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Discovery of protein markers and profiles for diagnosis and prognosis of cancer

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In general, the earlier a disease is diagnosed, the more treatment options there are and the least invasive the treatment has to be. This principle is most evident for life-threatening diseases such as cancer. Early diagnosis and reliable prognosis are essential to significantly decrease mortality and morbidity from this disease.
Spectacular developments related to new diagnostic and prognostic tools, are seen in the area of basic and preclinical cancer research with the expanded knowledge on the human genome and the introduction of technologies to perform high-throughput DNA, RNA, and protein analyses. This combination has lead to a refined understanding of cancer progression and the discovery of novel markers and therapeutic targets. Moreover, expression profiles of tumor RNA and serum proteins might become the latest tools to reliably diagnose patients, predict disease outcome, and advise a patient-tailored treatment regiment.

Proteomics

In the past, protein assays were mainly focussed on expression analysis of a single protein of interest. The technology to identify marker proteins and study protein modifications has been refined and has become more accessible to cancer researchers. The main progress has been made in the application of mass spectrometry (MS) for high-resolution protein mass separation, low quantity detection, and sequencing. In general, proteomics MS can be divided into two applications: protein identification and protein profiling.

Protein identification

When the purpose is to go for a novel marker or therapeutic target, one can first separate and visualize potential marker proteins from an extract on 2-dimensional poly-acrylamide gel electrophoreses (2-D PAGE) and then identify differentially expressed proteins using MS applications. The result from this experiment is that a potential marker is identified and can be studied further for its potential in clinical applications. The current drawback is the limited number of samples that can be screened using this laborious approach and, therefore, the validity of the marker needs to be proven upon identification in follow-up experiments. The opposite procedure is to first screen many potential protein markers for correlation with disease in large groups of samples and then identify those proteins that positively contribute to diagnosis and prognosis.

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Protein profiling

Using MALDI-TOF or SELDI-TOF MS (matrix assisted and surface enhanced laser desorption ionization time of flight) one can detect hundreds to thousands of proteins in a microliter of serum or tissue extract. This has enabled researchers to generate protein profiles and to identify protein peaks of interest in a high-throughput manner. The strength of the MS-protein profiles is not the direct protein identification, but the potential to first link the presence or height of multiple individual protein peaks to clinical parameters. Once peaks are identified that distinguish, for example, normal from disease, one can continue to identify those particular protein markers. The protein-pattern linking has successfully been accomplished for ovarian and prostate cancer in which one could diagnose cancer with a sensitivity/specificity of 100/95 %, and 83/97 %, respectively. At present, there are no single diagnostic assays for these cancers with such a power. An important feature is the fact that these SELDI-TOF MS analyses were performed on serum, an easily accessible body fluid.

Significance for cancer research and clinical implications

In the past few years, we have seen a number of new developments for the analyses of DNA, RNA, protein, and tissues. Almost all of these new technologies will prove to be very useful in basic cancer research and will yield new markers and therapeutic targets for clinical applications. The value of genomics and proteomics in a clinical setting, however, is questionable due to the more stringent requirements. Diagnostic and prognostic assays must be cost-effective, reproducible, and uncomplicated. The microarray technology, for example, is complex and expensive and will less likely become a standard assay in diagnostic laboratories. The patient-derived material to perform the assays with, will also enforce restrictions on the assays. The tissue must preferentially be easily accessible and invariable. Extracting the easily degraded RNA or protein from biopsies for further analysis, is quite complicated for standard practice. From all technologies currently available, mass spectrometry on serum to generate complex protein profiles for diagnostic and prognostic evaluation, seems the most promising development for clinical implementation. A one hour, simple and cost-effective assay on the easily accessible serum, could become a valuable tool to reliably diagnose patients, predict disease outcome, and advise on patient-tailored treatment regiments.