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Application of Multiple Omics to Understand Postoperative Delirium Pathophysiology in Humans

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Abstract
Delirium, an acute change in cognition, is common, morbid, and costly, particularly among hospitalized older adults. Despite growing knowledge of its epidemiology, far less is known about delirium pathophysiology. Initial work understanding delirium pathogenesis has focused on assaying single or a limited subset of molecules or genetic loci. Recent technological advances at the forefront of biomarker and drug target discovery have facilitated application of multiple "omics" approaches aimed to provide a more complete understanding of complex disease processes such as delirium. At its basic level, "omics" involves comparison of genes (genomics, epigenomics), transcripts (transcriptomics), proteins (proteomics), metabolites (metabolomics), or lipids (lipidomics) in biological fluids or tissues obtained from patients who have a certain condition (i.e., delirium) and those who do not. Multi-omics analyses of these various types of molecules combined with machine learning and systems biology enable the discovery of biomarkers, biological pathways, and predictors of delirium, thus elucidating its pathophysiology. This review provides an overview of the most recent omics techniques, their current impact on identifying delirium biomarkers, and future potential in enhancing our understanding of delirium pathogenesis. We summarize challenges in identification of specific biomarkers of delirium and, more importantly, in discovering the mechanisms underlying delirium pathophysiology. Based on mounting evidence, we highlight a heightened inflammatory response as one common pathway in delirium risk and progression, and we suggest other promising biological mechanisms that have recently emerged. Advanced multiple omics approaches coupled with bioinformatics methodologies have great promise to yield important discoveries that will advance delirium research.

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Introduction

Delirium is an acute change in cognition characterized by inattention, disorganized thinking, altered levels of consciousness, and a fluctuating course [1, 2]. It affects approximately 1/3 of hospitalized older adults, up to 3/4 of all patients admitted to the intensive care unit (ICU), and 15–53% of major surgery in older adults [1, 2]. Delirium has been associated with poor outcomes, including greater complications, prolonged hospital stay, higher discharge rates to nursing homes, short- and long-term cognitive and functional decline, and increased mortality [2–11]. Moreover, the annual attributable healthcare costs of delirium have been estimated to range upwards of $164 billion/year [12], with $32.9 billion occurring after surgery [13]. Yet, delirium remains a purely clinical diagnosis with no biomarkers to guide its diagnosis or management. Understanding delirium pathophysiology and underlying molecular mechanisms is paramount to identification of at-risk patients and for development of preventive and treatment strategies.

Advances in technologies, especially multiple "omics" approaches, present the opportunity to efficiently identify biological pathways involved in delirium pathogenesis. This review summarizes challenges specific to understanding delirium pathophysiology, current biomarker discoveries in delirium, omics technologies, and their current and future applications in identifying biomarkers of delirium pathophysiology.

Challenges in Conducting Research in Delirium

Although applying omics approaches to understand delirium pathophysiology presents an exciting area for future advances, several challenges remain, which are shared with other multifactorial syndromes in older adults, such as frailty. The foremost challenge is defining the phenotype and determining who has and does not have delirium. There are a variety of delirium measures, the foremost being the Diagnostic and Statistical Manual of Psychiatric Disorders (DSM-5) and the Confusion Assessment Method (CAM) [14, 15]. While DSM-5 is the "gold standard" for delirium diagnosis, its use is primarily limited to clinicians. The CAM is used more frequently in research, where its diagnostic features are assessed as part of a structured assessment performed by trained research personnel. In this context, the CAM has been shown to have high sensitivity (94–100%) and specificity (90–95%) [16]. Delirium diagnostic and severity measures have been reviewed elsewhere [16–18]. Once delirium status has been determined, additional barriers in identifying delirium biomarkers include (1) disparities in definition of a biomarker, (2) proper acquisition of biospecimens, (3) appropriate identification of suitable control samples, and (4) multiple, possibly divergent, triggers of delirium resulting in different delirium subtypes.

In this paper, we adopt the biomarker definition of the NIH working group panel: a "characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes (as in our case), or pharmacological responses to a therapeutic intervention [19]." A "good" biomarker could then be identified based on three criteria: accuracy, reliability, and ability to inform underlying biological processes.

In general, an "ideal" disease or condition for discovering specific biomarkers would be static, homogeneous, and exhibit a pure milieu. In contrast, the dynamic, heterogeneous, and complicated milieu of delirium has made identifying biomarkers difficult. Given its acute onset and fluctuating course, it is critical to assess for delirium daily, at minimum, over the course of a hospital stay. Delirium assessment can be difficult given the wide spectrum of psychomotor phenotypes that characterize delirium (ranging from wildly agitated to nearly comatose, i.e., hyperactive to hypoactive delirium), as well as the range of delirium severity (from mild to very severe, including patients with subsyndromal delirium who meet some, though not all, criteria for delirium).

The challenges with obtaining multiple delirium assessments are further compounded by prioritizing collection of biospecimens (e.g., blood, cerebrospinal fluid [CSF]) to align with the time of the delirium assessment. Based on the many logistic obstacles, several unanswered questions remain: are all delirium subtypes "the same" (i.e., have the same pathoetiologic origins and mechanisms); how do comorbidities, medical treatments, and medication use (all common in older patients, in whom delirium most commonly occurs) affect internal milieu and our ability to disentangle a biomarker of delirium from other conditions and circumstances?

Although these challenges are substantial, the field has begun to address these obstacles via a multi-prong approach. Actions to consider include (1) assessing delirium over multiple time points (daily, if possible), (2) collecting biospecimens for biomarker detection at several time points linked to delirium assessments, (3) carefully characterizing clinical phenotypes (e.g., identifying a non-delirium control group excluding patients with subsyndromal delirium), and (4) focusing on settings that

Table 1. Review of literature on delirium biomarkers and pathophysiology in human studies

Pathophysiology model[a]	Representative publications[b]	Summary of evidence	Limitations/unknowns
Cholinergic deficiency, anti-cholinergic drug effects	[23, 24], and many earlier papers	Reduced cholinergic transmission in CNS may be associated with delirium. Serum anticholinergic activity findings not reproducible in later studies	Serum anticholinergic assay not a useful biomarker for overall anticholinergic burden
Neuronal injury, reduced neuroprotection	[25–35]	Elevated levels of neuronal injury markers S100β, neuronal specific enolase measured in plasma, CSF in delirium; reduced neuroprotective proteins (IGF-1) may be risk factor for delirium	Inconsistent results across studies. Levels of neuronal injury markers variably correlated in plasma and CSF.
Inflammation and neuroinflammation	[27, 36–59]	Elevated levels of cytokines (IL-1β, IL-2, IL-6, IL-8, TNF-α) and CRP before and during delirium. Inflammation may interact with tau pathology	Variable cytokines identified in different studies
Hypothalamic-pituitary axis, chronic stress	[27, 52, 60–62]	Altered HPA with elevated cortisol associated with delirium	Studies of HPA axis methodologically challenging
Impaired blood-brain barrier integrity	[63, 64]	Preliminary evidence of impaired BBB integrity in delirium	BBB hard to measure; no established biomarkers

