

Dermato-Venereological Research at Oulu University

AARNE OIKARINEN AND KAISA TASANEN

Department of Dermatology and Venereology, Oulu University Hospital, Oulu, Finland.

E-mail: aarne.oikarinen@oulu.fi

Research in dermatology has continued in our department for 47 years. Our department has so far contributed to 30 doctoral dissertations. The first professor of Dermatology and Venereology at the University of Oulu was Katri Rehtijärvi, who was appointed in 1964. Professor Rehtijärvi was interested in hereditary skin diseases and under her guidance Kirsti Kuokkanen finished her thesis on ichthyosis in Northern Finland. Professor Matti Hannuksela acted as a professor between 1975 and 1992 and during this period research on allergy flourished. Matti Hannuksela and Professor Jaakko Karvonen were pioneers in the use of bath PUVA to treat psoriasis and other skin diseases. Professor Karvonen was also involved in many studies into the genetics and aetiology of psoriasis. The close association between alcohol and psoriasis was revealed in one of these studies.

Since 1998, our department has had its own research laboratory, which is currently located in the Clinical Research Center of Oulu University Hospital. The center is located in the same building as Biocenter Oulu, which offers a great opportunity for close collaboration with other research groups and excellent core facilities/tools for modern life science research, such as transgenic animals, tissue imaging and gene analysis services.

Our dermatological research focuses on a number of areas, which are discussed in detail below.

Connective tissue and wound healing

Collagen is the most abundant protein in the skin, accounting for about 70% of the skin's dry weight. Types I and III are the most abundant skin collagens, with other types being more minor components. The biosynthesis of collagen is complex and is vulnerable to disturbances in various genetic diseases, such as Ehlers-Danlos syndrome, and acquired diseases, such as scleroderma and keloid scarring.

Many external and internal factors affect the synthesis and degradation of collagen. Ultraviolet radiation increases the degradation of collagen and topical and systemic glucocorticoids reduce its synthesis. Collagen synthesis and degradation are also altered during ageing.

We have developed numerous methods to investigate the rate of synthesis and degradation of collagens I and III in human skin in close collaboration with Professor Juha Risteli from the Department of Clinical Chemistry. Collagen synthesis and degradation have been measured in human skin using the suction blister method, originally developed by the late Dr Urpo Kiistala.

By this method, tiny amounts of blister fluid can be used to analyse collagen propeptides and collagenases.

During recent years we have studied the effects of systemic and topical glucocorticoids, thyroid hormones, smoking and radiotherapy on skin connective tissue. Altogether, seven completed doctoral theses have so far covered this subject in our department.

We are also using the suction blister model to investigate the molecular mechanisms of healing of wounds in diabetes, and in patients with severe sepsis. Recently, in the dissertation by Fiia Gäddnäs, marked changes in collagen metabolism and wound healing were found in patients with sepsis.

Glucocorticoid receptors and glucocorticoid insensitivity in inflammatory dermatoses

Glucocorticoids are widely used, both topically and systemically, to treat inflammatory dermatoses. The response to glucocorticoid treatment is usually good and reasonably quick. However, the value of glucocorticoid treatment is limited by the side effects of long-term usage. In addition, some patients do not respond to glucocorticoid treatment and are therefore considered to be glucocorticoid resistant.

At the cellular level, the actions of glucocorticoids are mediated by the intracellular glucocorticoid receptor (GR). The alpha GR isoform mediates the effect of glucocorticoids and is expressed in most human tissues and cell lines. Alternative splicing of the GR mRNA generates GR- α , but also GR- β , which does not bind glucocorticoids, but instead antagonises the activity of GR- α in a concentration-dependent way. Thus, increased expression of GR- β could account for glucocorticoid insensitivity. GR expression has not been studied in detail in inflammatory dermatoses other than atopic dermatitis. For this reason, Päivi Hägg and Minna Kubin are currently investigating the expression of GR- β at both the protein and mRNA levels in various inflammatory dermatoses and in cultured keratinocytes and fibroblasts. Notably, they will study the regulation of GR- β and GR- α in patients before and during topical and systemic glucocorticoid treatment.



Prof Aarne Oikarinen, Head of the Department of Dermatology and Venereology.



Investigators at our department. First row (left to right): Kaisa Tasanen, Anja Mattila and Jyri Moilanen; second row: Tiina Hurskainen, Päivi Hägg, Minna Kubin and Anna-Kaisa Heikkinen.

Hemidesmosomal proteins in epidermolysis bullosa and epithelial cancers

Basement membranes are not only important structural barriers, but additionally possess many functional properties and contribute to cell adhesion, migration, molecular ultrafiltration and signalling in various physiological and pathological conditions in many tissues. Hemidesmosomes are multiprotein complexes that connect the cytoskeleton of epithelial cells to the basement membrane. The molecular components of hemidesmosomes include collagen XVII, BP230 and plectin. Lack of or disturbed function of hemidesmosomal components leads to the detachment of epithelial cells from the underlying connective tissue.

Defects in the genes coding for laminin-332, the $\alpha 6 \beta 4$ integrin and collagen XVII lead to epidermal adhesion and skin blistering in human junctional epidermolysis bullosa (JEB). To better understand the pathogenesis of JEB, we are currently investigating the biological consequences of various collagen XVII and laminin-332 mutations in human skin samples, cultured keratinocytes and mouse models.

While laminin-332 and the $\alpha 6 \beta 4$ integrin are known to be involved in cell growth and invasion in squamocellular carcinoma (SCC) and colorectal carcinoma (CRC), the function of collagen XVII in these cancers is largely unknown. In a current project, we are analysing the function of collagen XVII and other hemidesmosomal components in the pathogenesis of epithelial cancers using siRNA techniques, in SCC and CRC cell migration assays, and through tumorigenicity studies in a mouse model.

Our research group (Kaisa Tasanen, Tiina Hurskainen and Jyri Moilanen) has a long-term collaboration with the research group of Professor Leena Bruckner-Tuderman (Department of Dermatology, University of Freiburg, Germany). In addition, we collaborate locally with experts in various fields, such as pathology, transgenic animals, cell migration assays and siRNA techniques.

Epidemiological studies

As a novel research branch, we have two ongoing projects in the field of epidemiology. In collaboration with the National Institute of Health and Welfare, Erika Wikström is investigating the incidence of chlamydial genital infection in the Finnish Maternity Cohort and the National Infectious Diseases Register. Anna-Kaisa Heikkinen is interested in the incidence of pemphigoid and pemphigus in Finland.

Oulu University Central Hospital with an arrow of Department of Dermatology.



Facts

The first professor of Dermatology and Venereology at the University of Oulu was Katri Rehtijärvi, who was appointed in 1964.

Oulu University was founded in 1958. The University has 2,868 employees and a total of 15,880 students. There are six faculties in Oulu.

The first professor in Dermatology and Venereology was appointed in 1964.

Currently the group of researchers at the Department of Dermatology and Venereology in Oulu consists of:

- 1 Professor and 1 Clinical instructor
- 2 Senior researchers
- 5 Registered PhD students

The Department has published some 50 original publications during the last five years and four doctoral thesis have been finalized during the same period.