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Commentary: Novel but nascent

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High-throughput technologies have led to the development of multi-omics, a stimulating new method of scientific investigation. This avenue affords the potential to elucidate the flow of information. It may be ideal for the study of post-operative atrial fibrillation (POAF), a vexing clinical problem the etiology of which has not been elucidated and for which efficacious prophylaxis has not yet been identified. In this edition of the *Journal*, Li and colleagues¹ use novel technologies to identify potential biomarkers as well as explanatory metabolic pathways for POAF. By combining proteomics (the large-scale experimental analysis of proteins and proteomes) and metabolomics (the comprehensive analysis of metabolites) with bioinformatics, the authors identified 8 metabolic pathways that were then integrated into 2 combined pathways: peroxisome proliferator-activated receptor α (PPAR α) and glutathione metabolism.

The exact mechanisms by which these pathways alter POAF susceptibility remain unknown, but as the authors discuss, these proposed pathways are concordant with previous animal and human studies. The several possibilities include altered beta-oxidation of fatty acids and electrical remodeling. These exciting findings have promise, not only for predictive capabilities, but also for the use of pharmaceuticals to more effectively prevent this problem.

The study findings must be interpreted with some caution, however, for several reasons. First, the study did not use any true statistical matching and could not fully control for other significant group differences or potential confounders. Second, multi-omics is a relatively new field still in development. Sample collection and processing techniques vary across laboratories; as others have noted, there are “comparatively few standard operating procedures commonly adopted across laboratories,”² with differences

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CENTRAL MESSAGE

Multi-omics and gene enrichment analysis hold possibilities for scientific discovery, but the field's nascency means that studies should be read with caution until tools and techniques reach maturity.

in the precision of measurement and degree of certainty in metabolite identification.^{3,4} This has implications for the replicability of the authors' findings. Bioinformatics is also an evolving field, with unanswered questions regarding the most reproducible and reliable tools and methods. Gene Ontology enrichment analysis, used to interpret the data generated by multi-omics, relies on both ontology and annotation. While ontology data is being generated at an astronomical rate, annotation databases frequently lag behind this rate of scientific discovery and also may exhibit annotation bias for a subset of genes.⁵⁻⁷ Finally, the choice of pathway database has recently been shown to potentially alter the results of statistical enrichment analysis.⁸ Consequently, future studies building on the work of Li and colleagues should remain cognizant of these challenging issues in multi-omics research.

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Commentary: Potential preventive peroxisomal policing of postoperative atrial fibrillation

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The authors¹ postulate that before coronary artery bypass grafting, pre-existing circulating proteins and metabolites predict the vulnerability of some patients to postoperative atrial fibrillation (POAF). Multiple studies have reported that the presence of POAF is associated with coincident additional postoperative trouble. Therefore, the identification of preoperative markers predicting POAF should both warn clinicians of postoperative challenges but perhaps more importantly suggest a potential target for preoperative pharmacologic preparation of the vulnerable patient.

During the study period, the authors performed 549 coronary artery bypass grafting procedures, of whom 391 patients met the study's inclusion criteria. By matching "the most relevant clinical variables of age, sex and ethnicity..." and including the additional characteristics of body mass index, smoking, hypertension, previous myocardial infarction, left ventricular ejection fraction, and bypass time, their goal was to eliminate, to the extent possible, clinical factors that might provoke POAF other than the putatively culprit circulating proteins and metabolites that the authors were sampling before surgery.

In this analysis, the preoperative dysregulation of peroxisome proliferator-activated receptor (PPAR)-alpha and glutathione pathways bubbled up as predisposing to POAF.

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CENTRAL MESSAGE

Dysfunctional peroxisomal anti-oxidant pathways appear to leave patients vulnerable to post-CABG atrial fibrillation.

This finding sort of makes intuitive sense. The circulating PPAR-alpha proteins and glutathione metabolites should reflect 2 of a patient's major strategies of confronting systemic toxic oxygen metabolites. Many, if not most, patients with coronary artery disease experience frequent microinfarctions. When these patients harbor disabled anti-oxidant policing systems, they should be vulnerable to the heterogeneous patterns of microfibrosis that appear to be essential to the micro-reentry characteristic of POAF.

A peroxisome is a cell membrane organelle that uses oxygen to produce hydrogen peroxide, which is its signaling molecule and from which it derives its name. Peroxisomes also contain a team of antioxidant enzymes that detoxify blood-borne damaging substances. PPARs are nuclear receptor proteins that serve as transcription factors by binding to the promoter region of target genes. PPARs are present in almost all eukaryotic cells, where they both enhance and/or depress gene activity. Glutathione teams up with activated peroxisomes to scavenge toxic oxygen metabolites.