CNS, central nervous system; CRP, C-reactive protein; CSF, cerebrospinal fluid; BBB, blood-brain barrier; HPA, hypothalamic-pituitary axis; IGF-1, insulin-like growth factor 1; IL, interleukin; S100β, S100 calicium-binding protein B; TNF-α, tumor necrosis factor alpha. [a]Models are not mutually exclusive-they may work in synergy. [b]Several references map to more than one model.

reduce heterogeneity (e.g., patients with comparable elective surgical interventions, which apply a similar physical insult) and enable assessment of delirium and collection of biospecimens before, during, and after an episode of delirium. With regard to time course, three classes of markers can be defined as (1) risk markers (differentially expressed prior to delirium onset), (2) disease markers (differentially expressed at delirium onset and reversed at delirium resolution), (3) end-product markers or markers of damage (differentially expressed after delirium in proportion to the resulting long-term "damage"), and (4) combinations of the above patterns [20, 21].

In addition to the approaches outlined above, during data analysis potential confounding factors can be ameliorated by: (1) excluding patients with certain comorbidities (either in the study design or analytic stage), (2) using a matched case-control study design with delirium cases and non-delirium controls matched on predetermined confounding variables [22], or (3) statistical adjustment for confounders. While all such approaches may not be used in a single study, careful consideration of these challenges will greatly contribute to expanding our knowledge of delirium pathophysiology. Lastly, key considerations to improve the scientific rigor of biomarker studies in general, and delirium specifically, are (1) having adequate sample size, (2) performing independent validation, and (3) considering generalizability of findings across different populations.

Review of Current Biomarker Discoveries in Delirium

Until quite recently, most studies of delirium pathophysiology have focused on pre-selected candidate proteins associated with inflammation, neuronal protection or injury, and stress response. Despite the heterogeneous nature of these studies (involving different patient populations [e.g., medical, surgery, ICU], using different delirium-based measures [e.g., prevalent delirium, incident delirium, or duration of delirium] [23–66]), a common theme surrounding the immune response in delirium has emerged: (1) elevated levels of molecules indicative of stress response (e.g., acute phase reactants in serum and plasma, such as C-reactive protein (CRP) and cortisol) [67, 68]; (2) elevated levels of pro-inflammatory cytokines (e.g., IL-6) [69]; (3) elevated markers of neuronal injury in blood and CSF (e.g., S100β and NfL) [70–73]; and (4) lower serum levels of neuroprotective proteins (e.g., insulin-like growth factor 1 [IGF-1]) [74].

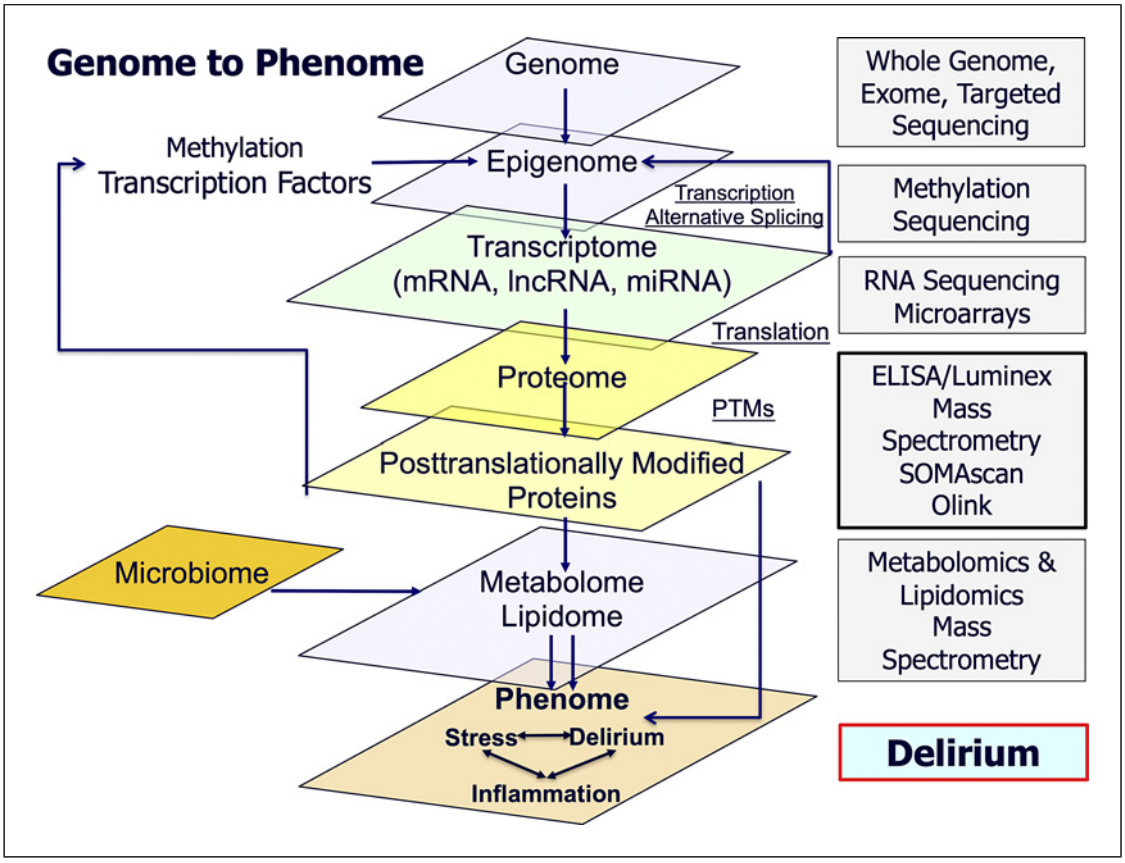

Fig. 1. Schematic summarizing different omics components and technologies. This diagram presents the different measurable omes in a linear progression from top to bottom in the format of the central dogma of molecular biology: gene -> transcript -> protein -> metabolites/lipids. The right side of the figure lists the primary technology that is generally applied to measure its corresponding ome. There is cross-talk between the molecules in the different omes. One example of this cross-talk is illustrated here: post-translational modification by methylases results in epigenetic changes in the DNA which influence the transcription of genes. Other examples not represented here also exist (e.g., studies of the microbiome). lncRNA, long non-coding ribonucleic acid; miRNA, microRNA; mRNA, messenger RNA.

