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Systems modeling of metabolic dysregulation in neurodegenerative diseases

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Abstract

Neurodegenerative diseases (NDDs) encompass a wide range of conditions that arise due to progressive degeneration and ultimate loss of nerve cells in the brain and peripheral nervous system. NDDs such as Alzheimer's, Parkinson's and Huntington's disease negatively impact both length and quality of life, without effective disease-modifying treatments. Herein, we review the use of genome-scale metabolic models, network-based approaches and integration with multi-omics data to identify key biological processes that characterize NDDs. We describe powerful systems biology approaches for modeling NDD pathophysiology by leveraging *in silico* models that are informed by patient-derived multi-omics data. These approaches can enable mechanistic insights into NDD-specific metabolic dysregulations that can be leveraged to identify potential metabolic markers of disease and pre-disease states.

Introduction

Neurodegenerative diseases (NDD) are a major cause of morbidity and dependency among older people. Over the past fifty years these diseases have become increasingly prevalent as global life expectancy increased from 66.2 to 73.0 years [1,2]. Without a change in our trajectory, the number of Alzheimer's dementia cases in Americans age 65 and above is predicted to be 13.8 million by 2060 [3]. Parkinson's disease case burden in the US is predicted to rise to more than one million people by 2030 [4]. Aging is a critical risk factor for many NDDs including Alzheimer's disease (AD), Parkinson's disease (PD), and Huntington's disease (HD) that afflict millions of people worldwide [5,6]. By definition, these diseases involve progressive damage to cells in the brain and affect the sensory and/or motor functions and cognitive abilities of the individuals [7]. AD is characterized by

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Conflict of interest statement

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cognitive impairment, language difficulty, problems with orientation, attention, and carrying out simple daily tasks [8]. Parkinson's signs and symptoms vary between individuals and can range from tremors, rigid muscles, bradykinesia, gradual decrease in unconscious movements and change in behavior [9]. HD affects the motor, cognitive, behavioral, psychological and emotional faculties of the individual [10]. As diseases with complex etiologies with many different known risk factors, it is important to understand the disease manifestation and pathophysiology in a systems context to inform the development of new therapies for the treatment of the diseases.

Aging is accompanied by progressive declines in energy metabolic capacity in the brain, which is accompanied by substantial individual variability in the rate of this decline [5,6,11]. This decline in metabolic capacity is one of the common physiological processes associated with NDDs. Longitudinal studies of NDDs are hampered by the prolonged prodromal period, and the clear safety issues that impede accessing primary CNS tissue during life. The lack of inexpensive, effective biomarkers coupled with the long prodromal period make it difficult to screen for adequate numbers of at-risk individuals from whom biological samples can be obtained and analyzed in a longitudinal manner. Subsequently, the field often utilizes data generated from postmortem brain tissue samples, from non-invasive imaging, or measures from peripheral sources such as the blood to investigate the physiological changes associated with initiation and progression of NDDs [12,13]. Most *in vitro* models focus on the function of a specific cell type and, while informative, are unable to adequately capture the complex interactions among immune, neuronal and other cell types important for vascularization, metabolism and aging. Animal model systems of NDDs are also frequently used and provide insight, but there are major challenges in translating findings from these model systems to humans due to profound differences in disease complexity, physiological response, lack of environmental and microbiome exposure and immunological response, and the different time scales of aging [14,15]. In this scenario, to bridge the gap between *in vitro* and *in vivo* approaches, *in silico* techniques that allow us to translate findings in the context of the surrounding systems hold promise to help identify marker patterns associated with the diseases, predict disease trajectories and design novel molecules or identify drugs that might be repositioned for treatment [16–18].

Metabolic dysfunction is an important factor associated with neurodegenerative disorders. Dysfunction in glucose homeostasis is associated with cognitive decline and pathophysiology in AD, PD and HD [19]. Additionally, altered lipid metabolism, mitochondrial dysfunction and endoplasmic reticulum stress are also associated with the negative endophenotypes of AD, PD and HD [20–22]. Challenges abound in performing experimental approach that capture the complexities of the human brain, making modeling an important framework piecing together disparate information to yield mechanistic insights and hypotheses to be tested through the means available in humans (e.g., postmortem brain tissue, peripheral measurements, and neuroimaging). One such computational tool is metabolic network modeling [23]. This approach integrates patient-derived multi-omics data in the form of transcriptomics, proteomics, and/or metabolomics within the context of the enzyme-catalyzed biochemistry of the cell [24,25]. Such models can be used to help identify metabolic changes in the brain contributing to human health and disease. These models include brain region-specific metabolic networks that have been developed

to analyze differences in the brains of people with AD compared with control samples [26]. About 30 different brain tissue-specific metabolic networks were constructed using metabolic network topology and expression data [27]. Such models can be used by the research community to explore *in silico* differences and identify potential metabolic markers that could be monitored prior to disease manifestation [26]. Transcription factors (TFs) are a critically important regulatory layer that drives the expression of metabolic genes and, in turn, influences metabolism. Transcriptional regulatory networks of the brain have helped to identify candidate TFs interacting with metabolic genes and exploring the metabolic regulatory landscape in NDD [26]. In this review, we focus on the initial advances in genome-scale metabolic models, transcriptional regulatory networks (TRNs) and multiscale causal network models for the investigations of NDD, highlighting challenges and scope for future developments.

