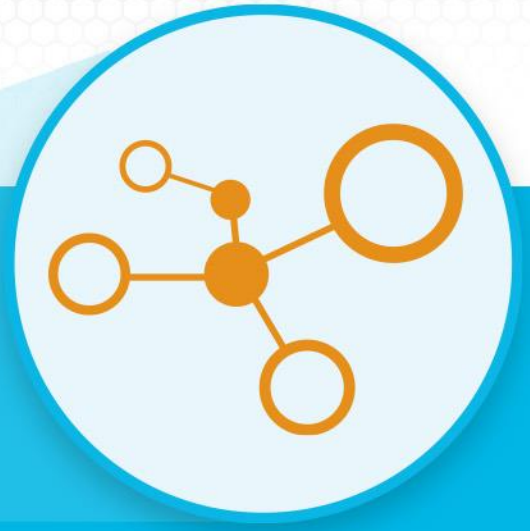
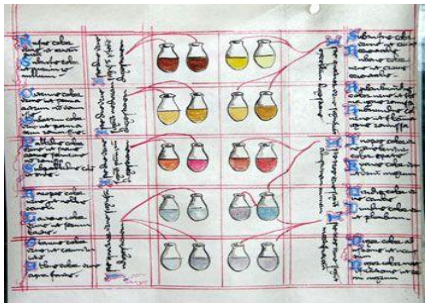


METABOLOMICS:
A Revolution in Omics

METABOLON®

A Heritage of Biochemistry

Biochemistry is a key pillar of biological & clinical understanding



From the earliest days of medicine, metabolites (low molecular weight biochemicals) have been an important clinical ally. Even in Medieval times, urine chemical properties guided physicians.

Fast-forward to 1908, and the English physician Archibold Garrod postulated that human disease was caused by missing or altered steps in the body's chemical pathways, establishing the concept of inborn errors in metabolism (IEMs). His work ultimately established a connection between heredity (genes), metabolic composition and the phenotype.

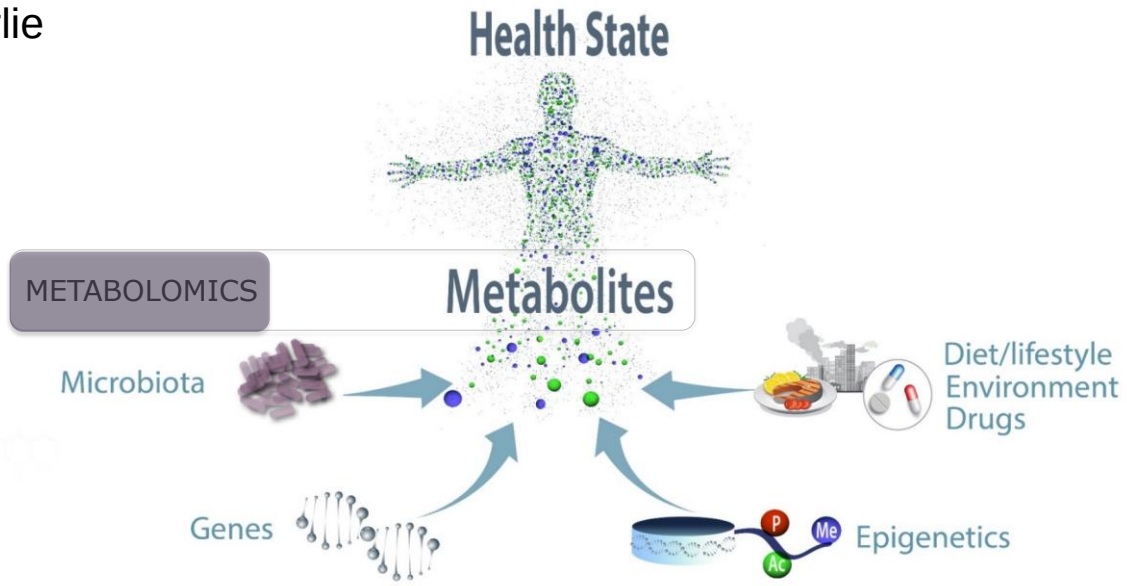
The connection of metabolism to the phenotype was further developed during the next 50 years during the "golden age of biochemistry." Great scientific minds such as Otto Heinrich Warburg, Gertrude Cori and Hans Adolf Krebs worked to understand how biochemistry impacts complex biological processes such as muscle metabolism, diabetes and cancer. Through their work, these scientists were able to create and populate the first metabolic pathway maps. Today, we use this framework to derive mechanistic understanding from the measurement of metabolites.

