Keloids: a Fibroproliferative Disease

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Oliver Seifert, from the Department of Dermatology, County Hospital Ryhov, Jönköping, Sweden, defended his doctoral thesis on 11 January 2008 at the University of Linköping, Sweden. The thesis publication is available at Linköping University Electronic Press: http://liu.diva-portal.org/smash/record.jsf?searchId=1&pid=diva2:17111.

Wound healing is a fundamental, complex tissue reaction leading to skin reconstitution and thereby ensuring survival. While foetal wounds heal without scarring, a normal "fine line" scar is the clinical outcome of undisturbed wound healing in adults. Alterations in the orchestrated wound healing process result in hypertrophic or keloid scarring. Keloids develop in the skin after injury or spontaneously. They are defined as scars growing continuously and invasively beyond the confines of the original wound, in contrast to hypertrophic scars, which stay within the boundaries of the original wound and after a period of continuous growth slowly regress. The active keloid edge is often erythematous and pruritic. Keloids cause significant cosmetic defects and deformities and may limit joint mobility.

Research in the past decades has attempted to identify genetic, cellular and molecular factors responsible for these alterations. Despite increasing knowledge about the molecular regulation of scar formation, no unifying theory explaining keloid development has been put forward until now. The aim of this thesis was to gain a deeper insight into the role of transforming growth factor-beta (TGF-β) and its signalling pathway proteins, SMADs, in the pathogenesis of keloids, and to describe the gene expression profile in different keloid sites in the search for potential target genes for future treatment. A further aim was to develop an instrument to describe the quality of life of patients with keloids.

We found that cultured keloid fibroblasts express an increased level of TGF-β1 mRNA and a decreased level of TGF-β3 mRNA compared with control skin. Keloid-derived fibroblasts exhibit significantly decreased mRNA levels of TGF-β receptor type II (TβRII), and the ratio of TβRI and TβRII mRNA expression is increased. This suggests that a certain expression pattern of TGF-β subtypes and receptors may be important in keloid pathogenesis.

Analysis of keloid-derived fibroblasts revealed decreased SMAD3 mRNA expression and a decreased ratio of SMAD2/SMAD3 mRNA, implicating disturbed SMAD signalling. Keloid fibroblasts upregulate SMAD4 protein after stimulation with TGF-β1 and display diminished levels of the inhibitory proteins SMAD6 and 7. This may contribute to unlimited and deregulated TGF-β signalling, leading to increased production of extracellular matrix (ECM).

The gene expression pattern is described in fibroblasts from different keloid sites using microarrays covering the whole human genome. This study reveals 105 regulated genes (79 genes were upregulated and 26 downregulated) resulting in a unique gene expression profile in different sites of keloids, where progression or regression of the keloid process occurred. In cells from the central part of keloids with clinical signs of regression, an upregulation of apoptosis-inducing genes, such as ADAM12, and ECM-degrading genes, such as MMP19, was found. These genes may contribute to regression of keloids and might be possible future target genes for treatment. Over-expression of apoptosis inhibitors, such as AVEN, and downregulation of angiogenesis inhibiting genes, such as PTX3, found at the active margin of keloids, may be responsible for the invasive character of the keloid margin.

We developed a disease-specific questionnaire to measure the quality of life of patients with keloids. We found two scales, psychological and physical impairment, that described the dimensions of quality of life in patients with scars. These two scales have a high test-retest reliability and are independent of each other. Single items that clinically characterize the disease show correlations with these scales. The results of this study demonstrate for the first time a severe impairment of quality of life of patients with keloids and hypertrophic scars.

In conclusion, the described alteration in TGF-β expression and its receptors, the disrupted SMAD signalling pathway and the unique gene expression patterns in different keloid sites provide new information about ECM formation and degradation in keloids. Regulatory genes in ECM homeostasis may be future target genes for keloid prevention, regression and treatment. The disease-specific quality of life instrument for patients with keloids and scars will be a useful tool for estimating success in future therapeutic efforts over time.

Cutaneous Porphyrias: Clinical and Histopathological Study

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Kaisa Timonen, from the Department of Dermatology and Allergology, University of Helsinki, Helsinki, Finland, defended her PhD thesis on 3 April 2009 in Helsinki. The opponent was Docent Leena Koulu from the Department of Dermatology, Turku University Central Hospital, and the thesis was supervised by Docent Raili Kauppinen, from Porphyria Research Centre, Department of Medicine, Division of Endocrinology and Docent Kirsti-Maria Niemi, Department of Medicine, Division of Dermatology and Venereology, University of Helsinki, Finland. The thesis book is available at: http://urn.fi/URN:ISBN:978-952-10-5287-3.

The prevalence of variegate porphyria (VP) (2.1:100,000 in 2006, *n* = 108) was higher in Finland than elsewhere in Europe due to a founder effect (R152C). The incidence of VP was estimated at 0.2:1,000,000 based on the number of new symptomatic patients yearly. The prevalence of porphyria cutanea tarda (PCT) was 1.2:100,000 (in 2006, *n* = 63), which is only one-quarter of the numbers reported from other European countries. The estimated incidence of PCT was 0.5:1,000,000. Based on measurements of the uroporphyrinogen decarboxylase activity in erythrocytes, the proportion of familial PCT was 49% of the cases. The prevalence of erythropoietic protoporphyria (EPP) was 0.8:100,000 (in 2006, *n* = 39) including asymptomatic carriers of a mutation in the ferrochelatase (FECH) gene. The incidence of EPP was estimated at 0.1:1,000,000.

After 1980 the penetrance was 37% among patients with VP. Of the mutation carriers (*n* = 57) 30% manifested skin symptoms. Frequency of skin symptom as the only clinical sign was stable before or after 1980 (22% vs. 21%), but acute attacks became infrequent (29% vs. 7%). Of the symptomatic patients, 30% had both acute attacks and skin symptoms and 80% had skin symptoms. Fragility (95%) and blistering (46%) of the skin on the backs of the hands were the most common skin symptoms. Transient correction of porphyrin metabolism using eight haem arginate infusions over a period of 5 weeks had no effect on the skin symptoms in three of four patients with VP. In one case the skin symptoms disappeared transiently.

Fig. 1. Kaisa Timonen (left) defended her thesis on cutaneous porphyrias in Helsinki on 3 April 2009. The opponent was docent Leena Koulu (*right*) from Turku. Annamari Ranki. Helsinki, was the custos.

One patient with homozygous VP had had severe photosensitivity since birth. Sensory polyneuropathy, glaucoma and renal failure developed during the 25-year follow-up without the presence of acute attacks. The I12T mutation was detected in both of his alleles in the protoporphyrinogen oxidase gene. Lack of skin symptoms and infrequency of acute attacks (1/9) in the patients with I12T mutation at the heterozygous stage indicate a mild phenotype (penetrance 11%).