From these initial findings, differences in inflammation, a common pathway in aging-related conditions such as frailty, cancer, and cardiovascular disease, have emerged as one pathway in delirium pathophysiology [44, 75–79]. Certain individuals may be predisposed to an exaggerated inflammatory response (via chronic stress or a pre-inflammatory state) in the setting of acute physiological stress, such as major surgery or infection [75, 80]. These circumstances may in turn lead to increased permeability of the blood-brain barrier (BBB), with inflammatory cytokines in the blood activating microglia in the central nervous system (CNS), the brain's equivalent to peripheral monocytes. These microglia may induce neuroinflammation, which can temporarily impair neuronal function and, if sustained, lead to neuronal injury or death. This model provides an intriguing and broadly encompassing link between predisposing risk factors, acute precipitating factors, and the long-term adverse sequelae associated with delirium [75, 81]. Current published data are consistent with this model of inflammation; however, given its complexity, it is unlikely that this single mechanistic pathway can be implicated in all cases of delirium.

In this context, Table 1 summarizes the current literature on delirium biomarkers and pathophysiology from human studies. The majority of these delirium biomarker studies have been summarized and included in a recently published meta-analysis, which highlights several candidate delirium markers also identified by omics approaches and reports on the role of inflammatory pathways in delirium [82]. Of note, most of the cited studies in Table 1 are based on targeted measurement of one, or at most a few, candidate biomarkers. Although hypothesis-driven targeted studies have provided insights into delirium

pathogenesis and identified several candidate biomarkers, omics offers an expanded and powerful, hypothesis-generating, unbiased approach that has been successfully applied to many other aging-related diseases (e.g., Alzheimer's disease, Parkinson's disease). Comprehensive, unbiased omics approaches, importantly followed by independent validation, will facilitate discovery of biomarker panels to improve the prediction of delirium and elucidate delirium pathophysiology.

Overview of Omics Technologies

Omics can be defined as "collective characterization and quantification of pools of biological molecules that translate into the structure, function, and dynamics of an organism" [83]. Each "omics" approach characterizes its respective "ome"; for instance, proteomics characterizes the proteome, the protein milieu of a given cell, tissue, fluid, or individual [82]. Figure 1 summarizes various omics approaches, including genes (genomics), epigenetic factors (epigenomics), RNAs (transcriptomics), proteins (proteomics), lipids (lipidomics), and metabolites (metabolomics). "Omics" technologies intend to interrogate the entire repertoire of molecules (genes, ribonucleic acids (RNAs), proteins, metabolites, lipids), their modifications, and their interactions, thus capturing the complexity of human health and disease. Omics can be performed on any biological tissue and fluid, and a general principle is that the fluid or tissue most proximal (i.e., closely aligned, either anatomically or functionally) to the condition of interest is likely to harbor the most specific biomarkers [84]. Taken together, multi-omics is the concurrent and integrated analysis of multiple "omes" [85, 86].

The different "omes" can be divided technologically into two major approaches: (1) technologies for genomics and transcriptomics, and (2) technologies for proteomics, metabolomics, and lipidomics. Next-generation sequencing (NGS) platforms and microarrays are the key modalities driving genomics and transcriptomics research. Up to now, mass spectrometry (MS) and, to a lesser extent, nuclear magnetic resonance (NMR) have dominated proteomics, metabolomics, and lipidomics but have yet to reach the same level of sensitivity as NGS. Recently, several innovative proteomics platforms (described in the section on "Unbiased Mass Spectrometric Proteomics") have revolutionized and accelerated progress in the field.

Genomics and Transcriptomics: Genomics focuses on analysis of genes for deoxyribonucleic acid (DNA) sequence changes including single nucleotide polymorphisms (SNPs; that are key for genome-wide association studies (GWAS)), that lead to mutations, deletions, insertions, fusions, translocations, rearrangements, and copy number variations (CNV). Another emphasis is on epigenetic changes of DNA such as methylation, which has a significant effect on regulation of gene expression [86, 87]. Similarly, transcriptomics focuses on RNA expression differences, alternative splice variants, as well as RNA modifications. Transcriptomics can analyze protein-coding RNAs (e.g., messenger RNAs [mRNAs]) as well as non-coding RNAs (e.g., including microRNAs [miRNAs], long-noncoding RNAs [lncRNAs], and small nucleolar RNAs [snoRNAs]) involved in regulation of gene expression. Moreover, recent evidence highlights the potential importance of the repeatome in human disease, which studies repetitive DNA sequences comprising over half of the genome [88, 89]. Finally, the assay for transposase-accessible chromatin with sequencing (ATAC-Seq), which determines chromatin accessibility within the genome by sequencing regions of open chromatin, could be used to determine how the role of chromatin packaging and related factors affects gene expression [90].

Proteomics, Metabolomics, and Lipidomics: In contrast to DNA and RNA, the study of proteomics, metabolomics, and lipidomics has not yet reached the same level of understanding due to the lack of comprehensive and reliable measurement techniques. Proteomics explores expression level alterations of proteins, protein-protein interactions, as well as more than 200 types of post-translational modifications (PTM) such as phosphorylation, glycosylation, acetylation, and proteolytic degradation. None of the current technologies can measure the entirety of this large protein repertoire; however, recent advances in affinity proteomics such as aptamer-based SomaScan [91–93] and antibody-based Olink [94–97] have greatly increased the number of proteins that can be measured. Moreover, several next-generation proteomics platforms with single-molecule sensitivity are under development to measure all proteoforms [97–101]. Equally complex is the metabolome and lipidome, each of which includes hundreds of thousands of different molecules, of which existing technologies only have the capacity to explore a subset.

While omics technologies provide new opportunities for discovery of novel biomarkers with the potential for future inclusion into predictive and risk stratification models, we acknowledge that clinical implementation of biomarkers identified from omics-based approaches will likely require use of well-established and readily available diagnostic technologies already approved by the Food

and Drug Administration (FDA) and other regulatory agencies (e.g., enzyme-linked immunosorbent assays [ELISAs]). Omics discovery technologies represent the first step in the development of future diagnostic tests that may be applicable for selecting surgical patients at highest risk for postoperative delirium. Various multiplex immunoassay platforms exist that have a rapid turnaround time, including the Ella multiplex platform from BioTechne that measures up to 8 proteins in 90 min. Ultimately, we envision that rapid, low-cost point-of-care (POC) tests will be developed that determine the risk of postoperative delirium prior to surgery at home, in outpatient practice, or at the bedside within less than 30 min. The recent development and implementation of numerous rapid POC tests for SARS-CoV-2 has accelerated the technological development of many novel POC devices. Such preoperative, low-cost delirium risk stratification tests have the potential to transform surgical patient stratification and allow for enrollment of high-risk participants into intervention trials to prevent or ameliorate delirium (e.g., the ongoing delirium prevention PANDORA trial has some indication of efficacy [102]).

