

VEGFR2) in 4q12 found in CTCL-associated lung cancers were of interest, since chromosome arm 4q is frequently deleted in primary lung cancer. These preliminary observations warrant further prospective studies to identify the common underlying factors between CTCL and CTCL-associated lung cancer.

To conclude, NAV3 gene aberrations are common to many different CTCL subtypes, and the pathways affected by its aberrant function, are currently being studied. Novel insights

to CTCL pathogenesis were achieved through the observation that several genes specific for Th1 type immune response are down-regulated in CTCL. Moreover, the finding of the difference in genomic aberrations of CTCL-associated and reference lung cancers raises a question as to whether cancer stem cells also have a role in the pathogenesis of CTCL. Demonstration of NAV3 deletion by FISH provides a novel diagnostic tool, and overexpression of certain membrane antigens will provide the basis for developing novel therapeutic means.

Matrix Metalloproteinases as Biomarkers in Premalignant and Malignant Tumours of the Human Skin

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Tiina Kuivanen, MD, defended her thesis “Matrix metalloproteinases as biomarkers in premalignant and malignant tumours of the human skin” at the University of Helsinki on 30 May 2008. The thesis was supervised by Professor Ulpu Saarialho-Kere and the opponent was Professor Veli-Matti Kosma from the University of Kuopio, Finland.



Cutaneous cancer is the most common human malignant disease and over 50% of all neoplasms arise in the skin. Basal cell carcinoma, squamous cell carcinoma and melanoma comprise the three most common types of skin cancer. Lifelong immunosuppression in organ transplant recipients increases the risk of skin cancer, leading to substantial morbidity and mortality in these patients. Tumour progression is a complex, multi-stage process by which a normal cell undergoes genetic changes that give the cell the ability to spread and colonize distant sites in the body. Excessive degradation of matrix components occurs during tumour growth and progression. Matrix metalloproteinases (MMPs) are associated with many types and stages of cancer in numerous studies. They are essential for extracellular matrix degradation, basement membrane penetration, and many signalling functions, such as induction or inhibition of apoptosis, angiogenesis, innate immunity, tumour growth and metastasis. This study aimed to investigate the roles of MMPs in various benign and malignant skin tumours in vivo and to shed light to the pathobiology of these lesions.

This is the first study on MMPs in extramammary Paget's disease. We found, among the several MMPs studied, expression of MMP-7 and -19 in Paget cells in extramammary Paget's disease. Their presence might predict an underlying

adenocarcinoma in these patients. Since this tumour is very rare, however, stainings with larger patient cohorts would be valuable in the future. Furthermore, expression of MMP-7 and -19 supports the theory that Paget cells originate from dermal adenocarcinoma cells of apocrine duct origin. Unlike in most cancers, upregulation of classical MMPs is not a general feature in extramammary Paget's disease, which may associate with the rather benign clinical behaviour of a subgroup of extramammary Paget's disease tumours.

This study was the first to compare MMP expression in primary melanomas and their sentinel nodes. In MM, MMP-21 was upregulated in the early phases of malignant progression, but disappeared from the more aggressive lesions and nodal micrometastases. In conclusion, MMP-21 might serve as a protective MMP in malignant melanoma. A murine MMP-21-knock-out model would be needed to examine this hypothesis further. MMP-13 was detected in the more aggressive malignant melanomas as well as in lymph node metastases, in agreement with previous studies. Thus, MMP-13 might serve as a marker for more aggressive tumours.

Adhesion molecules and the degree of angiogenesis have been studied previously to differentiate keratoacanthomas from well-differentiated squamous cell carcinomas. We were

the first to compare their protein profiles and observed that positive staining for MMP-7 and -9 in the epithelial pushing border should raise a suspicion of malignant conversion to squamous cell carcinoma. The expression of MMP-19 and tumour suppressor p16 were abundant in keratoacanthomas, but disappeared from squamous cell carcinomas, suggesting that lack of MMP-19 and p16 in clinical keratoacanthomas could indicate that keratoacanthomas are turning into squamous cell carcinomas. Frequent expression of the transformation-specific MMP-13 in keratoacanthomas supports their treatment by excision, as a subgroup of them are already incomplete squamous cell carcinomas.

Differences in the inflammatory cell profile, adhesion molecules, or the profile of proteases or their inhibitors might contribute to the exceptionally aggressive behaviour of cutaneous squamous cell carcinomas in organ transplant recipients. In squamous cell carcinomas and Bowen's diseases of the immunosuppressed patients, positive staining was found significantly more often for MMP-26 than in those of control patients. MMP-26 expression was also significantly stronger in patients using cyclosporin. According to previous studies, MMP-26 may function to promote inflammation or to activate MMP-9 and this may influence the more aggressive phenotype of the squamous cell carcinomas in immunosuppressed patients. Since MMP-26 is not present in rodents, more studies in human tissues are needed to specify its role in cancer progression, particularly as it is known that the progression sequence for cutaneous cancers may vary between the human disease and its corresponding mouse models. Expression of MMP-9 was significantly stronger in macrophages surrounding squamous cell carcinomas of the immunocompetent patients, and this is understandable as tumour-associated macrophages may have a protective role in progression of squamous cell carcinomas, possibly through participation in the host-response reaction provoked by the cancer. On the contrary, when our two patient groups were pooled irrespective of immune status, MMP-9 staining in neutrophils of patients using cyclosporin was significantly more abundant. MMP-9 expression in tumour cells was also upregulated in less differentiated squamous cell carcinomas



Fig. 1. Tiina Kuivanen (right) defended her thesis at the University of Helsinki in May 2008. The opponent was Professor Veli-Matti Kosma (left) from the University of Kuopio, and the custos was Professor Annamari Ranki.

and in carcinomas with histological signs of human papilloma virus infection. MMP-9-expressing neutrophils have been associated with tumour angiogenesis and progression in previous studies. Thus, they may have an important function in tumour progression in organ transplant recipients using cyclosporin. Surprisingly, classical cancer-related MMPs, such as MMP-1 and -13, did not differ in their expression between immunosuppressed and immunocompetent groups, nor did we observe diminished expression of TIMP -1 or -3 in immunosuppressed patients.

MMPs have an important role in tumour progression. Recent studies have revealed, however, that some of them might also provide protective effects in different stages of cancer progression or in certain cancer types. The future challenges in MMP research are to increase our understanding of the relevant *in vivo* substrates for specific MMPs. The actual role of an individual MMP in tumour progression and in different cancers is relevant for targeting the therapies more precisely. Expression of certain MMPs could also be used as prognostic markers in planning of treatment strategies or adjuvant therapies.