A Revolution in Omics

Metabolomics measures metabolites to provide a direct assessment of health and all of its influences.

We now understand that an individual's metabolic fingerprint reflects alterations in homeostasis that underlie health, disease and response. This fingerprint is also a key tool for understanding health influences that operate by changing metabolism, including:

- Genetics
- Microbiota
- Environment
- Diet
- Epigenetics
- Combined effects



Given metabolites' proximity to the phenotype, it is not surprising that many scientists increasingly view metabolomics as an important tool for unlocking the full potential of disease research, genomics and precision medicine.

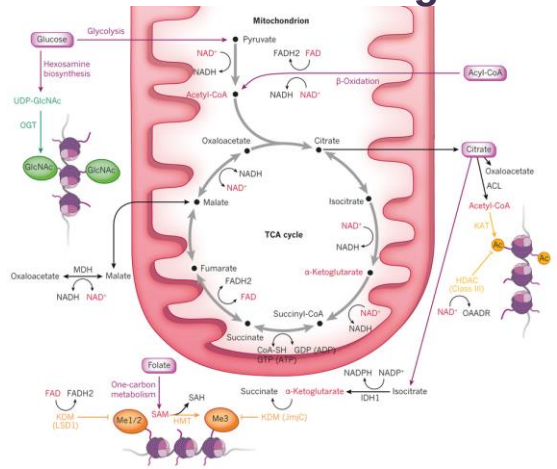
Metabolomics: A Biological Integrator

Measuring **metabolites** offers functional understanding of complex biological processes.

Although in the past, metabolism had a key role in defining diseases such as cancer and diabetes, the desire to unravel the genetic basis of disease has often overshadowed these successes.

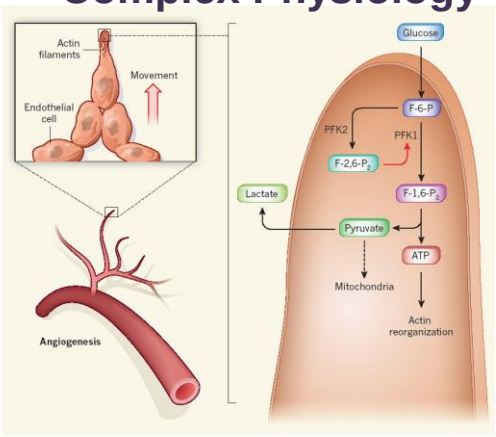
But, hundreds of studies conducted over the past decade have proven that metabolomics can provide tremendous insight into nearly all areas of contemporary biology, and it can serve as a key integrator for genomic, transcriptomic and proteomic data.

