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REVIEW article

Multi-omics approaches to understand depression associated Alzheimer's disease

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Abstract: Depression and Alzheimer's disease (AD) are commonly comorbid in the elderly, and an increasing body of evidence indicates that depression in late-life could be a prodromal manifestation and a risk factor on its own in AD. There is some similarity in the pathogenesis between the two disorders, with neuroinflammatory and hypothalamic-pituitary-adrenal axis dysregulation, synaptic damage, mitochondrial damage, and metabolic disruptions. This review will provide a summary of recent developments in the field of multi-omics in order to understand the molecular pathways underlying depression-related AD, as well as to outline their pharmacological consequences. The search and selection have taken place through standard articles published from 2020 to 2025 on the topic of genomics, epigenomics, transcriptomics, proteomics, metabolomics, lipidomics, and microbiomics in AD and major depressive disorders. Immune regulation and lipid metabolic pathways are among the common susceptibility loci identified by genomic data. Epigenomic studies reveal that DNA methylation and histone modifications of neurotrophic and inflammatory signals are caused by stress. Convergent attenuation of microglial activity and synaptic dysregulation of genes are found in transcriptomic and single-cell sequencing data. Proteomic and metabolomic studies point to the involvement of complement cascade activation, kynurenine pathway imbalances, oxidative stress, and phospholipid metabolism changes. Multi-omics integration will give a systems-level view of the biological continuum of depression and AD. These methods have a great potential to provide detection of the disease at an early stage, risk identification, and establishment of specific drug-based therapy of depression-related neurodegeneration.

Introduction

Alzheimer's disease (AD) is the most prevalent neurological disorder, accompanied by dementia in the entire world, which is progressive cognitive deterioration, dysfunction of the synapses, and neuronal death [1, 2]. Although therapeutic interventions have been made on a large scale to address amyloid-β and tau pathology, the clinical outcomes have been poor, which underscores the multifactorial and heterogeneous character of the AD pathogenesis. The recent evidence is pointing to the idea that the development of AD is caused by a complicated interplay of genetic predisposition, immune dysfunction, metabolic disturbances, and environmental stressor factors [3, 4].

Depression, especially late-life depression, has now become a prodromal symptom as well as a risk factor of AD on its own. Longitudinal and epidemiological research show that persons who experience episodes of depression repeatedly are at a great risk of developing cognitive impairment and dementia [5]. Notably, the two conditions (depression and AD) have some biological abnormalities, such as chronic neuroinflammation,

dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis, mitochondrial malfunctions, oxidative stress, impaired synaptic functions, and disrupted neurotrophic signaling [6]. These similar processes indicate that depression-related AD could be a biological continuum but not two separate disorders. The conventional research paradigms in which individual layers of the biology of the disease are studied in isolation (single genetic variants or individual protein biomarkers) have yielded valuable information, but they do not reflect the dynamic and integrative nature of disease biology. Multilevel molecular changes that interact in genomic, transcriptomic, proteomic, and metabolic networks are part of complex disorders such as depression-associated AD. This shortcoming has given rise to multi-omics methods, which combine a number of high-throughput biological data sets into a systems biology system.

Multi-omics is the integrative approach to analysis of various layers of molecules, that is, genomics, epigenomics, transcriptomics, proteomics, metabolomics, lipidomics, and microbiomics, to create a holistic understanding of disease pathology. Multi-omics allows the detection of common molecular pathways, disease subtypes, predictive biomarkers, and therapeutic targets that cannot be detected using single-omics analyses by combining these layers with computational modeling and machine learning algorithms [7]. Multi-omics integration, especially in the environment of depression-related AD, is especially useful in comprehending the mechanism of the convergence of genetic vulnerability, environmental stress, immune activation, and metabolic dysregulation to facilitate neurodegeneration. Genomics is the base layer of the multi-omics analysis, as it studies inherited DNA variations that cause susceptibility to disease. Genome-wide association studies have also found many risk loci of AD that are associated with immune response and lipid metabolism pathways, and large-scale genetic studies of major depressive disorder point to synaptic plasticity and inflammatory signaling genes [8]. Genomics thus identifies structural inherited susceptibility and joint genetic structure between depression and AD.

