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Chapter 1 : Proteomics in Cancer Biomarkers Discovery: Challenges and Applications

Use of Genomics To Assign Therapy in Lung Cancer The Lung Cancer Oncogenome Group: Bedside to Bench and Beyond Mark G Kris William Pao Memorial Sloan-Kettering Cancer Center.

 Abstract With the introduction of recent high-throughput technologies to various fields of science and medicine, it is becoming clear that obtaining large amounts of data is no longer a problem in modern research laboratories. However, coherent study designs, optimal conditions for obtaining high-quality data, and compelling interpretation, in accordance with the evidence-based systems biology, are critical factors in ensuring the emergence of good science out of these recent technologies. This review focuses on the proteomics field and its new perspectives on cancer research. The author of this review aims at presenting some of the relevant literature data that helped as a step forward in bridging the gap between bench work results and bedside potentials. Undeniably, this review cannot include all the work that is being produced by expert research groups all over the world. Introduction In the -omics era, the nature of high-throughput technologies, their capabilities, limitations, performance quality, and applicability are among factors determining their significance and influence not only in pure exploratory research, but also in potential clinical use. Advances to the field of genomics and related computational tools are constantly being produced and applied in cancer-related research [1]. However, other fields are needed to complement the limitations of the genomics approach. Proteomics-based strategy in studying diseases is considered one of the dynamic and innovative tools that could confirm, complement, or quite often provide more elaborate information beyond that obtained by other high-throughput approaches. While several genes were identified by genomics technologies to be specifically related to cancers [2], the function of such genes and the data interpretation in the context of functional networks require the power of proteomics. Moreover, although studies focusing on detecting the differential expression of mRNA have been extremely informative, they do not necessarily correlate with the functional protein concentrations. Macromolecules, in general, and proteins, in particular, are highly dynamic molecules. Mechanistically, proteins can be subjected to extensive functional regulation by various processes such as proteolytic degradation, posttranslational modification, involvement in complex structures, and compartmentalization. Proteomics is concerned with studying the whole protein repertoire of a defined entity, be it a biological fluid, an organelle, a cell, a tissue, an organ, a system, or the whole organism. Therefore, in-depth studying of proteomics profiles of various biospecimens obtained from cancer patients are expected to increase our understanding of tumor pathogenesis, monitoring, and the identification of novel targets for cancer therapy. In addition, an essential goal for applying proteomics to study cancers is to adapt its high-throughput tools for regular use in clinical laboratories for the purpose of diagnostic and prognostic categorization of cancers, as well as in assessing various cancer therapeutic regimens. Similar to other high-throughput technologies, proteomics has been generating a vast amount of data in the form of lists of hundreds or thousands of proteins that are differentially expressed, whether increase or decrease, as a cause or consequence of ongoing physiological, developmental, or pathological events. Interpretation and analysis of such flood of information depend on building on existing data stored in constantly updated databases. Obviously, researchers have to be extra-cautious in designing their work in the first place, ensuring that good analytical tracks are being undertaken, to avoid snow ball effect and erroneous outcomes [3]. Scientifically sound analysis of the information flow as it represents complex networks and interactions of intra-, inter-, and extra-cellular environments should be the ultimate goal. Unraveling such complexity is the focus of interest for several research groups. The complexity of proteomics technologies when applied to cancer research increases even more due to the current concept of cancer heterogeneity. As a matter of fact, cancer heterogeneity and biospecimen variables are considered by some researchers the most crucial and challenging

