A PROTEOMICS REVIEW

A recent review article by Matthias Mann, published in Proteomics Clinical Applications, provides an excellent overview of the benefits gained from incorporating proteomic analysis via tandem LC-MS/MS with next-generation sequencing genomic and transcriptomic techniques. The combination of multiple “omic” platforms applied towards the same samples (coined proteogenomics) can help elucidate relevant biological patterns compared to using a single “omic” strategy. The publication discusses proteogenomics in the context of cancer research, but the theories are not restricted to this field. In this issue of the IMSU newsletter, we would like to highlight some of the major points presented in the article.

GENOMICS AND PROTEOMICS

For several years, genomic and transcriptomic strategies have been implemented as discovery tools for developing targeted therapeutics. This publication cites several successful examples of genomic derived therapies, such as Herceptin, Crizotinib, and Gefinitib. However, the scenarios by which these drugs were derived, where quantitative changes and alterations in translating RNA correspond directly to changes in protein activity, are the exception rather than the rule. Post-translational modifications play a pivotal role in regulating protein activity, and consequently, phenotypic profiles. Additional factors such as subcellular localization and regulatory mechanisms also have significant effects on phenotypes. Therefore, it is not surprising that actionable genes identified from genomic and transcriptomic analyses may not generate meaningful changes when used as therapeutic targets.

Contrary to genomics and transcriptomics, proteomics has the ability to directly track protein and post-translation modification changes on a global or targeted scale. Several examples of proteomics aiding in therapy development are demonstrated in this publication. Notable instances include the phosphoprotein profiling of malignant pediatric medulloblastomas where phosphorylation sites were correlated to patient outcome, and the identification of CT45 as a biomarker of increased disease-free survival in ovarian patients treated with chemotherapy.
COMBINING GENOMICS WITH PROTEOMICS

However, the most complete information is obtained by combining the biologically relevant information from proteomics with that of genomics/transcriptomics. As an example, the authors highlight their own clinical workflow for an end-stage urachal carcinoma patient. Tumor tissue was used to isolate a subset of upregulated proteins, and the protein LSD1 was identified from that subset. Previous genomic experiments had already identified LSD1 as a potential therapeutic target, so treatment of the patient with a drug targeting LSD1 was rapidly approved. In this scenario, the combination of proteomics with genomics led to a precision treatment that would have otherwise been overlooked.

Another variation on proteogenomics uses genomics to broaden the proteomic reference database. Proteomics is usually restricted to identifying proteins that already have a complete sequence recorded in a reference protein database, while genomics is more capable of identifying novel, mutated sequences. These mutated genes can be translated into mutant proteins, and then included in the proteomic reference database, giving proteomics the ability to identify previously unsequenced proteins. This proteogenomic strategy has already been utilized to develop successful vaccines that promote an antitumor immune response and are currently approaching clinical trials.

PROTEOGENOMICS AT THE IMSU

The Integrated Mass Spectrometry Unit (IMSU) was created with the intention of serving the rapidly expanding medical and clinical research in Grand Rapids. To that end, it is one of our goals to incorporate proteomics with the wealth of genomic research already active in our area. We offer proteomic services that can be used as a standalone study or to reinforce genomic and transcriptomic data. All of our proteomic analyses take advantage of state of the art, high-resolution, accurate mass instrumentation offered via the Thermo Orbitrap series in conjunction with UHPLC, nano-flow separation technology.

Genomic and transcriptomic data comes in many forms. In order to best incorporate your genomic information with proteomics, the IMSU can schedule a complimentary consultation with our staff where we optimize an appropriate experimental workflow to isolate the most important, and most impactful aspects of your research.

This newsletter is based on the article by Doll et al.