Epigenomics has offered a revelation into the regulations that are environmentally mediated to regulate gene expression without a change in DNA sequence. Analysis of the epigenome-wide has shown that there are major changes in DNA methylation of the AD brain tissue [9], and epigenetic changes due to stress are highly correlated with depressive pathology. The findings suggest that chronic and senescent stress-induced regulatory alterations may mediate depressive episodes and neurodegenerative vulnerability.

Transcriptomics compares the patterns of expression of genes and determines the active dysregulation of functional molecular pathways during disease progression. The RNA sequencing analysis on single cell types in the AD shows cell-type-specific transcriptional alterations in neurons, astrocytes, and microglia, especially with regard to inflammatory and synaptic signaling [10]. Equally, transcriptomic studies in depression display immunofunctional and neuroplasticity-related gene networks to be out of control. Transcriptomics deals with the changes in the formation of altered cellular activity related to genetics and epigenetics [11].

Proteomics goes even further and examines the entire protein complement as it is expressed in a tissue or biofluid. Early changes in complement cascade proteins, metabolic enzyme proteins, and glial activation markers are shown by an extensive proteomic study in AD. Proteomic analysis of depression also shows inflammatory mediators and changes in the synaptic proteins. Since proteins are the functional effector of the biological processes, proteomics ascertains the active molecular phenotype of the neurodegeneration associated with depression [12]. Both metabolomics and lipidomics offer downstream biochemical data through the measurement of small-molecule metabolites and lipid species. Metabolomic analysis of AD demonstrates that mitochondrial bioenergetics, oxidative stress pathways, and amino acids are disrupted [13], and depression research has shown that there is a disruption in tryptophan-kynurenine metabolism and lipid homeostasis. Lipidomic studies also reveal phospholipid and sphingolipid dysregulation, which is vital in neuronal membrane stability and synapse activity. These functional outcomes are the metabolic derangements of the upstream molecular changes, and they can be used as an initial biomarker [14]. Besides the host molecular alterations, the gut-brain axis has been brought about by microbiomics as a significant cause of

depression as well as AD. Changes in gut microbial composition have been linked to neuroinflammation and impaired cognition in AD [15]. while multi-omics studies in depression have shown microbiota-mediated changes in immunological and metabolic pathways [16]. Combining microbiome data with host genomic and metabolomic profiles provides novel information on systemic factors of neurodegeneration. Together, multi-omics integration allows a systems perspective of the interacting molecular world between depression and AD. Multi-omics techniques offer a complete model to understand shared pathogenic networks by jointly examining genetic predisposition, regulatory alterations, gene expression, protein activity, metabolic status, lipid signaling, and microbial effects. This integrative approach can be promising towards early diagnosis, molecular subtyping, risk stratification, as well as designing targeted pharmacological interventions of depression-associated neurodegeneration.

Genomics: The study of the entire DNA genome of a living being to discover genetic variations that make the body vulnerable to an ailment. Genome-wide association studies (GWAS) and whole-genome sequencing are applied in more complicated neuropsychiatric and neurodegenerative diseases to identify single-nucleotide polymorphisms (SNPs), copy number variations, and structural genomic changes to evaluate the effect of disease. The genomics approach establishes inherited susceptibility, polygenic risk contribution, and shared genetic scheme among major depressive disorder and AD in the depression-linked AD. Integrated genomic analyses also enable pathway enrichment mapping, which can also determine biological processes, including immune regulation, lipid metabolism, and synaptic signaling, which are potentially genetically dysregulated in both conditions. Genomics, as such, therefore, largely defines background genetic susceptibility and causal genetic mechanisms involved in disease development and progression [17].