point for all â€”omics technologies at their application in cancer studies [5]. Moreover, an integrated approach for research performed on cancers and diseases, in general, is recommended when designing studies with the intention of discovering disease biomarkers as argued by George Poste: Such study designs have to comply with standardized and validated guidelines. Mechanisms of Proteomic Changes in Cancer Although exact causes of most cancers are not clearly defined, cancer is thought to result from a combination of genetic and environmental abnormalities. Several genomic defects have been implicated, including mutations, variation in copy number, chromosomal anomalies, and alternative splicing. One potential mechanism for the proteomic variation in cancer is the ubiquitous aneuploidy, which is defined as an imbalanced chromosomal content [7]. Aneuploid cells are thought to be under proteotoxic stress as a result of defective proteostasis; the latter is the state of dynamic equilibrium in which protein synthesis and correct folding are balanced with protein degradation. Therefore, defective proteostasis will result in not only proteotoxic stress, but also cellular dysfunction and subsequent pathologies [8]. Recent findings have shed some light into the yet-not-fully-understood mechanisms underlying the association between aneuploidy, proteotoxic stress, and abnormal cellular proliferation and tumorigenesis [7]. However, this association is still a matter of controversy and is lacking straightforward relationship pattern; for instance, an extra chromosome that results in increased gene expression and a theoretical increased protein production is not necessarily translated into an actual elevation of circulating protein levels, since there is high possibility of overwhelming the cellular protein folding apparatus, leading to chronic protein misfolding and subsequent protein degradation. It is proposed that certain proteins, such as various kinases and multimeric protein complexes, have increased requirements for the cellular protein folding apparatus, and hence they are more susceptible to misfolding than others. Emerging evidence linking aneuploidy, defective proteome, and cancer development is of obvious significance as it provides potential for treating aneuploid cancer cells using suitable antineoplastic agents targeting the proteostatic machinery [9]. This will be discussed in more details later. Another potential mechanism for proteomics changes in cancers is the consequence of defective protein structure and hence function. Mutations in cancer-associated genes can be manifested in defective protein structure. This is reviewed recently by Gulati and coworkers and is beyond the scope of the current review [11]. Challenges and Recommended Solutions 3. Cancer Heterogeneity The current concept of cancer heterogeneity and biospecimen variables is considered by some researchers as one of the most crucial and challenging points for proteomics as well as for other -omics technologies, at their application in cancer studies. Recently, intratumoral heterogeneity was examined in invasive breast cancer, comparing biospecimens obtained by intraoperative image-guided, core-needle biopsies to surgical biopsies taken from the center and the periphery of cancer breast. Proteomics techniques undertaken in that study have demonstrated that even though most biomarkers studied did not manifest significant intratumoral heterogeneity, protein and phosphoprotein levels were affected by biospecimen type, as well as by other preanalytic variables, including surgical manipulation and the duration of cold ischemia [5]. This approach is unique as it allows proteomics-based studies to provide both patient-specific and cancer-specific information as a means for biomarker discovery and cancer tissue classification. It also provides morphology-based proteomics analysis for cancer tissue [12]. In addition, studies using MALDI-IMS analysis of specific cancer tissues generate peptide reference datasets to facilitate peptide identification in future studies on the same cancer type. However, several technical challenges still exist including low signal to noise ratio and low mass accuracy [13]. Their approach has provided a useful model for predicting cancer aggressiveness through reliable biomarkers, regardless of sample variation [14]. Cancer Early Detection Detecting cancer at an early stage, when there is a better chance for its treatment, is a real challenge to the scientific and medical communities as most clinical blood biomarkers assays do not have the required sensitivity and specificity necessary for that purpose. In an interesting approach focusing on ovarian cancer, Hori and Gambhir have recently developed a mathematical model looking at the estimated time at which ovarian cancer can be detected by measuring the amount of the cancer antigen CA shed from the tumor during its growth. Surprisingly and despite the reported sensitivity of

the CA measuring assays, the authors reported that a tumor could grow unnoticed for more than 10 years and reach a size of more than 2. Nevertheless, a lot of debate has emerged regarding the applicability of this approach in other types of tumor and the sort of assumptions used in its calculation [16]. Combining panels of circulating biomarkers, rather than a single molecule, with newly developed or newly updated technologies such as imaging procedures might be more informative in terms of early diagnosis, accurate assessment of the prognosis, and response to therapy in cancer patients [16 , 17]. Protocols for Developing Tumor Biomarkers More than a decade ago, several research groups have formulated multisteps strategies for developing tumor biomarkers. Despite the strict step-wise analytical criteria of this strategy, preanalytical issues were not sufficiently addressed. Several years later, the same group has suggested a more rigorous study design for the development of tumor biomarkers, emphasizing that the described design would maintain a high research quality and improve the possibility of obtaining a clinically promising biomarker ready for subsequent rigorous scrutiny [20]. The design included prospective collection of specimens before outcome ascertainment from a case-control study cohort that is relevant to the clinical application under study, and blind assessment of the biomarker in specimens obtained from randomly selected case and control subjects. The authors described various aspects of their design in relation to the clinical context, biomarker performance criteria, biomarker test, and study size [20]. This was reviewed in more details elsewhere [21 , 22] and is summarized in the following section. Firstly, careful planning starting with the formulation of a research question supported by convincing evidence for its importance and relevance to a clinically pressing problem. A rational choice of the most suitable analytical tests to approach this research question is of equal significance. The performance characteristics for such test s , in terms of specificity, sensitivity, and positive and negative predictive power, should be appropriate for the experimental design and clearly described. Therefore, collecting a representative sample is important in order to obtain reliable data. Likewise, sample size calculation is a crucial component of the study coherence and if carefully conducted will average out sample heterogeneity. Moreover, protocols of executing the experiments should maintain basic and critical points, such as incorporating proper blank s , positive and negative control samples, and reference compound s within each run for the analytical procedure. The scientific communities have been working diligently to standardize the procedures of proteomics-generated data optimum utilization. Useful data repositories have been constructed such as Panorama https: Proteomics Techniques Used in Cancer Research Research studying protein alterations in cancer existed for more than 70 years [23]; however it was only in the last 3 decades or so that recent proteomics technologies have been extensively utilized in deciphering protein differential expression in human cancers [24]. Various approaches have been carried out, taking advantage of the recent analytical techniques and advanced bioinformatics. The following section starts by briefly describing basic techniques such as 2D gel electrophoresis, difference in gel electrophoresis DIGE , and MS, followed by introducing more recent technologies and combined applications such as protein microarray and combined proteomics and imaging methods. This approach has been frequently applied to analyze cancer cells proteins for more than 2 decades [25] and is still in use [26]. Further advancement in this approach has been the result of introducing fluorescent dyes and in-gel comparative proteomic analysis in the technique of 2D-DIGE. Advancements in MS resulted in optimal performance in the low mass range of proteins. In-depth profiling of plasma and other biofluids proteomes results in identification of proteins that span more than six logs of protein abundance. As such, it has been the method of choice in many cancer applications [24]. However, this carries the risk of depleting the samples from the low-abundance and low-molecular weight proteins that are bound to the circulating carrier proteins. The latter have been demonstrated to act as a reservoir storing diagnostic information within the accumulated bound low-molecular weight potential biomarkers [27]. Incorporation of bead-based immunoassays may also be used to better identify low abundance proteins [17]. MS use in protein analysis has undergone several stages of technical advancement and improved instrumentation efficiency. This has been thoroughly reviewed in several articles [24 , 29 â€” 31]. More recently, proteomics approach has been extended to involve studying of epigenetic processes in cancer

