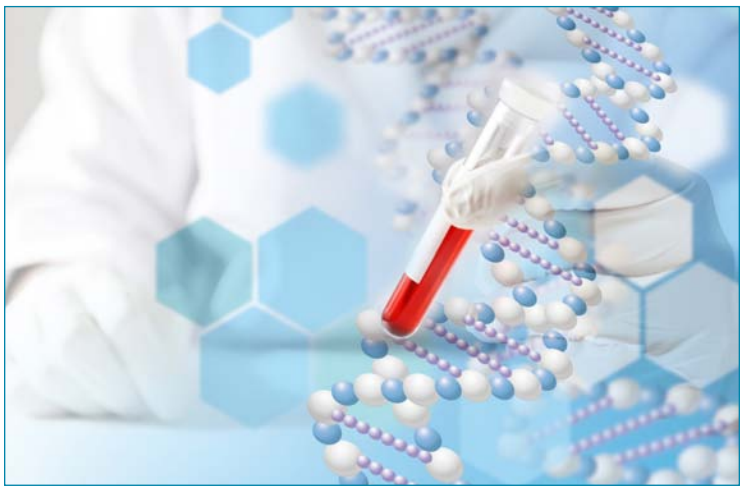
Perspectives on Proteomics & Cancer

BY DIBASH KUMAR DAS, PHD

Despite continuous progress in detection, diagnosis, and therapy, cancer remains the leading cause of death worldwide. According to the World Health Organization, approximately 9.6 million cancer-associated deaths were reported globally in 2018. This has sparked major efforts in the quest of novel and more efficient biomarkers that can serve as diagnostic tools, prognostic predictors, or therapeutic targets in the fight against cancer.

The complexity and heterogeneity of cancer makes it evident that cancers progress via multiple pathways involving complex protein networks and clinical events (*Nat Comm* 2020; https://doi.org/10.1038/s41467-019-13803-0).

Proteins are omnipresent, practically involved in every single biological phenomena, from providing structural support for cells to regulating host responses to inflammation and infection. Moreover, their expression levels reflect much more accurately the cellular phenotype and the regulatory processes within them than gene levels, mutations, and even mRNA levels.



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Furthermore, analysis of post-translational protein modifications allows for the detection of signaling network adaptations driven by genomic as well as micro-environmental changes. Researchers now believe proteomics can revolutionize the diagnosis and treatment of cancer (*Cell* 2018;173(3):535-539).

It is unsurprising then that recent advances in proteomic technology have now enabled researchers to map the protein landscapes of biological samples, and it can be applied for the precise, accurate, and sensitive quantification of relevant proteins in a range of clinical materials, including cells, tissues, and body fluids. Thus, proteomic analysis allows for a look at a level that's directly actionable, with the proteins themselves potential clinical biomarkers or druggable targets.

Two recent studies published in the journal *Cell*, highlight examples of proteomics research applications in lung adenocarcinoma (LUAD) to provide the most comprehensive picture of the disease yet.

Lung cancers are the leading cause of cancer deaths in the United States and worldwide, with a global ratio of lung cancer mortality-to-incidence of 0.87 (*Ann Transl Med* 2016; doi: 10.21037/atm.2016.03.11). The genetics and natural history of LUAD, the most common lung malignancy, are strongly influenced by smoking status, ethnicity, and gender, among other factors. Yet, how various gene mutations lead to this disease remains unclear.

Investigators from the National Cancer Institute's (NCI) Clinical Proteomics Tumor Analysis Consortium (CPTAC) and International Cancer Proteogenome Consortium (ICPC) addressed this challenge by adding comprehensive proteomics to genomics, or proteogenomics, to create a new dimension of lung cancer biology.

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In one collaborative study, working through CPTAC, the research team collected 110 lung adenocarcinomas and 101 matched normal adjacent tissues (NATs) from eight countries representing a diverse range of ancestries, as well as a balance of patients with and without a history of smoking (*Cell* 2020; doi: https://doi.org/10.1016/j.cell.2020.06.013).

The investigators focused on discovering novel and clinically relevant LUAD biology across tumor subtypes and stages. Comparison between these groups revealed several biological pathways previously undetected by genomic analysis alone. Multi-omics clustering identified four different clusters, variably enriched for place of countries of origin, gender, and key driver mutations mutation status.

Proteomics also provided many unique and significant new observations. For example, phosphoproteomics identified candidate ALK-fusion diagnostic markers and targets. Association analyses revealed significant outliers seen only in the phosphoproteomic data, including potential therapeutic targets, such as SOS1 in KRAS-mutant and PTPN11 in EGFR-mutant tumors. Furthermore, evident exclusively in the proteomics dataset, CPTAC researchers observed a clear neutrophil degranulation signature in immune "cold" tumors (those without active cancer-killing immune cells) with STK11 mutations.

Another large-, deep-scale proteogenomic study of LUAD was performed for the first time in the Taiwanese population (*Cell* 2020; doi: https://doi.org/10.1016/j.cell.2020.06.012). In Taiwan, more than 50 percent of lung cancer patients are never-smokers, and many with early onset of the disease. The high number of East Asian LUAD never-smokers presented an opportunity for the ICPC-Taiwan team with colleagues from other institutions to shed some light on the molecular phenotype of this demographically distinct disease.

The researchers prospectively collected patient-matched tumor and NAT from 103 treatment-naive patients from Taiwan, representing early-stage, predominantly female, non-smoking LUAD. Integrated proteogenomic and phosphoproteomic analysis described the demographically distinct molecular attributes and hallmarks of tumor progression.

