Metabolomics and Pulmonary and Critical Care Medicine

Over the past two decades, systems biology has made significant progress, with metabolomics emerging as the latest field. Metabolomics involves the systematic study of metabolites, which reflect the physiological state of a biological system. This field has been applied to various disciplines, including pulmonary and critical care medicine.

Metabolomics provides insights into altered metabolism under different conditions, offering a closer view of biological phenotypes than other omics sciences like genomics and proteomics. Its application in pulmonary and critical care medicine could improve the understanding of complex diseases, enhancing diagnostic and management strategies.

Metabolomic profiling is based on the idea that the metabolome reflects molecular processes driven by the genome and shaped by environmental influences. The metabolome provides insights into molecular determinants closely tied to phenotypes. Profiling can be targeted or untargeted: targeted metabolomics focuses on identifying specific metabolites of interest, while untargeted metabolomics seeks to identify all metabolites in a sample, although no single method covers all metabolites due to their varying properties.

There is increasing focus on integrating metabolomics with other omics technologies (genomics, proteomics, transcriptomics) for a more comprehensive understanding of biological systems. Metabolomics in biomedical research serves several key objectives: understanding disease mechanisms, identifying subtypes of diseases (endophenotyping), discovering new therapeutic targets, and identifying biomarkers. In observational epidemiology, biomarker identification aims to enable earlier or more accurate diagnoses, monitor disease progression or treatment response, and predict critical clinical events like exacerbation, worsening, or death.

A line of research in critical care suggests that metabolomics may help identify metabolically targeted therapies. In a study by Jennaro and colleagues, elevated acylcarnitine levels were linked to delayed extubation and prolonged organ support in septic shock patients. Another study found that higher baseline acylcarnitine levels were associated with worse 28-day survival outcomes in septic shock patients. A phase II clinical trial, RACE, investigated L-carnitine therapy for septic shock but did not find statistically significant survival improvement. However, a metabolomics analysis revealed that patients with high pre-treatment acylcarnitine levels had reduced 90-day mortality after therapy. This suggests that metabolomics could help target therapies for patients with severe metabolic dysfunction, warranting further study of L-carnitine in such patients. Metabolomics could also enrich clinical trials by selecting participants most likely to benefit from metabolic interventions.

Technological advances in metabolomics, such as microfluidic devices for single-cell metabolomics and spatial metabolomics (metabolic imaging), are uncovering detailed metabolic variations at the cellular level. These techniques, alongside innovations like live-cell microscopy, the Seahorse Analyser for real-time cellular metabolism, and stable isotope labelling, are improving the understanding of metabolic processes. In parallel, methodologic advances like the adaptation of gene analysis techniques for metabolomics and new statistical tools for causal inference are helping extract more biological insights from metabolomics data.

However, challenges persist. Standardising protocols across the field is critical to ensure comparability of results, as variability in sample collection, processing, and analysis poses significant obstacles. The curse of dimensionality in metabolomics, where high feature counts relative to sample sizes can lead to overfitting, requires careful data handling. Additionally, semiquantitative data, batch effects, and confounding clinical variables need better management. Moreover, integrating complex models with clinical practice remains difficult, and compartment-specific metabolism analysis in living subjects presents a key area for future research.

Efforts like the Consortium of Metabolomics Studies Network aim to address some of these challenges by promoting harmonisation, while the development of novel tools and techniques promises to expand metabolomics' utility in understanding diseases and therapeutic targets.

The future of metabolomics in pulmonary and critical care medicine is shifting towards hypothesis-driven studies that validate pathways and mechanisms identified by omics analyses. This evolution calls for molecular and functional validation of findings through mechanistic experiments. Collaborative, interdisciplinary research involving clinicians, epidemiologists, bench scientists, and statisticians is essential to tackle the complex questions in the field.

Metabolomics has already uncovered novel disease mechanisms and therapeutic opportunities, but challenges like standardisation and data complexity remain. However, ongoing technological advancements and a focus on collaborative research will propel the field forward. As metabolomics continues to develop, it holds promise for enhancing personalised medicine and improving clinical decision-making in pulmonary diseases.

Source: [American Journal of Respiratory Cell and Molecular Biology](#)

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Published on : Mon, 23 Sep 2024