Epigenomics: The field of epigenomics involves the study of reversible chemical modifications of DNA and histone proteins known to regulate gene expression, but leaves the underlying DNA sequence intact. They are DNA methylation, histone acetylation, histone methylation, and changes in chromatin accessibility. Epigenomic profiling establishes the effect of environmental exposures, chronic stress, aging, and inflammatory signals on temporal changes in gene activity. Epigenomics in depression-related AD is used to determine the presence of stress-induced changes in methylation in neurotrophic and inflammatory genes, long-term changes in chromatin restructuring in neuronal circuits, and neurodegenerative effects of age-related epigenetic drift. In contrast to genomics, which represents inherited risk, epigenomics establishes the environmentally mediated regulatory processes that have the potential to mediate depression and neurodegenerative pathology [18].

Transcriptomics: The whole set of RNA transcripts present in the nucleus at a particular point is assessed using transcriptomics, which is usually conducted using bulk RNA sequencing or single-cell RNA sequencing (scRNA-seq). In this method, the genes that are actively being transcribed are identified, and the gene expression dynamics over the stages of the disease are measured. Transcriptomic studies establish depression-linked AD changes in inflammatory gene expression, programs of synaptic dysfunction, glial activation states, and patterns of neuronal vulnerability. By identifying cell-type-specific transcriptional changes in neurons, astrocytes, and microglia, transcriptomics in single cells expands scientific knowledge. Consequently, transcriptomics identifies the activity of functional genes and dysregulated activated molecular networks that contribute to the development of diseases [19-21].

Proteomics: It is defined as the entire set of proteins that are expressed in a living organism, along with their abundance, structure, interactions, and post-translational modifications. Since proteins are the main functional effectors of cell events, proteomics identifies active cellular pathways more directly compared to transcriptomics. The proteomic analysis of the brain tissue, cerebral spinal fluid, and plasma in depression-related AD identifies the inflammatory cascades, complement activation, loss of synaptic proteins, mitochondrial malfunction, and disruption of signaling pathways. Large-scale protein analysis or

quantification and biomarker discovery are made possible by using high-throughput mass spectrometry and affinity-based platforms. In this way, proteomics is able to establish the pathophysiological molecular phenotype of disease [22, 23].

Metabolomics: It is a methodical quantification of small-molecule metabolites that exist in cells, tissues, or biofluids by mass spectrometry or nuclear magnetic resonance spectroscopy. These are the debris of biochemical response and, as such, will give a real-time picture of the cellular biochemical status. Changes in energy metabolism, oxidative stress indicators, amino acid turnover, and neurotransmitter precursors linked to depression in AD are explained by metabolomics. It also determines pathway derangements like disturbed tryptophan metabolism and mitochondrial bioenergetic malfunction. Since the cumulative effect of upstream molecular changes is captured in metabolites, metabolomics identifies the functional biochemical effect of disease processes [24].

Lipidomics: It is a scientific field of metabolomics that only studies lipid species, which are phospholipids, sphingolipids, sterols, and fatty acids. Since the brain is very rich in lipids, lipidomic profiling identifies changes in the membrane integrity, lipid signaling pathways, and neuroinflammatory mediators. Lipidomics in depression-associated AD identifies phospholipid rearrangement, maladjustment of sphingomyelin, and lipid peroxidation mechanisms and pathways that could contribute to synaptic dysfunction and neuronal death. Sophisticated lipidomic systems can be used to accurately determine the lipid subclasses of cognitive decline and neuropsychiatric symptoms [25, 26].

Microbiomics (metagenomics): The composition and functional capacity of microbial communities, especially within the gut, is microbiomics, which is commonly investigated by metagenomic sequencing. This method identifies diversity, abundance of taxa, and gene pathways used in the production of metabolites by microbes. Microbiomics identifies the role of gut dysbiosis in regulating systemic inflammation, metabolic, and neuroactive compound production in neurodegenerative and psychiatric disorders. Microbial metabolites, which are observed in convergent microbiome-metabolome studies, could facilitate neuroinflammatory and neurodegenerative pathways. Hence, microbiomics identifies peripheral factors that cause central nervous system malfunction by interacting with the gut-brain axis [27-29].