Bioinformatics, Systems Biology Analyses: Once a set of molecules is measured using the techniques described above, bioinformatics is used to identify the molecules most differentially expressed (altered) in the disease or condition of interest and to combine them into a predictive model. Based on these differentially expressed molecules, systems biology analysis identifies the involved pathophysiological pathways, regulators, and interactions. Each omics field utilizes different, and partially overlapping, bioinformatics and statistical tools as each measurement technology creates different data types. A brief overview of bioinformatics and systems biology analysis is provided below.

Bioinformatics uses inferential statistics to identify statistically significant differentially expressed molecules, adjust for multiple comparisons (using approaches such as Benjamini-Hochberg [103]), and consider the magnitude of alteration (fold change). These differentially expressed molecules are then used to develop predictive classifiers, using standard techniques such as logistic regression, or a variety of newer machine learning (ML) methods such as support vector machine (SVM), random forest, elastic net, Lasso, neural networks, gradient boosting (GBM), and K-nearest neighbors (KNN) [104–106]. Newer ML approaches are able to model complex, nonlinear relationships between the molecules and disease outcome [107]. Multi-marker models generally have higher predictive accuracy than single marker models, particularly for complex, heterogeneous syndromes like delirium.

Based on the identified differentially expressed molecules ("biomarkers"), systems biology analysis combines information from multiple databases with an inference engine to create models of disease or biological processes [85, 108]. Gene ontology (GO) tools connect genes or proteins to biological processes, molecular functions, and cellular components. More comprehensive systems biology tools (e.g., Ingenuity Pathway Analysis (IPA), Cytoscape, Advaita, Network Analyst, Metacore) offer much more in-depth analysis that identifies functional categories, interactive networks, upstream regulators, disease and biological functions, canonical pathways, and regulator effect analyses of differentially expressed biomarkers [107, 109, 110] by linking biomarkers to well-annotated public genome, transcriptome and proteome databases. For instance, a set of proteins associated with delirium can be entered into such a software tool, and it will show the potential protein interrelationships and plausible biological pathways involved. Thus, combined bioinformatics and systems biology analyses yield a set of predictive biomarkers and a deeper understanding of the pathophysiological mechanisms underlying disease states that may also enable the identification of key drivers of a disease and potential therapeutic targets.

Application of Genomics, Proteomics, Metabolomics, and Lipidomics to Delirium Biomarker Discovery and Development of New Insights into Delirium Pathophysiology

Genomics and Transcriptomics

Initial GWAS of delirium have begun to shed light on genetic loci linked to predisposition for delirium and biological mechanisms contributing to delirium development [111, 112]. Although several candidate genotyping studies have indicated an association between Apolipoprotein E (APOE) and, to a lesser extent, solute carrier (SLC) family 6 member A3 (SLC6A3) and glutamate ionotropic receptor NMDA type subunit 3A (GRIN3A) loci, to delirium [113–116], only a single published GWAS of delirium using electronic health record data has been conducted [111]. In this GWAS of 421 delirium cases and 5,614 controls, one locus on chromosome 2, involving SLC9A4, SLC9A2, interleukin (IL) 1 receptor like 1 (IL1RL1), IL18R1, and IL-18 receptor accessory protein (IL18RAP), surpassed the genome-wide significance threshold for association. If

Table 2. Summary of literature on the proteomics of delirium

Proteomics method	Study population	Matching variables	Findings	Reference
2D-DIGE (CSF)	Hip fracture surgery – from double blind randomized control study (derivation cohort: 53 patients [36% delirium], validation cohort: 52 patients [21% delirium])	Not applicable	10 differently expressed proteins[a]	[45]
iTRAQ MALDI-TOF/TOF MS (CSF)	Two pooled cohorts: (1) Geriatric Medicine Unit: 12 mild or moderate/severe delirium, 8 mild AD and 9 moderate AD (2) Hip fracture surgery: 5 mild/moderate delirium, 4 SSD, and 4 no delirium	Not described	16 proteins differentially expressed in 8/17 delirium cases (9 of these proteins exhibiting the same direction of expression)[b]	[65]
iTRAQ MALDI-TOF/TOF MS (plasma)	Major elective surgery (iTRAQ [discovery]: 12 delirium, 12 no delirium; ELISA [validation]: 75 delirium, 75 no delirium)	Age, sex, surgery type, preoperative cognition vascular comorbidity, APOE ε4 carrier status	CRP, AZGP1, SERPINA3	[66]
iTRAQ MALDI-TOF/TOF MS (plasma)	Major elective surgery (iTRAQ [discovery]: 5 delirium, 5 no delirium; ELISA [validation]: 75 delirium, 75 no delirium)	Age, sex, surgery type, preoperative cognition vascular comorbidity, APOE ε4 carrier status	Several differently expressed proteins; CRP identified as strongest protein from iTRAQ and validated with ELISA	[67]
SELDI-TOF MS (urine)	ICU (10 hyperactive delirium, 10 no delirium)	Age, sex, ICU length of stay, APACHE-II, CRP, aorta clamp time, Euro score, creatinine level, MDRD-GFR, surgery type	No detected differences in protein profiles	[121]
SELDI-TOF MS (plasma and serum)	Hip fracture surgery (test cohort: 8 delirium, 8 no delirium; validation cohort: 8 delirium, 8 no delirium)	Sex, anesthesia type, postoperative day with delirium	Protein peaks at 7.97, 15.9, and 16.0 kDa (presumed to correspond to hemoglobin-β)	[122]
SomaScan (plasma)	Major elective surgery (SomaScan [discovery: 18 delirium, 18 no delirium; Ella [validation]: 560 patients, 24% delirium)	Age, sex, surgery type, preoperative cognition vascular comorbidity, APOE ε4 carrier status	CHI3L1	[123]
SomaScan (serum)	Cardiac surgery with cardiopulmonary bypass (8 delirium, 16 non-delirium)	Age, sex, BMI, cardiopulmonary bypass time, PROMIS physical T-scores	IL-6, TIMP-1, PDE3A	[124]
PEA (serum and CSF)	Thoracic aorta surgery (serum: 7 delirium, 14 non-delirium; CSF: 6 delirium, 13 non-delirium)	None listed	Serum: TR4, EXH2, CHI3L1, IL6, SFRP2, PMP2, RTN4R CSF: KLF6	[125]
Olink (serum)	Cardiac surgery with cardiopulmonary bypass (12 delirium, 12 non-delirium)	Age and sex	IL-6, FGF-21, FGF-23, MCP-3	[126]
LC-MS/MS (CSF)	Hip fracture patients (LC-MS/MS [discovery] and PRM [validation] in 10 delirium, 30 non-delirium)	Age and MMSE	VSTM2B and FA5	[127]
LC-MS/MS (plasma)	Cardiac surgery with cardiopulmonary bypass (7 delirium, 8 non-delirium)	Age, sex, comorbidity	CRP, amyloid A-1, cathepsin-B	[128]

