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Department of Medical Biochemsitry and Biophysics (MBB)

Identification of protein signatures of genomic stability/instability in epithelial cancers

AKADEMISK AVHANDLING
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av
Timo Gemoll
Master of Science

Huvudhandledare:
Professor Hans Jörnvall
Karolinska Institutet
Department of Medical Biochemistry and Biophysics

Bihandledare:
Docent Jens K. Habermann
University of Lübeck
Department of Surgery

Docent Uwe J. Roblick
University of Lübeck
Department of Surgery

Professor Gert Auer
Karolinska Institutet
Karolinska Biomic Center

Fakultetsopponent:
Professor Jonas Bergquist
Uppsala University
Department of Physical and Analytical Chemistry

Betygsnämnd:
Professor Ingemar Ernberg
Karolinska Institutet
Department of Microbiology (MTC)

Professor Dan Grandér
Karolinska Institutet
Department for Oncology-Pathology

Professor Gunnar von Heijne
Stockholm University
Department of Biochemistry and Biophysics

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ABSTRACT

Aneuploidy is a consistent genetic alteration of the cancer genome. At early steps in the sequence of malignant transformation during human tumorigenesis, chromosomal aneuploidies can be the first detectable genetic aberrations found. Since late diagnosis results in a significant reduction of average survival times, it is of high interest to elucidate proteins and pathways of genomic instability or stability. This may also give new insights into tumorigenesis and reveal clinically relevant targets for improved diagnostics and therapeutics.

The high variability of protein expression complicates the clinical application of 'proteomics', but continuous improvements in instrumentation, analytical methodologies, and labeling chemistries nowadays allow the thorough study and detection of tissue protein biomarkers. In addition, the need of strict quality controls of samples and clinical validation in large patient cohorts is important to transfer novel biomarkers into clinical use. In this manner, we detected genomic instability-specific protein alterations in colorectal and endometrial malignancies as detailed in this thesis.
A comprehensive proteomic analysis of diploid and aneuploid colorectal cell lines and clinical tissues was carried out. We found that two proteins, TXNL1 and HDAC2, were not only significantly expressed in our 2-DE analysis and validated by Western blotting, but showed expression differences also in clinical samples discerning aneuploid from diploid carcinomas. We then analyzed protein expression patterns between normal endometrium and endometrial carcinomas that profoundly differed in their degree of genomic instability and their histopathologic subtype. We detected 121 ploidy-associated proteins to be differentially expressed. Interestingly, one protein, TXNL1, was expressed at low level in both aneuploid colorectal and endometrial malignancies. In order to identify the impact of chromosomal aberrations onto the protein expression in the clinical setting, we further mapped genomic imbalances with associated gene and protein expression changes of the endometrial cancer patients. AKR7A2 and ANXA2 were identified to show similar trends of changes at the gene and protein levels. We conclude that the grade of genomic instability correlates with a recurrent pattern of chromosomal imbalances and dominates specific gene and protein expression changes, irrespective of the histopathological subtypes in endometrial cancers. To further elucidate the relevance of highly conserved chromosomal aberrations in colorectal cancer, we used specific chromosomal aneuploidies in cancer cells and dissected the consequences of genomic imbalances on the proteome: three artificial trisomic clones of the diploid colorectal cancer cell line DLD1 were analyzed. Chromosomal aneuploidies resulted in a significant increase in the average translational activity of proteins encoded by genes not located on the trisomic chromosome, indicating pathway-related regulation of the cellular proteome equilibrium. A malignancy related protein-profile could also be identified for colorectal cancer: 31 proteins showed differential expression between normal mucosa and colorectal carcinomas in general, while 39 polypeptides were distinctly expressed between diploid and aneuploid carcinomas only. Overall, distinct genes and proteins not known to be associated with colorectal and endometrial cancer or genomic (in)stability will likely reveal novel targets involved in personalized medicine.

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