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OPINION ARTICLE

## Advancing Physiology with Expanded Multi-Omics

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Advances in molecular biology in the second half of the 20th century shifted the view of human biology from one that was exclusively based on organ systems to one that emphasized molecules. In the last decade or so, the view of human biology has begun to shift again, this time towards an increasing recognition that humans are molecular systems in which molecules interact to take on emergent properties within the context of cells and organ systems. The increasing recognition that humans are molecular systems has led to the emergence of the new scientific discipline of molecular systems medicine<sup>1</sup>.

One of the pillars of molecular systems medicine is the integration of genome-scale molecular analysis, or omics, with physiology. The idea of using omics to advance physiology is not new. What is new is the unprecedented opportunity in this area provided by the substantial expansion of omics toolbox and knowledgebase in the last 10–15 years.

The first RNA-seq paper was published 15 years ago. Since then, deep sequencing-based methods have been developed for genome-scale analysis of chromatin conformation (e.g., Hi-C and Micro-C), chromatin accessibility (e.g., assay for transposase-accessible chromatin with sequencing, or ATAC-seq), histone binding (e.g., cleavage under targets and tagmenta-

tion, or CUT&Tag), and DNA methylation (e.g., reduced representation bisulfite sequencing, or RRBS). Methods for genome-scale analysis of RNA (including RNA modifications, e.g., methylated RNA immunoprecipitation sequencing, or MeRIP-seq), small noncoding RNA, proteins, and metabolites have also continued to advance. Many of these assays can now be performed in single cells or single nuclei (i.e., single cell omics) as illustrated by recent reports of pan-tissue single-cell transcriptome atlases in humans<sup>2</sup>. Furthermore, several omic assays may be integrated with spatial distribution of cells in native tissues (i.e., spatial omics).

The power of multi-omics is enabled and amplified by advances in bioinformatics and the integration with computational modeling. For example, a recent study used experimental analysis and mathematical modelling to quantify the effect of long-range chromatin interactions on transcriptional activities in single cells<sup>3</sup>. The analysis revealed a nonlinear relation between the transcriptional effect of an enhancer and the enhancer's contact probabilities with the promoter, which might arise from the transient nature of enhancer-promoter interactions coupled with slower promoter bursting dynamics in individual cells.

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Application of this ever-expanding multi-omics toolset has led to the generation of extensive multi-omics knowledgebases. For example, ENCODE (The Encyclopedia of DNA Elements), along with NIH Roadmap Epigenomics, have developed laboratory and data standards for an array of epigenomic assays and applied these assays to analyze several hundred cell lines and tissue specimens<sup>4</sup>. A core product of this effort is the Registry of candidate regulatory elements (cREs). The current version of the Registry contains 1310152 human cREs and 527001 mouse cREs. The GTEx (Genotype-Tissue Expression) program has established an extensive catalog of genetic variants associated with gene expression, which are called expression quantitative trait loci (eQTLs)<sup>5</sup>. The final dataset from GTEx (V8) contains DNA data from 838 postmortem donors and 17382 RNA-seq datasets across 54 tissue sites and two cell lines.

The rapid expansion of multi-omics toolbox and knowledgebase provides unprecedented opportunities to advance our understanding of physiology and pathophysiology as illustrated by an increasing number of studies. Gupta, et al., integrated genetic fine mapping, genome editing in stem cells, and gene expression and chromatin conformation analyses to identify and study a DNA sequence variation associated with five vascular diseases<sup>6</sup>. They found evidence for a long-range effect of rs9349379, a common single nucleotide polymorphism, on the expression of *EDN1* (encoding endothelin 1) located more than 600 kb away.

In a study of human kidney biopsy specimens, we developed an approach to perform small noncoding RNA deep sequencing analysis in several hundred glomerular and tubulointerstitial regions, each with a known pathological state<sup>7</sup>. The analysis generated pathologically resolved small RNA maps and revealed novel insights into kidney disease progression such as the presence of substantial molecular changes in patient glomeruli and tubulointerstitial regions that are histologically indistinguishable from kidney tissue regions in healthy people.

We recently performed an analysis of more than 26 000 single nucleotide polymorphisms in more than 1000 genomic loci that had been associated with human blood pressure with genome-wide significance<sup>8</sup>. The analysis integrated 14 data types, including eQTL data from GTEx and enhancer data from ENCODE, and incorporated a list of 251 genes that we called “blood pressure physiology genes” as they had been associated with blood pressure regulation in the literature. The analysis provided a wide range of new insights into how genes relevant to the physiology of blood pressure might be regulated at the genome level.

Physiology and multi-omics are mutually beneficial. Multi-omics provides global views of the molecular basis of physiology and can reveal unsuspected dimensions of regulatory mechanisms important for understanding physiology and linking physiology with genetics and disease. Physiology moves multi-omics from cataloging molecular parts and features and studying reductionist models to generating new insights into complex organ systems function under normal, stressed, or diseased conditions.

Studies that organically integrate multi-omics with physiology will be especially powerful. Such integration will require team science collaborations between forward-looking physiologists, genomicists, and computational biologists or, better yet, scientists who are cross-trained in physiology, multi-omics, and computational biology. The integration will benefit from precise experimental interventions made possible by advanced genome

editing technologies and the development of model systems that are highly relevant to human health and disease, including animal models and human induced pluripotent stem cell models. Just like the integration of physiology and multi-omics, molecular perturbation in informative model systems is a pillar of molecular systems medicine.

Molecular systems medicine is the future of medicine and biomedicine. One must understand humans as molecular systems to truly understand human health and disease. Advancing physiology with expanded multi-omics will help to put physiology at the center of the molecular systems medicine revolution and keep it there.

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## Conflicts of interest

Allen W. Cowley, Jr., holds the position of Executive Editor for Function and is blinded from reviewing or making decisions for the manuscript.

## Data availability

Not applicable.

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