2D-DIGE, two-dimensional fluorescence differential gel electrophoresis; AD, Alzheimer's disease; APOE, apolipoprotein E; APACHE-II, Acute Physiology and Chronic Health Evaluation-II; AZGP1, zinc alpha-2 glycoprotein; CHI3L1 (or YKL-40), chitinase 3-like protein 1; CRP, C-reactive protein; CSF, cerebrospinal fluid; Ella, Ella System SinglePlex cartridge (ProteinSimple San Jose, CA); ELISA, enzyme linked immunosorbent assay; FA5, coagulation factor V; FGF, fibroblast growth factor; ICU, intensive care unit; IL-6, interleukin-6; iTRAQ, quantitative isobaric tags for relative and absolute quantitation; LC-MS, liquid chromatography-mass spectrometry; MALDI-TOF/TOF MS, matrix-assisted laser desorption ionization of time-of-flight tandem mass spectrometry. MALDI-TOF/TOF has the advantage of analyzing multiple peptides of proteins and fragmenting these peptides, which allows the derivation of actual amino acid sequences for each of these peptides that can then be matched to existing peptide and protein databases. Based on this fragmentation pattern, candidate parent proteins can be identified based on a probability score linked to known protein patterns. MALDI-TOF/TOF has the ability to analyze several protein peptides that can be subsequently matched to existing peptide and protein databases. MCP, membrane cofactor protein; MDRD-GFR, modification of diet in renal disease – glomerular filtration rate; MMSE; Mini-Mental State Examination; PDE3A, cGMP-inhibited 3′, 5′-cyclic phosphodiesterase 3A; PEA, Proximity Extension Assay; PRM, parallel reaction monitoring; SERPINA3, alpha 1 antichymotrypsin; SELDI-TOF MS, surface-enhanced laser desorption/ionization time-of-flight mass spectrometry; SELFI-TOF only reveals protein peaks and mass of proteins (i.e., no specific proteins can be identified); SSD, subsyndromal delirium; TIMP1, tissue inhibitor metalloproteinases-1; VSTM2B, V-set and transmembrane domain-containing protein 2B. [a]These 10 proteins included complement C3, contactin-1 (CNTN1), neural cell adhesion molecule (NCAM2), fibulin-1 (FBLN1), fibrinogen α-chain, β-chain, and λ-chain, zinc alpha-2 gylcoprotein (AZGP1), and hemopexin (HPX). [b]These 9 proteins included orosomucoid 1 (ORM1), transferrin (TF), alpha-1-antichymotrypsin (SERPINA3), complement C3, chromogranin A (CHGA), chromogranin (CHGB), Apolipoprotein E (APOE), clusterin (CLU), and apolipoprotein A-1 (APOA1).

confirmed in additional large cohort studies, these results suggest the possibility that polymorphisms in interleukin receptors, which play a key role in inflammatory processes, may increase delirium risk. A recent candidate gene association study of 745 surgery patients of the European BioCog project identified three genetic variants in the cholinergic CHRM2 and CHRM4 genes associated significantly with postoperative delirium, which may link delirium to acetylcholine release and synaptic plasticity [117]; however, GWAS analysis of the same samples did not identify any variants with genome-wide significance.

While GWAS is powerful for large cohort studies, it only captures static, inherited traits. To address the dynamic changes of molecules associated with delirium development, other genomic tools (epigenomics, transcriptomics) are required. Recent studies on the epigenetics of delirium further confirm the role of inflammation in delirium pathophysiology. Enrichment analysis based on the top 1,000 "hits" of genome-wide DNA methylation CpG sites identified pathways related to delirium from different biospecimens: regulation of glial cell differentiation from brain tissue, immune function from blood, and circadian rhythm from saliva and buccal samples [118]. Separately, findings from genome-wide methylation studies have linked decreased CpG methylation in IL-6 and tumor necrosis factor alpha (TNFα) loci in the brain and blood to aging and in the blood to postoperative delirium after neurosurgery [119]. Taken together, these two bodies of epigenetic findings suggest that reduced methylation of cytokine genes, which upregulates their expression, may impact delirium pathogenesis.

Transcriptome analysis of delirium is limited to a single recent RNA sequencing study of mRNA expression in peripheral blood mononuclear cells (PBMCs) in 41 patients [120]: 8 urinary tract infection (UTI)-positive patients with delirium and 11 without delirium, and 22 UTI-negative patients with delirium and 10 without delirium. The main result was an enrichment of the interferon signaling pathway in delirious patients with UTI and 123 genes separating delirium from non-delirium cases, irrespective of UTI. Despite these promising findings, small sample size precludes major conclusions about delirium-specific gene expression in PBMCs.

Unbiased Mass Spectrometric Proteomics

In contrast to multi-loci genomic and transcriptomic studies of delirium, several untargeted proteomics studies of delirium applying mass spectrometry (MS) to cerebrospinal fluid (CSF), blood, or urine are now published. Unfortunately, mass spectrometry has limited dynamic range (ability to detect proteins across a wide range of concentrations), thus limiting its ability to discover delirium biomarkers. There is a broader literature on targeted, candidate protein analysis using either standard ELISAs or bead-based multiplex assays (e.g., Luminex) that can measure 20–30 proteins simultaneously (see section on "Overview of Omics Technologies"). In this section, we briefly review the unbiased mass spectrometric studies (details in Table 2 [44, 65–67, 121, 122]).

Two early proteomics publications on delirium used the nearly obsolete surface-enhanced laser desorption/ionization time-of-flight (SELDI-TOF) MS [121, 122], which measures protein masses but is unable to identify specific proteins. Urine analysis of ICU patients with and without hyperactive delirium was unable to identify any relevant differences in protein profiles [121]. A plasma and serum study of patients with and without postoperative delirium on postoperative day 2 (POD2) [122] identified several delirium-enriched protein peaks in plasma but not serum that may be derived from hemoglobin-β. Thus, SELDI-TOF yielded few promising results.

