whereas in hyperproliferating tissues, like psoriasis, it is decreased. We investigated the elemental composition in ten nodular basal cell carcinomas with the patient's buttock skin as control. A scanning electron microscope with an energy dispersive X-ray device (EDX) was used on frozen thick sectioned BCCs. In all 80 analysis times seven elements were performed. The intracellular ratio of Na/K in BCC decreased. Considering the clinical picture and the findings in our study inevitably raises the question; whether BCC is a malignant tumour or more related to hyperproliferative tissues.

To summarise the findings:

1. A significant increase of BCC has occurred during the last two decades in southern Stockholm. This is probably representative of the development in the whole country.
2. Half of the patients with one primary BCC will develop a second BCC in life.
3. Risk factors associated with risk of developing multiple BCC are: skin tumour in family and burned by the sun after the age of 60 years.
4. No associations with HLA-DRB, HLA-DQA1 or HLA-DQB1 was found in Swedish patients with four or more BCCs.
5. The elemental composition of BCC has more in common with hyperproliferating tissues rather than the elemental composition of other cancer tumours.

List of original publications

I. Wallberg P, Skog E. The inicdence of basal cell carcinoma in an area of Stockholm county during the period 1971–1980. Acta Derm Venereol 1991; 71: 134-137.

II. Wallberg P, Kaaman T, Alsterborg E, Lindberg M. Two decades of basal cell carcinoma. A retrospective follow-up study and the incidence 1996–1997 in Stockholm. In manuscript.

III. Wallberg P, Kaaman T, Lindberg M. Multiple basal cell carcinoma. A clinical evaluation of risk factors. Acta Derm Venereol 1998; 78: 127–129.

IV. Emtestam L, Wallberg P, Aldener A, Olerup O. Multiple basal cell carcinomas: no association with HLA-DRB, HLA-DQA1 or HLA-DQB1 in Swedish patients. Br J Dermatol 1996; 134: 886-891.

V. Wallberg P, Lindberg M, Alsterborg E., Roomalns GM, Wróblewki R. Elemental changes in skin from patients with basal cell carcinoma. Submitted.

Regulation of the Expression of Human Collagenase-3 (MMP-13) - Implications for Wound Repair and Dermal Fibrosis

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Controlled degradation of extracellular matrix (ECM) is required for several aspects of wound healing, including keratinocyte migration,

angiogenesis, degradation of the provisional matrix, and remodeling of the newly formed granulation tissue. Matrix metalloproteinases (MMPs) are a family of zinc-dependent endopeptidases, which as a group can degrade essentially all ECM components. They can be divided into collagenases, gelatinases, stromelysins, stromelysin-like MMPs, membrane-type MMPs and other MMPs based on their substrate specificity and structure. Collagenases are the principal proteinases which can cleave native fibrillar collagens of types I, II and III. Compared to other MMPs, collagenase-3 (MMP-13) has a very wide substrate specificity. In tissues, the expression of MMP-13 is detected in pathological situations with excessive collagen degradation, for example in rheumatoid arthritis, and in many malignancies. The only physiological situation, in which MMP-13 expression is detected is in development of human fetal bone. During wound healing, MMP-13 is not expressed in acute cutaneous wounds, but is expressed by fibroblasts in chronic cutaneous ulcers *in vivo*. In this study, the regulation of human MMP-13 expression in fibroblasts from adult and fetal skin and gingiva in culture, and during gingival wound repair *in vivo* was examined. In addition, the signal transduction mechanisms, in particular, the role of mitogen-activated protein kinases (MAPKs) regulating MMP-13 gene expression by fibroblasts was studied.

In adult human skin fibroblasts, MMP-13 expression was detected only when the cells were cultured inside three-dimensional type I collagen. The induction of MMP-13 expression by collagen was mediated by α1β1 and α2β1 integrins, and p38 MAPK pathway, whereas ERK1,2 served as an inhibitory pathway. During gingival wound repair, which is characterized by minimal scarring, MMP-13 was expressed by fibroblasts in acute gingival wounds *in vivo*. In contrast to adult skin fibroblasts, transforming growth factor-β (TGFβ) induced MMP-13 expression by human gingival fibroblasts in monolayer culture on plastic. Using chemical MAPK inhibitors and recombinant adenoviruses, it was shown that TGFβ-elicited MMP-13 induction was p38 MAPK-dependent. As wounds of human fetal skin heal also with minimal scarring, fibroblasts from fetal skin were studied. As noted in gingival fibroblasts, fibroblasts from fetal skin also expressed MMP-13 when cultured in monolayer, and this MMP-13 production was upregulated by TGFβ via p38 MAPK pathway. In contrast, neonatal skin fibroblasts did not express MMP-13 in monolayer culture. In this study, the role of MMP-13 in skin fibrosis was also elucidated. In fibrotic scleroderma skin, MMP-13 expression was not detected, but the expression of tissue inhibitor of metalloproteinases-3 (TIMP-3) was noted in fibroblasts. Systemic scleroderma fibroblasts in culture expressed elevated levels of TIMP-3 mRNA, compared to fibroblasts from non-affected skin, suggesting a role for TIMP-3 in dermal fibrosis by inhibiting the degradation of collagenous ECM.

The results of this study show a fundamental difference in MMP-13 regulation between adult human skin fibroblasts and gingival and fetal skin fibroblasts. This suggests a role for MMP-13 in rapid remodeling of the granulation tissue ECM during normal gingival and possibly fetal wound repair, resulting in minimal scarring. This study also shows that the activity of p38 MAPK is essential for the induction of MMP-13 gene expression in fibroblasts. These results suggest p38 MAPK as a possible target for therapeutic inhibition of MMP-13 expression in pathological situations with excessive ECM degradation, such as in chronic ulcers. In contrast, controlled overexpression of MMP-13 in fibrotic tissues such as in scleroderma skin or in hypertrophic scars and keloids may enhance ECM turnover providing a new therapeutical approach for fibrotic disorders.

Original publications:

I. Ravanti (Mattila) L, Heino J, López-Otín C, Kähäri V-M. Induction of Collagenase-3 (MMP-13) expression in human skin fibroblasts by three-dimensional collagen is mediated by p38 mitogen-activated protein kinase. J Biol Chem 1999; 274: 2446–2455.

II. Ravanti (Mattila) L, Häkkinen L, Larjava H, Saarialho-Kere U, Foschi M, Han J, Kähäri V-M. Transforming growth factor-β induces collagenase-3 expression by human gingival fibroblasts via p38 mitogen-activated protein kinase. J Biol Chem 1999; 274: 37292–37300.

III. Ravanti (Mattila) L, Penttinen R, Foschi M, Han J, Kähäri V-M. Human collagenase-3 (MMP-13) expression in fetal Skin Fibroblasts is Induced by transforming growth factor-β via p38 mitogen-activated protein kinase. (Manuscript)

IV. Mattila L, Airola K, Ahonen M, Hietarinta M, Black C, Kähäri V-M. Activation of tissue inhibitor of metalloproteinases-3 (TIMP-3) mRNA expression in scleroderma skin fibroblasts. J Invest Dermatol 1998; 110: 416–421.