Next Gen Metabolomics Technologies: Unknown Annotation, Single Cell, Ion Mobility and Imaging.

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The highly dynamic nature of metabolites and their abundances makes metabolomics a powerful endpoint of the 'omics' cascade, yielding a molecular profile that is closest to the physiological phenotype. Metabolomic profiles are therefore sensitive to subtle perturbations observed in early disease stages or disease progression, which may be difficult to detect at the proteome or transcriptome levels. Human diseases are multi-factorial in nature, and studying small parts of their associated molecular changes is generally insufficient for understanding the full spectrum of disease phenotypes.

The metabolome is the total collection of biologically-active small molecules with molecular weights lower than about ~1.5 kDa in an organism. This includes endogenous molecules that are biosynthesized by metabolic networks in "primary metabolism", specialized "secondary metabolite" signaling or defense molecules, molecules derived from diet or environmental exposures (the exposome), and molecules derived from the biosynthetic interactions with associated microbes (the microbiome). Metabolomics can either be "targeted" to a set of known compounds, for example certain lipids, or "non-targeted", which attempts to detect and relatively quantify as many metabolites as possible.

The vast chemical diversity of the metabolome (lipids, sugars, amino acids, etc.), and its wide dynamic range (mM to fM) implies that no single analytical method can adequately profile all metabolites in a single metabolomics experiment. Along these lines, the "fusion" of mass spectrometry (MS) and nuclear magnetic resonance spectroscopy (NMR) has emerged as one of the most powerful avenues to increase metabolome coverage. Nested separations that work in a time frame compatible with mass spectrometry, such as those performed by ion mobility, are also playing a key analytical role in metabolomics as a way of increasing peak capacity and identifying metabolites through ion mobility collision cross section measurements. Further, localization of metabolites at the tissue level with imaging mass spectrometry experiments, allows linking their abundance with changes observed in biofluids. In this seminar, I will introduce the typical workflow used in non-targeted metabolomics experiments, describe potential pitfalls through examples related to our efforts within the Molecular Transducers of Physical Activity Consortium (MoTrPAC), and showcase the challenges involved in identifying unknowns with this growing 'omics approach.