Our group was among the first to utilize iTRAQ-based (quantitative isobaric tags for relative and absolute quantitation) matrix-assisted laser desorption ionization time-of-flight (MALDI-TOF/TOF) tandem MS to study postoperative delirium [67]. We used five sets of matched delirium case/no-delirium control pairs of heparin plasma samples from the Successful Aging after Elective Surgery (SAGES) cohort of major scheduled non-cardiac surgery patients. Tandem MS has the advantage of deriving actual amino acid sequences and identifying candidate proteins. The iTRAQ quantitative analysis covalently modifies each sample with a unique mass tag, allowing (1) the multiplexing of 8 samples into a single MS run and (2) the relative quantitative comparison of each peptide across all 8 samples. Using these approaches, we identified several proteins that differed between delirium cases and matched no-delirium controls, including CRP that was significantly increased in cases before (preoperatively) and after postoperative day 2 (POD2) surgery. This CRP finding was further validated using ELISA in the entire SAGES cohort of 560 patients preoperatively and on POD2 [129]. We extended this iTRAQ work in 12 matched pairs of delirium cases and non-delirium controls, identifying several additional delirium-related proteins, which created a dynamic multi-protein signature for delirium [66]. Taken together, this work demonstrates the feasibility of applying proteomics for delirium biomarker discovery. While the iTRAQ-identified proteins CRP and zinc alpha-2 glycoprotein (AZGP1) were replicated using ELISA in follow-up studies, other proteins (orosomucoid 1 [ORM1] and

hemopexin [HPX]) were not confirmed. This underscores the importance of validation studies with more standard quantitative methods (e.g., ELISA).

A similar iTRAQ MS approach has been applied to CSF samples from 2 different patient cohorts that were pooled for statistical analysis: (1) 12 mild and moderate/severe delirium cases in older emergency room (ER) patients in Sydney, Australia, compared to 8 mild Alzheimer's disease (AD) and 9 moderate AD cases, and (2) 5 mild and moderate postoperative delirium cases compared to 4 subsyndromal delirium and 4 normal control patients in an acute hip fracture surgery cohort from Edinburgh, Scotland [65]. CSF represents the most proximal fluid in delirium and therefore is anticipated to yield a stronger biological "signal" for delirium than blood. Nine proteins were differentially expressed in at least 8 of 17 delirium cases (see Table 2 for details), a relatively low stringency threshold for identifying candidate biomarkers. Furthermore, this study used pooled controls rather than direct comparisons between matched delirium cases and non-delirium controls, a limitation in the identification of statistically significant delirium-specific proteins. Moreover, due to the lack of healthy controls, it is difficult to know which of these CSF proteins are delirium or AD specific, and none of the proteins were further validated. One of the identified proteins, ORM1, was confirmed as differentially expressed in CSF; however, as previously mentioned, ELISA validation of our own plasma-based proteomics work did not confirm ORM1 as differently expressed in delirium [67]. In contrast to our plasma analysis, CRP was not differentially expressed in this CSF analysis; however, CRP is not easily detectable in CSF by MS.

Another proteomics study used two-dimensional fluorescence differential gel electrophoresis (2D-DIGE) protein separation of preoperative CSF from patients admitted for hip fracture surgery who did or did not develop postoperative delirium [45]. MS analysis of 17 protein spots that discriminated between 19 patients with delirium and 34 patients without delirium identified 10 different proteins (see Table 2). Complement factor C3 was the only protein in-common with the other CSF study, but in the opposite direction. ELISA for these proteins using an independent patient cohort failed to confirm the MS data.

In summary, several proteomics studies demonstrate feasibility for discovering delirium biomarkers in bodily fluids; however, only few findings from MS proteomics have been replicated and validated by independent methods such as ELISA (key steps to adoption of biomarkers in clinical settings, shown in Fig. 2), highlighting the challenges with reproducibility of MS methods. New advances in sample processing such as the recently released nanoparticle-based Proteograph platform (SEER), in combination with advances in MS instrumentation and protein tagging methods [107], enable increased sample multiplexing and a deeper dive into the proteome, thereby increasing throughput and reproducibility and, most importantly, allowing identification and quantification of an increasing number of proteins [130].

Affinity Aptamer- and Antibody-Based Proteomics

Despite strengths of MS-based protein biomarker discovery approaches, they have notable weaknesses. Due to its limited dynamic range, MS analysis on serum, plasma, or CSF typically does not identify more than a thousand proteins, since protein concentrations in blood range across at least 12 logs of dynamic range [131]. It is particularly difficult to identify low-abundance proteins (e.g., cytokines), likely some of the most pathophysiologically relevant proteins in delirium. This constraint, combined with a complex workflow and relatively large CVs, limit application of current MS methods for delirium biomarker discovery.

New opportunities for discovery of highly accurate protein biomarkers have emerged. This includes an aptamer-based, highly sensitive, high-throughput affinity proteomics platform: SomaScan (SomaLogic), and an antibody-based, proximity extension assay (PEA) platform: Olink. SomaScan v4.1 simultaneously quantifies 7,000 human proteins in all biological fluids, cells, and tissues, and represents currently the most comprehensive proteomics platform available. SomaScan uses modified DNA aptamer protein-capture reagents, SOMAmers (Slow Off-Rate Modified Aptamers) [132–138], highly specific oligonucleotides that form three-dimensional structures similar to antibodies and bind with high selectivity and affinity to pre-selected proteins. SomaScan transforms each individual protein concentration into a corresponding SOMAmer concentration, quantified by hybridization to its complementary DNA strand on a microarray [137, 138]. SomaScan advantages over MS-based proteomics methods include a greater dynamic range (>10 logs), a median lower limit of detection of 40 fM (<1 pg/mL), high reproducibility (~5% median coefficient of variation [CV]), and high throughput (>85 samples per run). Recent applications of SomaScan for biomarker discovery in delirium have identified multiple candidate preoperative risk and POD2 disease biomarkers for delirium including chitinase 3-like protein

