Karolinska Institutet

DEPARTMENT OF ONCOLOGY AND PATHOLOGY

PROTEOME PROFILING OF HUMAN BREAST CANCER

AKADEMISK AVHANDLING
som för avläggande av medicine doktorsexamen vid Karolinska Institutet offentligen försvaras i Lecture Hall, CCK R8:00.

Friday 29 April, 2011, kl 09.00

av

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PhD degree

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ABSTRACT

Breast cancer (BC) takes thousands of woman's lives yearly. Several factors have been found to influence initiation and development of breast cancer, and to affect prognosis and treatment of this disease. This thesis is focuses on opening-out this complexity and search for approaches that may lead to individualized treatment of breast cancer patients.

We studied clinical samples of breast tumors and adjacent normal tissues using protein-based proteomics. By studying each patient individually, we identified proteins that changed expression during carcinogenesis (p53, Smad2, etc). We observed significant differences in the lists of cancer-related proteins between individual patients. We demonstrated that meta-data analysis of the identified proteins is the most efficient way to describe common and individual features of tumors from different patients. Our validation study by immunohistochemistry analysis of identified molecules (PYK, Smad2, CK2α) confirmed the changed expressions between tumor and normal tissue, and thereby confirmed the conclusions obtained with proteomics analysis. Thus, we found that meta-data analysis approach is suitable for improved and individualized diagnostics and selection of treatment.

Transforming growth factor-β (TGFβ) is a potent regulator of tumorigenesis. In our study of the clinical cases, we demonstrated that TGFβ signaling might be influenced in breast tumorigenesis. Phosphoproteomics analysis of TGFβ action on MCF10A human breast epithelial cells showed a complex regulation of cell signaling, with strong representation of functional domains such as metabolism. One of the targets of TGFβ is 14-3-3σ protein, and we found that 14-3-3σ was of a crucial importance for the cross-talk between TGFβ and p53 signaling.

We reported also proteins identified by expression proteomics, which are regulated by TGFβ in human breast epithelial cells that have phenotype similar to normal breast epithelial cells. We found more than 100 proteins that were regulated by TGFβ. Among them, Casein Kinase 2α (CK2α), Structure-Specific Recognition Protein-1 (SSRP1) and protein convertase-4 (PC4) may be involved in TGFβ-dependent inhibition of cell proliferation by modulating p53 phosphorylation.

Therefore, presented here study describes development of tools for individualized treatment of patients, and provides insights in the complexity of cancer related signaling in breast epithelial cells.

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