Gene and Protein Regulation



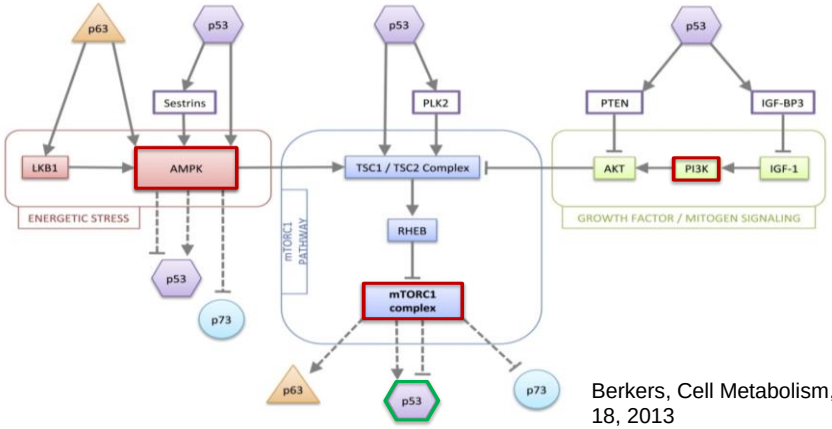
Gut & Verdin, Nature 502, 2013

Complex Physiology



Jang & Arany, Nature, 500, 2013
(original research in De Bock, Cell, 154, 2013)

Signaling, Cell Cycle & Growth



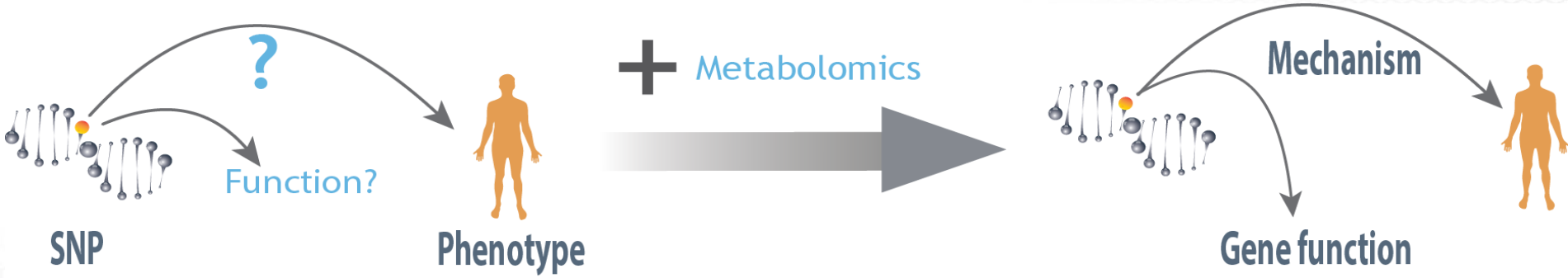
Berkers, Cell Metabolism, 18, 2013

Metabolomics & Genomics

Research has shown the metabolomics can detect important **genomic signals** and define what they mean.

The last decade of genomics research has provided many important discoveries. But, in many situations, genomics data is difficult to interpret. This is due to the polygenic nature of many traits, the frequency of mutations in non-coding regions, the tendency towards high allelic variation, and the elusive influences of the microbiome and epigenetics.

Metabolomics provides a framework for understanding this complexity. Genetic, transcriptional, signaling, and protein activity all converge to a focused set of **tightly regulated** metabolic pathways (~2500 metabolites). Tracking the signals in these pathways provides a powerful focus for genomic data streams, particularly those with vast associations.