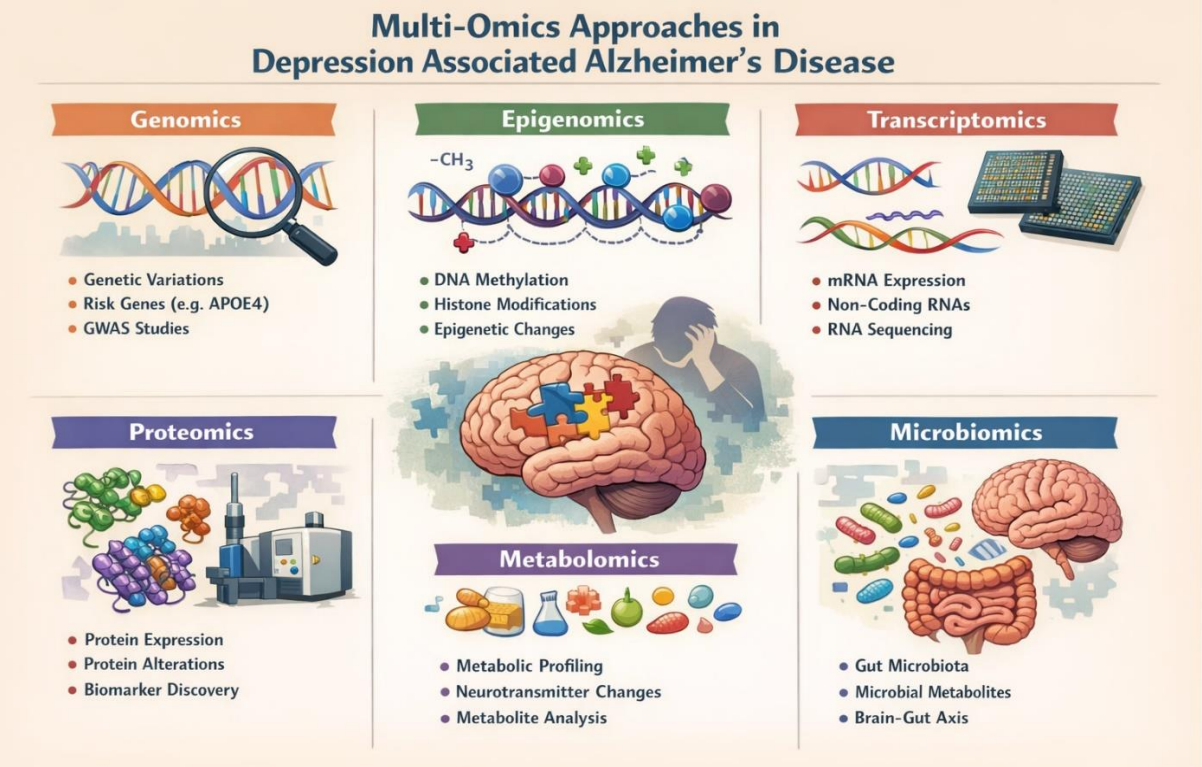

Figure 1: Multi-omics approaches in depression associated Alzheimer's disease

Alzheimer's disease is depression-related and is a spectrum of biologically interrelated phenotypes of which neuropsychiatric susceptibility and neurodegeneration intersect at multiple molecular levels. There is mounting evidence that late-life depression is not a comorbidity but perhaps a prodromal variant and can enhance amyloid deposition, tau pathology, loss of synapses, and cognitive decline. The long-term effects of stress, frequent depressive mood swings, and long-term inflammatory stimulation provide a permissive environment that predisposes the aging brain to neurodegeneration. This continuum cannot be understood without integrative approaches that are able to separate multi-layered and complex biological interactions.

