

Identification of Novel Target Genes in Different Subtypes of Cutaneous T-cell Lymphoma

SONJA HAHTOLA

Department of Dermatology, Allergology and Venereology, Institute of Clinical Medicine University of Helsinki and Helsinki University Central Hospital, University of Helsinki, Finland

Sonja Hahtola, MD, defended her PhD thesis on 18 April 2008 in Helsinki. The thesis was supervised by Professor Annamari Ranki and the opponent was Professor Rudolf Stadler, from the Department of Dermatology, University of Hannover. The thesis book is available at: <https://oa.doria.fi/handle/10024/36535>.

Cutaneous T-cell lymphomas (CTCL) represent a group of non-Hodgkin's lymphomas with an increasing incidence, especially in the Western world. The mechanisms leading to the disease are largely unknown, diagnosis is difficult and therefore often delayed, and no curative therapy exists. CTCL presents with skin symptoms, although the malignant cells are not derived of human skin but rather of human immune system. The malignant cells are mature T-helper memory cells, and preferentially express cytokines characteristic of T-helper 2 (Th2) type immune response. Chromosomal instability is a typical feature of CTCL. Some secondary cancers occur in CTCL patients more often than in the general population, the most common of which are lung cancers and non-Hodgkin's lymphomas.

The aim of the study was to identify genes relevant to CTCL pathogenesis in order to clarify the poorly understood pathomechanisms behind the disease group. The two most common subgroups of CTCL, mycosis fungoides and Sezary syndrome, as well as the difficult-to-diagnose subcutaneous panniculitis-like T-cell lymphoma, were studied. To reveal the molecular pathogenesis underlying CTCL-associated lung cancer, CTCL-associated lung cancer samples were analysed moleculocytogenetically and compared with primary/reference lung cancer samples. Identification of potential novel diagnostic markers as well as target molecules for therapy was a special focus of the study. To achieve this, patient-derived material was studied using molecular cytogenetic techniques, microarrays and gene expression analysis.

This study identified the first specific recurrent common gene level aberration in CTCL, namely the deletion/translocation of neuron navigator 3 (NAV3) in chromosome 12q21 occurring in 50% of patients with early CTCL and in 85% of patients with advanced CTCL. NAV3 is hypothesized to function as a non-classical, i.e. haplo-insufficient tumour suppressor influencing the differentiation of T-helper cells by increasing the production of cytokine interleukin-2. NAV3 deletion was observed in many CTCL subgroups, and its demonstration by



Fig. 1. Sonja Hahtola (right) defended her thesis in Helsinki. The opponent was Professor Rudolf Stadler (left), from the University of Hannover, and the custos was Professor Annamari Ranki (centre).

fluorescent in situ hybridization (FISH)-technology provides a novel diagnostic aid. Also, additional chromosomal hot spots of loss and gain were identified, with both DNA and RNA copy numbers changing to the same direction. Future studies will concentrate mainly on these areas to search for further target genes in CTCL.

Using microarray technology, changes in gene expression were identified, which could clarify the CTCL pathogenesis. A panel of genes with a central role in Th1-type immune responses, e.g. T-bet, RANTES and NKG7, was down-regulated in CTCL, thus explaining the previous observation of the Th2 type cytokine profile of CTCL cells. Moreover, overexpression of potential target molecules for antibody-based therapy, e.g. membrane antigens MS4A4A, LIR9 and CD52, was identified.

For the first time, CTCL-associated lung cancers were observed to show chromosomal aberrations differing from primary lung cancers. In particular, amplifications of chromosome arm 4q and selected receptor tyrosine kinase genes (KIT, PDGFR α and

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

TIINA KUIVANEN

Department of Dermatology and Venereology, Helsinki University Central Hospital, and Biomedicum Helsinki, University of Helsinki, Finland

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