> "In the next decade, proteomics integrated with genomics (proteogenomics) will be well-entrenched into the fabric of precision medicine."
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> *—Henry Rodriquez, PhD, MS, MBA, Director of the NCI Office of Cancer Clinical Proteomics Research*

Comparison of tumor/normal matched tissue pairs revealed strong associations between APOBEC mutagenesis and carcinogenesis. The APOBEC family of RNA-editing enzymes function to make precise changes to transcripts and permit a single protein to operate differently in different organs. Mutational signature analysis identified age, sex-related endogenous, and environmental carcinogen mutagenic processes, characterized by increased prevalence of APOBEC mutational signature in younger females and increased representation of environmental carcinogen-like mutational signatures in older females.

Additionally, proteome-informed classification distinguished the clinical characteristics of early-stage patients with EGFR mutations. And, integrated protein network analysis identified tumorigenesis hallmarks, biomarkers, and druggable targets. These study results

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indicate an early point of divergence in tumor phenotype where health care providers can identify high-risk patients to receive closer monitoring and possible adjuvant therapy.

As part of a series of studies supported by The NCI's Office of Cancer Clinical Proteomics Research (OCCPR), both of these studies have produced proteogenomic datasets that are available as a unique public resource for researchers and clinicians seeking to better understand, as well as help develop strategies for detection and management of lung adenocarcinomas.

Oncology Times spoke with Henry Rodriguez, PhD, MS, MBA, Director of the OCCPR at the NCI, and Ana Robles, PhD, Program Director in the OCCPR at the NCI, about the proteomics research program and how they envision their work will help cancer patients in the long run.

One of the big problems with cancer is that it's caused by mutations, so it doesn't look like the reference genome. What approaches does the NCI Clinical Proteomic Tumor Analysis Consortium (CPTAC) employ to address this?
Rodriguez: "I see this not as a problem, rather an opportunity. While today it is well understood that cancer is a disease of the genome, the true difficulty is that we are discovering that genetic mutations don't always result in a predictable change of function in the corresponding protein. In addition, most tumors have many mutations, making it difficult to establish which are the important drivers.


HENRY RODRIGUEZ, PHD, MS, MBA

For these reasons, NCI's CPTAC is pioneering the innovative approach of combining genomics and proteomics (known as proteogenomics) to identify biology (cancer molecular information) that is either difficult or impossible to obtain through genomics alone, to help make precision oncology more 'precise.'"

The clinical and molecular heterogeneity of cancer currently presents clinicians with difficult problems when choosing adjuvant treatment for individual patients. How can proteomics assist oncologists working in the clinic?
Robles: "The gained understanding of biology through proteogenomics can inform patient stratification, so that patients receive the treatment they are most likely to benefit from. Among other tools, proteomics-based biomarkers of prognosis and response can be easily interrogated in tissue samples that are procured during routine clinical care using, for example, targeted mass spectrometry methods. Within-patient heterogeneity is also challenging, but comprehensive proteomic analysis can help prioritize and understand which genomic alterations are cancer drivers."


ANA ROBLES, PHD

What are some examples of cancer proteomics that have already resulted in improve routine care for patients?
Robles: "Many cancer diagnostic biomarkers currently in use for routine patient care are based on protein expression. While proteomics profiling can identify tumor markers, their implementation in the clinic is challenging. Cancer proteogenomics is an emerging field that builds on the knowledge of genomics. Promising discoveries that leverage the integration of genomic information with comprehensive proteomics are under clinical development."

How important is national and international collaboration in translating the enormous amounts of ever-increasing cancer proteomic information into novel clinical knowledge and tools with a favorable impact for cancer patients around the world? What is an example of a key outstanding collaboration?
Rodriguez: "Advancements in science and health care are made possible through widespread access to results from cutting-edge research, enabling scientists to use and build on this knowledge. This is achieved by breaking down the walls between organizations and across sectors.

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Learning Objectives for This Month's Activity:

After participating in this activity, readers should be better able to: 1. Assess recent advances in proteomics technology. 2. Evaluate the clinical significance of proteomics for the evolution of cancer research, diagnosis, and treatment.

Disclosure: The author(s), faculty, staff, and planners, including spouses/partners (if any), in any position to control the content of this activity, have disclosed that they have no financial relationships with, or financial interests in, any commercial companies relevant to this educational activity.

"At the national level, NCI's CPTAC was established with collaboration and community resources as a core competency. As a result, NCI hosts some of the largest open access repositories of unified cancer proteogenomics datasets, assays, and reagents. Recently, CPTAC paved the way for the NCI Cancer Moonshot inspired initiative on global health—the International Cancer Proteogenome Consortium (ICPC)—that connects more than a dozen countries with projects focused on multiple cancers. ICPC contributes to the public sharing of cancer-associated proteogenomics data for use by cancer researchers and physicians around the world to accelerate the understanding of cancer and its translation to patient care."

What are you most excited about in the field cancer proteomics?
Rodriguez: "It's potential to transform clinical trials. In March 2019, outgoing FDA commissioner Scott Gottlieb stated that modernizing clinical trials was a priority for the FDA. He cited proteomics as one such approach, pointing out that, in an age of precision medicine, 'enrichment' strategies of this kind are important for guiding patient selection. I believe that proteomics is ready to be applied more broadly in clinical trials and, in the next decade, proteomics integrated with genomics (proteogenomics) will be well-entrenched into the fabric of precision medicine."
Robles: "What he said. Through extensive benchmarking and continuous development, CPTAC and others have made it possible to apply discovery proteomics to clinical trials. Scientists are starting to unravel the causes of treatment failure at the protein level to help oncologists build on and move beyond genomics-based patient stratification." OT

Dibash Kumar Das is a contributing writer.