Multi-omics technologies offer a systems-level framework to decipher this complexity. Multi-omics, in contrast to the reductionist models, combines genomics, epigenomics, transcriptomics, proteomics, metabolomics, lipidomics, and microbiomics to describe interactions between biological hierarchies. In depression-related AD, where genetic susceptibility interacts dynamically with environmental factors, aging, immunological processes, and metabolic changes, this combination approach is particularly crucial. Genomic studies indicate that depression and AD are susceptible to common loci of vulnerability, especially genes that control immune response, synaptic plasticity, lipid metabolism, and stress response signals. Genetic risk in itself cannot be fully attributed to disease manifestation, however. Epigenomic alterations provide a mechanistic pathway between environmental stress and chronic inflammation and a change in gene expression. Stress-induced epigenetic reprogramming in AD depressive disease affects neurotrophic factors, glucocorticoid receptor signaling, and inflammatory mediators to increase susceptibility to neurodegeneration.

Transcriptomic studies shed more light on the way these regulatory modifications are converted to functional modifications. Convergent dysregulation of microglial activation, astrocytic reactivity, synaptic signaling genes, and mitochondrial transcripts is shown in both disorders by majority RNA sequencing and single-cell investigations. Incessant microglial stimulation enhances neuroinflammation, and synaptic downregulation of genes affects cognitive impairment. These transcriptional changes are evidence that depression can precondition glial cells to a pro-inflammatory state, accelerating AD pathology. Proteomics builds on this insight by determining disruptions at the functional level of proteins. Both conditions are always accompanied by altered complement cascade proteins, inflammatory cytokines, synaptic scaffolding proteins, and mitochondrial enzymes. These protein dynamics indicate dynamic biological pathology, and not transcriptional variation. Notably, cerebral proteomic profiling of both the cerebrospinal fluid and plasma has provided good prospects in the initial finding of biomarkers in individuals with depressive symptoms who are at risk of developing AD.

Metabolomics and lipidomics record the downstream metabolic effects of these molecular instabilities. Depression-related AD is typified by disruptions of the energy metabolism, oxidative stress mechanisms, amino acid turnover, and neurotransmitter precursors. The additional association of inflammation with neurotoxicity is on the dysregulation of the kynurenine pathway, mitochondrial bioenergetics, and redox homeostasis. Lipidomic changes, especially in phospholipids and sphingolipids, destroy membrane integrity, synaptic transmission, and amyloid processing. The dysfunction of the CNS (brain and spinal cord) and the peripheral part as a whole is evidenced by these shifts and the metabolic level of functioning. The other dimension is that microbiomics is also involved in the gut-brain axis. The changed gut microbial composition affects tryptophan utilization, short-chain fatty acid synthesis, systemic inflammation, and the blood-brain barrier's integrity. Peripheral immune activation can be maintained by chronic dysbiosis and can promote neuroinflammatory mechanisms that are associated with depression and AD. These omics layers can be integrated using computational biology, network models, and machine learning to find the molecular subtypes, as well as a predictive biomarker panel. Multi-omics does not distinguish between depression and AD but shows a common pathogenic network, characterized by immune dysregulation, metabolic stress, and synaptic vulnerability. This integrative approach contributes to the strategies of precision medicine by providing the possibility to identify people at the high-risk stage early and create specific pharmacological user

interventions. Overall, multi-omics paradigms can change the paradigm of classification with symptoms to the concept of molecular stratification, which holds transformative opportunities in the understanding of depression-related neurodegeneration and its management.

Conclusion: Alzheimer-related depression is a biologically linked disorder that is motivated by pathways such as neuroinflammation, dysregulation of the stress axis, synaptic damage, metabolic disproportion, and changes in the gut-brain axis. The multi-omics integration, that is, genomics, epigenomics, transcriptomics, proteomics, metabolomics, lipidomics, and microbiomics, is a holistic systems-level approach to understand these complicated interactions. Multi-omics methods allow early diagnosis, risk stratification, and precise development of therapy by convergent molecular network and predictive biomarker identification. These molecular findings need to be translated into clinically feasible measures to prevent and cure depression-related Alzheimer's disease through future longitudinal and integrative computational research.

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