Metabolon

ARTICLE

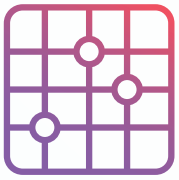
Metabolomics

The Common Denominator to Achieve Fully Integrated, Multi-Omic Drug Development

Perhaps the most meaningful measure of a technology's success lies in the universality of its acceptance. The completion of the Human Genome Project spawned the various 'omics sciences nearly two decades ago. Since then, they have risen to prominence worldwide as a means for studying how genes, RNA, and proteins affect health and disease, and how they can be modified by drug treatments. 'Omics assays are now a mainstay of drug discovery and development. While the efficacy of genomics, transcriptomics, and proteomics for providing valuable information is irrefutable, they can be limited in their scope and utility[1,2,3].

In defining the ultimate phenotype, classical biology describes the flow of information as moving from DNA to protein and then to metabolites. More recent technological advances have shown that analyzing the genotype alone may fail to predict a phenotype. Indeed, a single 'omics approach does not correspond with an observed phenotype and may even lead to misinterpretations.

A Look at Other 'Omics



Certainly, we can measure genes. We cannot, however, be sure whether we are measuring their active or the inactive forms.

Recent evidence reinforces the notion that the relationship between genotype and phenotype is not linear, and that genomics often reveals only predisposition, or risk, of disease[1-5]. Certainly, we can measure genes. We cannot, however, be sure whether we are measuring their active or the inactive forms. Furthermore, a series of biological processes control the transcription of DNA into RNA and the translation of the RNA into proteins. These processes make the transcript levels alone unsatisfactory predictors of protein levels and therefore unable to elucidate genotype-phenotype relationships[6]. In fact, the correlation between gene expression and an individual protein measurement is relatively poor[6,7].

In addition, proteins by themselves are regulated by protein-protein interactions, post-translational modifications (PTMs), and a series of feedback inhibition and activation mechanisms. Owing to various genetic and translational factors, we estimate the presence of as many as 100 proteoforms per protein, on average. Moreover, the functions of different proteoforms can be as different as those from proteins encoded by different genes[8,9].

Biological networks and the streaming of biological events complicate predicting an individual's ultimate phenotype based on genes, transcripts, or proteins alone. In addition, environmental and lifestyle factors, including diet, exposure to pollution and medications, and microbiome can further affect cellular processes, altering the ultimate phenotype in unpredictable, genotype-independent ways[4-10,11]. Accordingly, over the years, we've come to recognize that any single 'omics study cannot reveal what we want to know about disease and its treatments. Instead, we must integrate diverse 'omics data to find a coherent genotype-phenotype association.

Enter Metabolomics, the 'Omics Integrator

Metabolomics measures metabolites, the small-molecule end-products in biological systems. In fact, metabolites represent the downstream products resulting from interactions between genes, transcripts, and proteins, making metabolomics an ideal tool to assist with the integration of multi-omics data sets.

Metabolites mediate many of the inhibitory and activation mechanisms bearing on the genome, transcriptome and proteome. By contributing to epigenetic regulatory mechanisms as direct substrates, cofactors, or coenzymes and by acting as ligands for nuclear receptors, metabolites directly or indirectly affect gene expression.

Metabolomics, then, serves as a first-line phenotyping tool to track alterations in metabolite levels and map them to the appropriate biochemical pathways. By measuring the metabolite content—the metabolome—metabolomics links genotype to phenotype. This linkage supports the interpretation of other 'omics data that, when considered alone, may not translate in the observed phenotypes, resulting in misinterpretation. Through its synergism with other 'omics approaches, metabolomics sheds new light on gene-metabolite networks, mechanisms of diseases and drug actions. It also provides useful biomarkers, establishing new areas of research and clinical practice[12-27]. Multi-omics studies involving metabolomics are gaining interest because they are consistently among the most informative or most highly cited.

The phenotyping power of metabolomics makes it a pivotal tool for understanding an individual's phenotype. In offering a snapshot of an individual's current state of health, metabolomics provides actionable information that helps advance research and clinical decision-making. Consequently, in drug discovery and development, metabolomics has been given a meaningful role in these widely varied applications:

- Establishing molecular pathways leading to disease
- Drug target selection
- Determining mechanisms of action
- Pharmacokinetic and pharmacodynamic (PK-PD) modeling
- Dose selection
- Off-target effects
- Patient selection
- Disease stratification
- Safety assessment
- Efficacy assessment
- Functional genomics, transcriptomics, proteomics and microbiome research
- Biomarker discovery and development
- Bioprocess optimization

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