research. The use of MS-based proteomics in studying various aspects of chromatin biology and in evaluating specific histone posttranslational modifications resulted in the discovery of chromatin-associated proteins and multisubunit complexes that can be considered epigenetic biomarkers with future potential in cancer diagnosis and therapy. This has gained a wide attention and was recently reviewed by Bartke et al. Microarray is considered one of the most exciting developments in high-throughput technologies. Recently, such technologies have been applied to study a relatively uncommon category of cancer patients who are presenting with metastatic cancer without any obvious anatomically detectable primary tumor, the so called cancer of unknown primary or CUP [33]. In addition, the targeted proteomic approach of selected reaction monitoring SRM has been developed and widely applied, for instance, to detect mutant proteins in the colorectal cancer tissue and in the fluid obtained from potential precancerous pancreatic cysts [34]. Combining proteomics and imaging-based methods has been recently described. Shipitsin and coworkers were able to identify a panel of 5 protein biomarkers for prostate cancer lethality using an automated, integrated quantitative multiplex immunofluorescence in situ imaging approach [36]. Such combination is thought to produce more clinically representing data in terms of the actual in vivo environment where the active proteins exert their functions. This is because such approach was designed to measure the levels and activity status of protein biomarkers in defined intact tissue regions, avoiding the need to lyse the tissues of interest that is commonly performed in the traditional proteomics approaches. Wider range of applications and comparative studies to more established proteomics approaches is still in progress. In a different context, integrating proteomics and imaging tools to gain more insight into the pathogenesis of cancer progression and penetrability at the molecular level is recently experimented. An article describing such mechanistic-oriented approach was recently published by Oh and colleagues [37]. This group used their advanced integrative tools to study caveolae at the blood-solid tumor interface in vivo aiming to reveal molecular portals to infiltrate solid tumors of mammary, prostate, and lung origins. They were able to reveal a transvascular pumping system and define some of its component proteins, as caveolin 1 and annexin A1, that are affecting tumor uptake of various agents. Such approach will probably get a large scale attention as it can be applied to assess the effectiveness of therapeutic agents based on their ability to cross the biological barriers in vivo and find their way into the solid tumors. Examples of Proteomics Research Applications in Various Cancer Types In various types of cancer, the biomarkers discovery is expected to improve one or more of the following critical applications: High-throughput hypothesis-generating methods have revealed hundreds to thousands of cancer associated proteins CAPs. This implies that hundreds to thousands of potential protein biomarkers have been suggested in the literature and are awaiting proper validation.

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Phosphoproteomics is making contributions to preclinical modeling for molecularly driven therapy in lung cancer; the combination of chemical proteomics, phosphoproteomics, and SH2 interactions provided detailed mechanistic views of the protein-protein interactions and signaling networks targeted by tyrosine kinase inhibitors.

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Comprehensive proteomics were also performed using lung tumor xenografts treat with citreovirdin that reveals its antitumorigenic effects in lung cancer, which may lead to a better understanding of the links between metabolism and tumorigenesis in lung cancer drug development [62, 64].