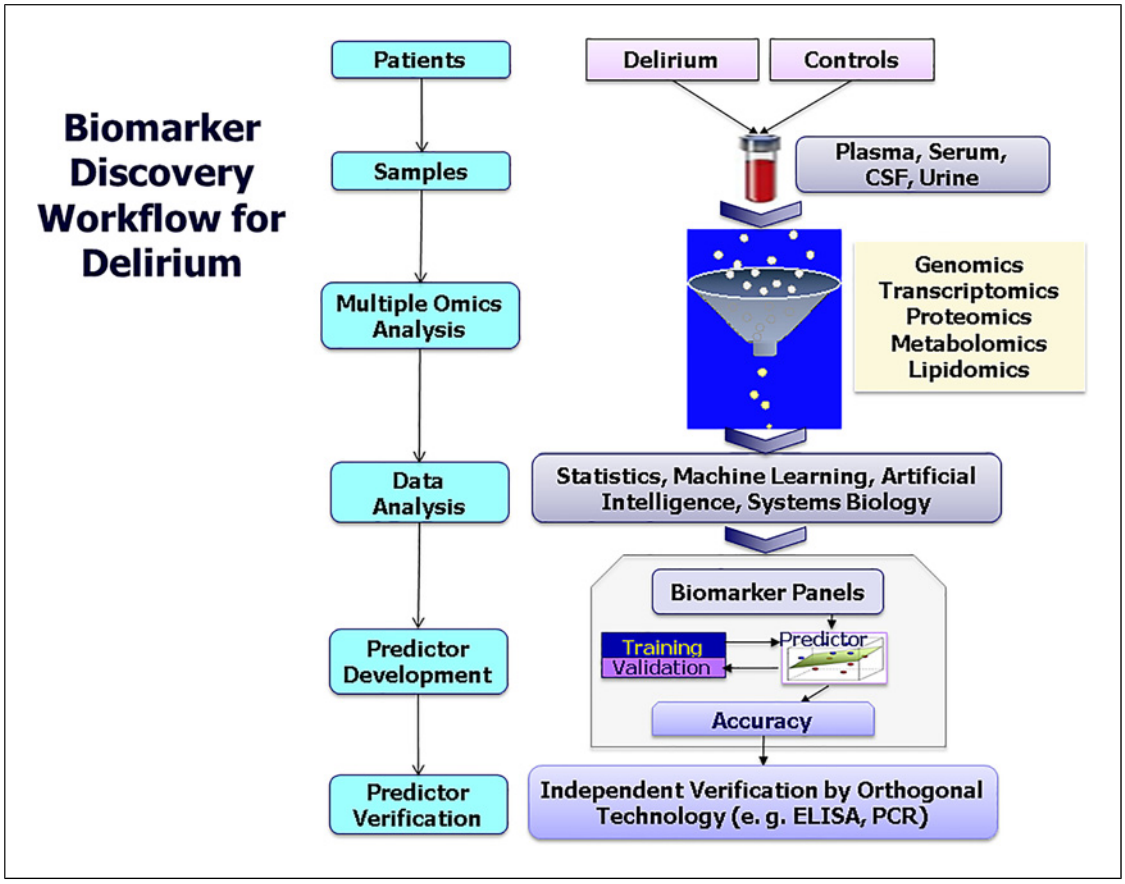

Fig. 2. Workflow for the identification and validation of biomarkers of delirium. Progressive steps show the overall study design from collection of patient samples to the validation of delirium specific biomarkers. This workflow can be applied to any disease to identify specific biomarkers. CSF, cerebrospinal fluid; ELISA, enzyme-linked immunosorbant assay; PCR, polymerase chain reaction.

(CHI3L1/YKL-40), involved in the type 2 innate immune response [123], as well as IL-6 and phosphodiesterase 3 (PDE3), involved in leukocyte recruitment and upregulation of metabolic processes [124]. CHI3L1/YKL-40 was subsequently validated using ELISA in more than 550 patients of the SAGES cohort, demonstrating not only high correlation between SomaScan and ELISA data but also validity of CHI3L1/YKL-40 as both a delirium risk and disease biomarker [123].

The second innovative affinity proteomics technology, Olink, relies on measuring proteins from interactions of two antibodies with each protein (similar to ELISA). Olink measures 2,943 proteins in biological fluids, cells, and tissues across a similar dynamic range as SomaScan. Olink developed PEA, which enables highly specific and sensitive immunoassays with either polymerase chain reaction (PCR) or next-generation sequencing read-out of the oligonucleotide tags linked to each antibody, which have overlapping complementary sequences that allow them to hybridize to each other only if in proximity to the same protein molecule [96].

Three studies of delirium serum and CSF biomarkers have been reported using subset panels of Olink [125, 126, 139]. In an analysis of 184 CSF-based inflammatory and neurology-related proteins from patients with and without delirium, increased expression of chemokine C-X3-C motif ligand 1 (CX3CL1) and seven other inflammatory proteins, and decreased expression of 23 proteins, was observed in delirium [139]. CSF was not collected prior to delirium onset, precluding determination of whether these proteins are risk versus disease markers. An Olink study of serum biomarkers associated with delirium after major cardiac surgery measured 184 inflammatory and neurology-related proteins in 12 patients with and 12 without postoperative delirium using blood collected preoperatively and on postoperative days

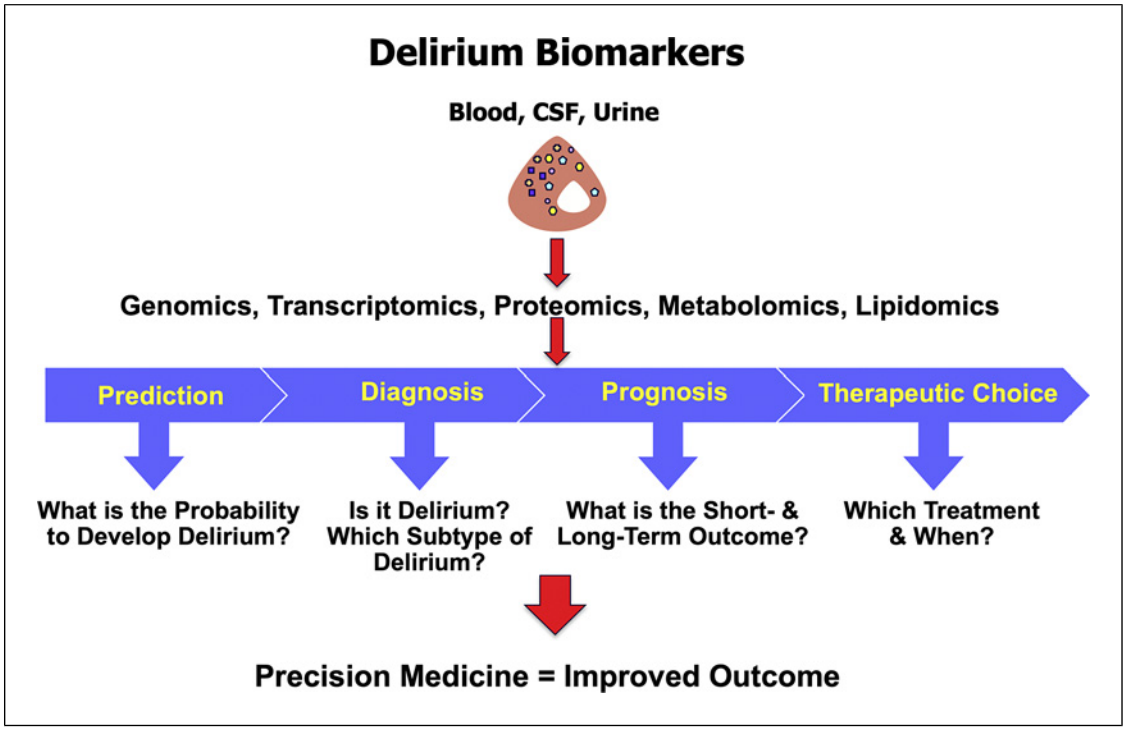

Fig. 3. Application of delirium biomarkers discovered through multi-omics approaches towards prediction medicine. The impact of multi-omics analysis of different bodily fluids on prediction, diagnosis, prognosis, and therapeutic choice for delirium is anticipated to result in a precision medicine approach to (a) predicting and diagnosing delirium, and (b) improving short- and long-term outcomes associated with delirium, and (c) treatment of delirium. This workflow could be applied to other conditions and diseases for the identification of biomarkers. CSF, cerebrospinal fluid.

