sclerosing keratoderma (KLICK) and ichthyosis prematurity syndrome, which involve errors in lipid metabolism and protein degradation. Many of these diseases already benefit from treatment with retinoids, but knowing the pathogenesis, and by tailoring retinoid therapy, improved results are anticipated.

Skin barrier failure in ichthyosis and atopic eczema

A link exists between ichthyosis vulgaris and atopic eczema in the form of filaggrin mutations; as a result, both conditions are characterized by skin dryness and an impaired barrier function. The type of emulsifying cream applied to the skin will determine whether the skin barrier improves or deteriorates during therapy. By comparing the effects of different creams on transepidermal water-loss (TEWL) and expression of various "repair genes", we hope to determine in clinical trials on patients with eczema or ichthyosis which cream composition is best suited for supporting barrier homeostasis, says Berit Berne, working in close collaboration with other members of the group and the Karolinska Institute.

Inflammation in psoriasisiform dermatoses

Psoriasis vulgaris, psoriatic arthritis and palmoplantar pustulosis (PPP) represent a broad spectrum



Prof Anders Vahlquist, Head of the Unit of Dermatology and Venereology.



Berit Berne, Adjunct Professor of Dermatology and Venereology.



Ola Rollman, Associate Professor of Dermatology and Venereology.



Hans Törmä, Associate Professor of Dermatology.



Eva Hagforsen and Inger Pihl discussing some lab results with Hans Törmä.

of diseases, which may have an autoimmune aetiology, but no specific auto-antigens have yet been identified, says Mohammad Alimohamadi. PPP is associated with several autoimmune disorders. It affects mainly women who smoke. The inflammation is directed against the palmo-plantar sweat duct. Details of the underlying inflammation and the negative influence of tobacco smoking are being studied; attempts to identify autoantigens are also ongoing. In all types of psoriasis we have found increased numbers of inflammatory cells in the gut mucosa; findings

that have generated new ideas concerning the pathogenesis of psoriasis, says Eva Hagforsen.

Finding new treatments for hyperproliferative disease

In order to study epidermal formation *in vitro*, a skin explant culture technique has been developed. We utilize fluoroprobe-based imaging to visualize outgrowth of fresh epithelium on a substrate of cell-free dermis. Growth rates and morphological features of newly formed epidermis are studied. Current research is focused on human epidermal growth factor receptor (HER)-mediated signalling and the effects of inhibitors targeting members of the epidermal growth factor (EGF) receptor superfamily. Our aim is to identify new means by which growth abnormalities in psoriatic skin and other hyperproliferative disorders can be reversed, says Ola Rollman.

Concluding remarks

Research in dermatology and venereology has a long tradition in Uppsala with nearly 40 theses produced over the years. We try to combine investigative and clinical research. Ever since the late 50s we run a research laboratory of our own with several full time employed researcher and staff. Many of the clinicians and PhD students go between the clinic and the laboratory, which benefits our goal of always trying to improve diagnostics and therapy for patients with severe skin diseases.

Uppsala University Hospital

White arrow indicates the location of the Department of Dermato-Venereology.



Facts

The University of Uppsala was founded in 1477 and medical education began here in the 17th century. The Department of Dermatology and Venereology within the Faculty of Medicine appointed its first Professor in 1955. The Faculty today encompasses 10,000 students, 180 professors and 480 university teachers and researchers, and 300 other staff.

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

- 2 Professors
- 3 Associate Professors
- 7 PhD researchers
- 4 doctoral students

The group publishes approximately 15–20 original articles per year. Five theses have been published by the group during the past 2 years.