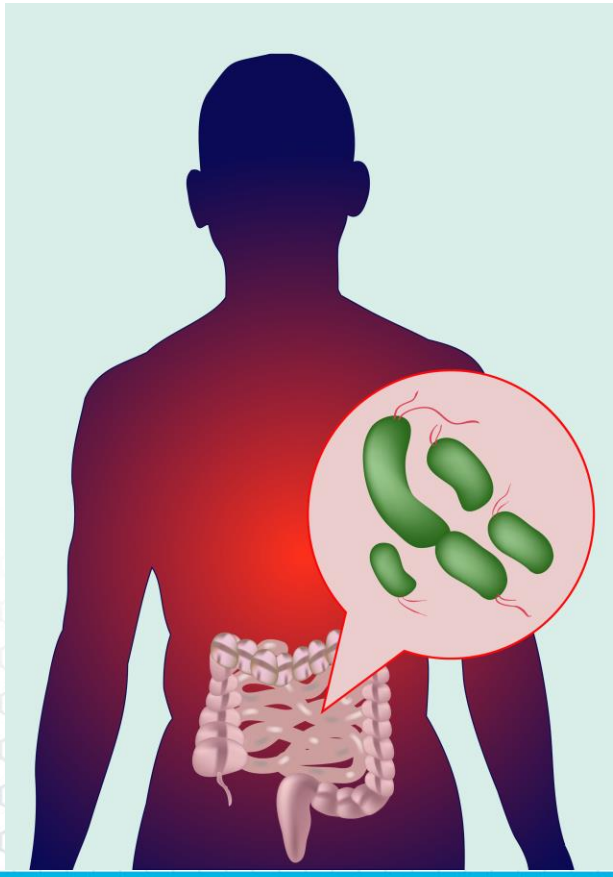


Metabolomics & The Microbiome

Metabolites are the language and currency of microbial communities throughout nature.

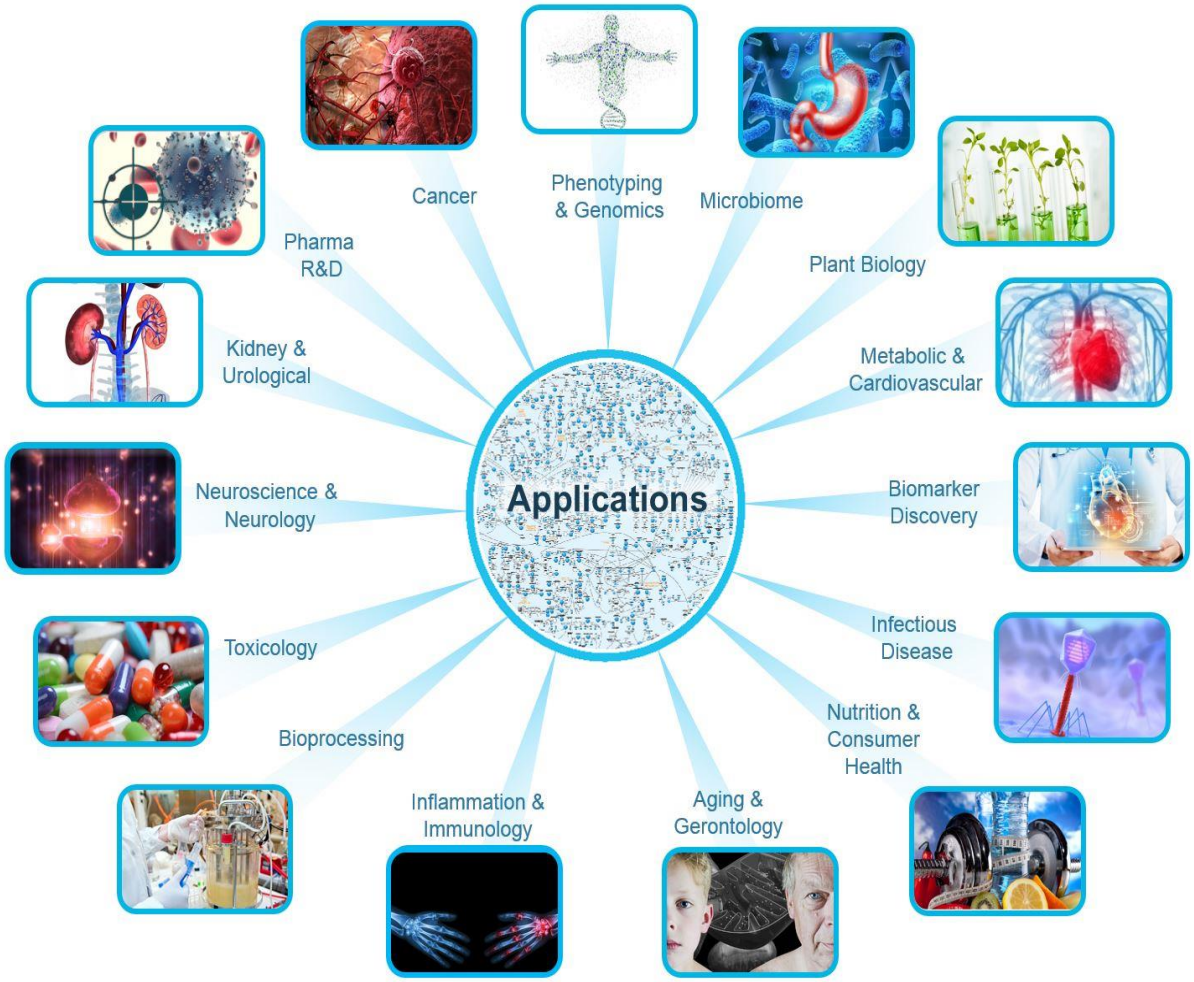
The collection of bacteria living in our gut and on our skin is referred to as microbiota or the microbiome, and its influence on our health is astonishing. While many recent publications associate different bacteria to health state, most do little to clarify how microbiota actually functionally influence health.