1 to 3 [126]. Fibroblast growth factor (FGF) 21, FGF23, interleukin (IL)-6, and monocyte chemotactic protein-3 (MCP3) were increased in delirium cases postoperatively but not preoperatively – likely characterized as disease markers. Analysis of the same 92 neurology-related proteins on serum and CSF from a small cohort of patients undergoing complex surgery on the thoracic aorta found two proteins with functions in cognition or myelination, enhancer of zeste homolog 2 (EZH2) and testicular receptor 4 (NR2C2), that were increased in serum but not CSF preoperatively and on POD1 or POD2 in patients developing postoperative delirium.

All SomaScan and Olink studies used relatively small patient cohorts, and except for the study by Vasunilashorn et al. [123], no study performed further independent validation. Both SomaScan and Olink present the latest and most advanced proteomics platforms for analysis of an increasing number of proteins across a large dynamic range, facilitating identification of delirium biomarkers with greater sensitivity and specificity. A recent systematic review of the major proteomics studies of delirium highlighted 370 unique perioperative biomarkers of delirium enriched in pathways that involve activation of the inflammatory response, immune system, and coagulation cascade [140].

Metabolomics and Lipidomics

Various methods, particularly MS, measure thousands of metabolites or lipids across a broad range in a quantitative fashion [141–144]. Given the relative novelty of metabolomics and lipidomics, technologies and methodologies in this field are still evolving. Two different general strategies are typically applied. Targeted analysis focuses on a pre-selected set of well-annotated metabolites or lipids, usually in the range of 200–400 different molecules. In contrast, untargeted analysis measures as many metabolites or lipids as can be detected by MS, including well-annotated and unknown molecules. The major advantage of targeted MS is the addition of internal standards, enabling accurate quantification of molecules in each sample; however, this results in a limited selection of molecules. Conversely, untargeted MS is more comprehensive in its ability to measure thousands of metabolites and lipids, though it remains limited in (1) its ability

to quantify and compare values across samples and (2) the identification and annotation of metabolites or lipids.

Three recent metabolomics studies of delirium exist. Among 86 older hip-fracture patients undergoing hemiarthroplasty (43 with delirium; 43 matched non-delirium controls), four delirium-associated metabolites were identified: S-methylcysteine, linoleic acid, and eicosapentaenoic acid [145]. In a nested case-control study of 28 patients who developed delirium following arthroplasty compared to patients who did not develop delirium, targeted metabolomics of preoperative CSF identified three metabolites (spermidine, putrescine, and glutamine) [146]. Within a nested case-control study of 52 delirium patients and 52 matched non-delirium controls undergoing major non-cardiac surgery, 37 preoperative and 53 postoperative day 2 (POD2) plasma metabolites were identified as associated with delirium [147]. Systems biology analysis highlighted enrichment of branched chain amino acids valine, leucine, and isoleucine biosynthesis at PREOP and the citrate cycle at POD2. No independent validation was conducted for any metabolomics study of delirium.

A single study of delirium-preoperative CSF in older hip fracture patients reported findings from both metabolomics and lipidomics approaches [127]. In this nested case-control study ($n = 10$ delirium, $n = 30$ non-delirium), 18 metabolites and 33 lipids were differentially expressed in delirium cases. Pathway enrichment analysis highlighted metabolic deviations in D-glutamine, D-glutamate, glycerophospholipids, alanine, aspartate glutamate, sphingolipids, histidine, and arginine biosynthesis. The overall findings from this combined metabolomics and lipidomics approach identified pathophysiological mechanisms pertaining to neuroinflammation, oxidative stress, energy metabolism, and neurotransmitter imbalances.

Conclusions and Future Roadmap

Until recently, studies of delirium pathophysiology were primarily based on evaluating individual gene or protein markers based on targeted hypotheses. With the emergence of multiple omics technologies, including some with next-generation advances, new opportunities for unbiased, comprehensive analysis of delirium on the DNA, RNA, protein, metabolite, and lipid levels exist, which will enable a deeper understanding of delirium risk markers and pathogenesis. This review places omics technologies in the context of delirium research, for which a more limited number of markers can be customized using multiple standard technologies (e.g., Ella) to target measurement of subsets of delirium biomarkers. The review additionally provides an overview of omics technologies as relevant to delirium to entice engagement of more investigators in applying omics strategies to study delirium and other aging-related conditions.

We acknowledge that the majority of omics studies conducted do not include adequate representation of diverse populations and minority groups, and no omics studies of postoperative delirium have been performed in developing countries. As a result of the limited diversity of study participants, particularly from developing countries, the current findings may not be generalizable to all populations. Future studies should aim to expand the pool of study participants to include more ethnically and racially diverse individuals across geographical regions, particularly in developing countries, to determine the validity of omics findings in delirium. We believe it is feasible, and important, to collect blood specimens from developing countries, which could be analyzed either locally or shipped to facilities in other countries with access to omics technologies.

Omics approaches have yielded several new hypotheses around delirium pathophysiology. These include inflammation, both as risk and disease factors, and may also link delirium with long-term cognitive decline, Alzheimer's disease, and other dementias. Other omics-supported hypotheses regarding delirium pathophysiology include factors regulating brain vulnerability and resilience in response to physiological stressors, with neuronal damage in delirium involved in its association with adverse long-term cognitive outcomes.

As omics technologies and systems biology analyses improve, it is opportune to employ the latest omics platforms to study delirium. Our team, as well as others, is currently applying omics approaches to identify biomarkers for delirium. We envision that an omics approach will help unravel the complex pathophysiology of delirium and identify risk and disease biomarkers, as well as the key drivers and triggers of delirium (shown in Fig. 3). Comprehensive strategies like combining information from multiple omics approaches (multi-omics) have the ability to capture the complexity of the multietiology delirium syndrome, define the underlying relationships between delirium and dementia, dissect divergent pathophysiological mechanisms, and integrate all these data into a unifying framework. Ultimately, the goal of this work is the development of risk-modifying, preventive therapies as well as targeted therapies to treat delirium and prevent its associated long-term cognitive decline.

Conflict of Interest Statement

The authors have no conflicts of interest to disclose.

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Author Contributions

Drs. Vasunilashorn, Dillon, Marcantonio, and Libermann all participated in the conceptualization, writing of the initial draft, and reviewing and editing the manuscript.

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