Genome-scale metabolic models to identify metabolic signatures in neurodegenerative diseases

Genome-scale metabolic models are widely used tools for systems-level metabolic studies and have been used to predict cellular behavior under diverse biological conditions and identify metabolic targets that can inform drug development efforts [23]. These models contain annotated gene-protein-reaction relationships for organisms and are used to predict metabolic fluxes (the rate of enzyme-mediated molecular turnover through a biological reaction) under diverse conditions. Some approaches include a mass balance accounting of molecules as a means to identify differences in metabolic flux between normal and diseased states. Metabolic models have been built for many organisms across the three domains of life: bacteria, archaea and eukarya [28,29]. To understand the role of different types of brain cells in NDDs, *in silico* metabolic models of neurons, astrocytes, and microglia along with multi-omics data have been used to recapitulate the metabolic interactions between these cell types during normal and pathologic states [30,31]. The cell type-specific models have shown promise by recapitulating observed physiological changes, and simulations show positive concordance with experimental studies [32].

Astrocytes perform many functions in the brain, but primarily provide metabolic support for neurons [33]. The astrocyte metabolic model is a comprehensive representation of known metabolism, and it has been used to simulate the metabolic behavior of astrocytes under normal physiological and ischemia conditions [31]. Using brain cell-specific metabolic models, we can predict metabolic changes in different cell types, decipher metabolic coupling, synergistic activities, cellular interactions, and identify potential drug targets of drugs for NDDs [30]. A recent study used reconstructed brain region-specific metabolic networks to investigate the role of circulating bile acids that may contribute to AD, along with altered cholesterol metabolism [26]. Increasing evidence suggests a role for primary and secondary bile acids, the end-product of cholesterol metabolism as predictors of pathophysiology in AD and PD [26,34,35]. Brain region-specific metabolic networks [26] capture in silico metabolic changes and can potentially identify metabolic markers associated with these NDDs prior to disease manifestation, thus making them useful in interpreting the relevance of interactions and mechanisms between different classes of

metabolites and NDD associated pathobiology. Figure 1 shows the application of cell- and tissue-specific metabolic models to understand the metabolic changes in NDD.

Evaluation of peripheral lipidomic profiles can also offer a valuable perspective on metabolic dysregulation observed in preclinical and clinical AD states. Huynh *et al* [36] presented a comprehensive lipidomic analysis from plasma samples derived from two independent cross-sectional AD cohorts and reported dysregulation of lipid species including phosphatidylethanolamine and triglycerides that are also dysregulated in AD comorbidities such as type 2 diabetes [37] as well as ether lipids and GM_3 gangliosides. This study demonstrated the critical importance of lipidomic profiling platforms that can differentiate between isomeric lipid species which demonstrate complex and heterogeneous associations with AD. Such profiling efforts also potentiate novel integrative opportunities to combine lipidomics with additional layers of multi-omics data collected on these same subjects to illuminate the genetic, epigenetic, transcriptomic, and proteomic context of these observed perturbations.

In order to better use these kinds of *in silico* models to interrogate NDDs, there is a critical need for longitudinal omics data and cell type-specific data (i.e. single cell RNA seq and metabolomics). To this end, the NIH and other funding agencies have created multiple consortiums to generate large, longitudinal omics datasets. These datasets take years to create, because of both cost and longitudinal nature, but are critical for providing a window into disease risk and progression. While many studies focus on the brain itself, there are also compelling data linking the gut-brain axis and transport of metabolites across the blood brain barrier (BBB) with physiological changes observed in NDD, especially in AD and PD [38]. *In silico* models of the gut microbiome have been successful in predicting the effect of diet, genetic predisposition and host-microbe interaction that may contribute to NDD [14,39].

Studying the metabolic regulatory landscape in NDD

With many of the loci identified in GWAS studies for NDDs found in non-coding regions enriched for eQTLs, there is an important need for understanding the role of transcriptional regulation of gene expression[40,41]. Transcription factors (TFs) play a key regulatory role in the expression of metabolic genes that encode enzymes [42]. Observed transcriptional changes and identified genetic associations with a disease generally converge on the same regulator TFs. For example, SREBF-1 and SREBF-2 are TFs that regulate lipid and cholesterol metabolism and their variants are associated with AD, schizophrenia, bipolar disorders and dementia risk [43–45]. A haplotype for the myeloid-specific transcription factor PU.1 (also known as SPI1) has been implicated in AD risk [46]. Genome-scale transcriptional regulatory network (TRN) models have been developed to predict TF-target gene interactions [47,48].