Metabolomics is capable of surveying host metabolism, xenobiotics, dietary metabolites and novel metabolites produced by the microbiota. Combining this data with traditional microbiome genetic research tools has resulted in discoveries about microbial impact on autism, CDIF, obesity, serotonin production and a host of digestive disorders.



A Diverse Array of Applications

Metabolomics can be applied to advance research across nearly every research area.



Not only does metabolomics allow you to extract value from other types of “omics data”, it can be used to discover biomarkers, elucidate disease taxonomy, and track treatment effects.

And, because the metabolite composition is central to every living organism, the in-depth biological insights metabolomics provides can advance research across a variety of areas.

Summary

Built upon the century-old science of biochemistry, **metabolomics** is a next-generation technology with extraordinary utility across the life sciences.

Researchers have successfully applied metabolomics in a variety of ways, including as a tool to:

- Better understand the phenotype
- Integrate environmental, microbiota, epigenetic and genetic data
- Discover dynamic biomarkers
- Identify disease condition and predispositions
- Elucidate the function of genes and mirobiota

To learn how metabolomics is advancing research in your field, visit www.metabolon.com/pubs, or access our illustrated Publication Index.

Sources

1. Wellen, K.E. & Thompson, C.B. A two-way street: reciprocal regulation of metabolism and signalling. Nat Rev Mol Cell Biol 13, 270-276 (2012).

2. McKnight, S.L. On getting there from here. Science 330, 1338-1339 (2010).

3. Yousri, N.A. et al. Long term conservation of human metabolic phenotypes and link to heritability. Metabolomics 10, 1005-1017 (2014).

4. Suhre, K. et al. Human metabolic individuality in biomedical and pharmaceutical research. Nature 477, 54-60 (2011).

5. Sassone-Corsi, P. Physiology. When metabolism and epigenetics converge. Science 339, 148-150 (2013).

6. Ried, J.S. et al. Novel genetic associations with serum level metabolites identified by phenotype set enrichment analyses. Hum Mol Genet (2014).

7. Rechavi, O. et al. Starvation-Induced Transgenerational Inheritance of Small RNAs in C. elegans. Cell 158, 277-287 (2014).

8. Kaelin, W.G., Jr. & McKnight, S.L. Influence of metabolism on epigenetics and disease. Cell 153, 56-69 (2013).

9. Garrod, A.E. The Inborn Factors of Disease. (Clarendon Press, Oxford, 1931).

10. Feero, W.G. Clinical application of whole-genome sequencing: proceed with care. JAMA 311, 1017-1019 (2014).

11. Dewey, F.E. et al. Clinical interpretation and implications of whole-genome sequencing. JAMA 311, 1035-1045 (2014).

12. DeBerardinis, R.J. & Thompson, C.B. Cellular metabolism and disease: what do metabolic outliers teach us? Cell 148, 1132-1144 (2012).

13. Beebe, K., Sampey, B., Watkins, S.M., Milburn, M. & Eckhart, A.D. Understanding the apothecaries within: the necessity of a systematic approach for defining the chemical output of the human microbiome. Clin Transl Sci 7, 74-81 (2014).