Using DNase footprinting data to help define gene regulatory regions, we constructed TRNs from multiple, independent post-mortem human brain RNA-seq cohorts, to help identify network differences that support a role for herpes viruses in AD [47]. In our aforementioned work looking at the metabolic differences in AD, the same brain TRNs associated TFs like *SREBF2*, *PPARA*, *RXRG* with bile acids and cholesterol metabolism genes previously

implicated in AD [26]. Widespread transcriptional changes have been detected throughout the progression of HD, and these kinds of changes are amongst the earliest known phenotypes in HD mouse models [49]. Analysis using TRNs of mouse striatum followed by experimental validation identified SMAD3 as regulating HD-related gene expression with many of SMAD3 target genes found to be downregulated early in HD [49]. A genome-scale human brain has been used to identify key regulator TFs that are associated with both psychiatric disorders and NDDs [47]. Brain gene expression changes have also been studied for psychiatric disorders such as schizophrenia, bipolar disorders, major depression disorder and autism [47]. This network-based approach identified key regulator TFs such as *POU3F2, SOX2*, *NPAS3* and RFX4 that also harbor risk associated DNA variants for schizophrenia and bipolar disorders [47]. Figure 2 represents the generation of genome-scale TRN models for the identification of TFs in the brain.

Using cell type-specific data, it is feasible to generate TRN models for different brain cells [48]. Such models are broadly applicable to future genetic and genomic studies of human diseases and there is scope for their improvement over time as open chromatin data like ATAC-seq [50] and DNase-seq [51] becomes widely available. Integration of these data types will likely provide insights into how variants in non-coding regions convey risk or protection for various NDDs. Using systems approaches that model and integrate both metabolic and the regulatory landscape enable a mechanistic framework to understand the disease etiology of NDDs.

Multiscale causal network models of NDDs

The neurodegenerative patterns in NDDs and the observations of disease-perturbed functional networks indicate a causal relationship, but little is known about the primary pathogenic mechanisms in these diseases across their progression [52]. The information available in causal biological network databases such as PD map and NeuroMMSig have mainly focused on causal relationships between genes, proteins and other biological entities [53]. Using multi-omics datasets (genome, transcriptome, proteome, and/or metabolome) and clinical features of NDDs, multiscale causal networks have been constructed to identify novel critical genes and pathways important in NDD [53,54]. In one such study, probabilistic causal reasoning was employed on a dataset of late-onset AD individuals and controls to construct a predictive multiscale network model of AD that identified VGF as a key driver of AD pathophysiology [53]. Thus, using a priori knowledge of metabolic and transcriptional changes, causal networks can help in generating hypotheses around novel targets, and derive mechanistic insights furthering our understanding of NDDs.

Future perspectives

Systems biology is an important tool to advance neuroscience research, elucidate mechanisms of NDD pathology, and improve clinical outcomes for patients. Although this review focuses on network approaches to understand metabolic dysregulation in NDD, there are many other computational studies of the brain in health and NDD, including drug designing aimed to target multiple drug intervention points in NDDs as well as computational neurotoxicology [55,56]. Machine learning frameworks have been developed to evaluate associations between disease and any biological process that can be described

by a set of genes, metabolites or proteins [57]. Increasingly sophisticated approaches that leverage heterogeneous multi-omic and clinical data types for patient subtype identification [58,59] and pseudotemporal trajectory mapping [60] in AD are also emerging. Such frameworks are expected to help accelerate the identification of predictive biomarkers that can improve early diagnosis, track disease progression and help prioritize candidate therapeutic strategies for further evaluation [59].

Summary

This review highlights the importance of *in silico* models such as genome-scale metabolic and regulatory networks in neuroscience research. We focused on the application of genome-scale metabolic networks of human brain and brain cells to identify alterations in NDD. We also described the importance of TRN models of the brain to identify key transcriptional regulators in HD, AD, and other psychiatric disorders. As the rapid generation of richly phenotyped, patient-derived multi-omic data continues apace, new and increasingly powerful *in silico* modelling opportunities will continue to emerge that can offer new glimpses into the earliest drivers of NDD. The reciprocal refinement and validation of *in silico* models with complementary multi-omics, and the exploitation of those models to prioritize the collection of additional molecular data can offer a powerful push-pull relationship that capitalizes on broad cross-disciplinary efforts and expertise within the NDD research community. Though challenging, the coordination of such efforts will be vital for building a cohesive multiscale understanding of NDD that is capable of spanning molecular and clinical domains, and will represent a valuable step towards the development of disease-modifying therapies for these devastating disorders.

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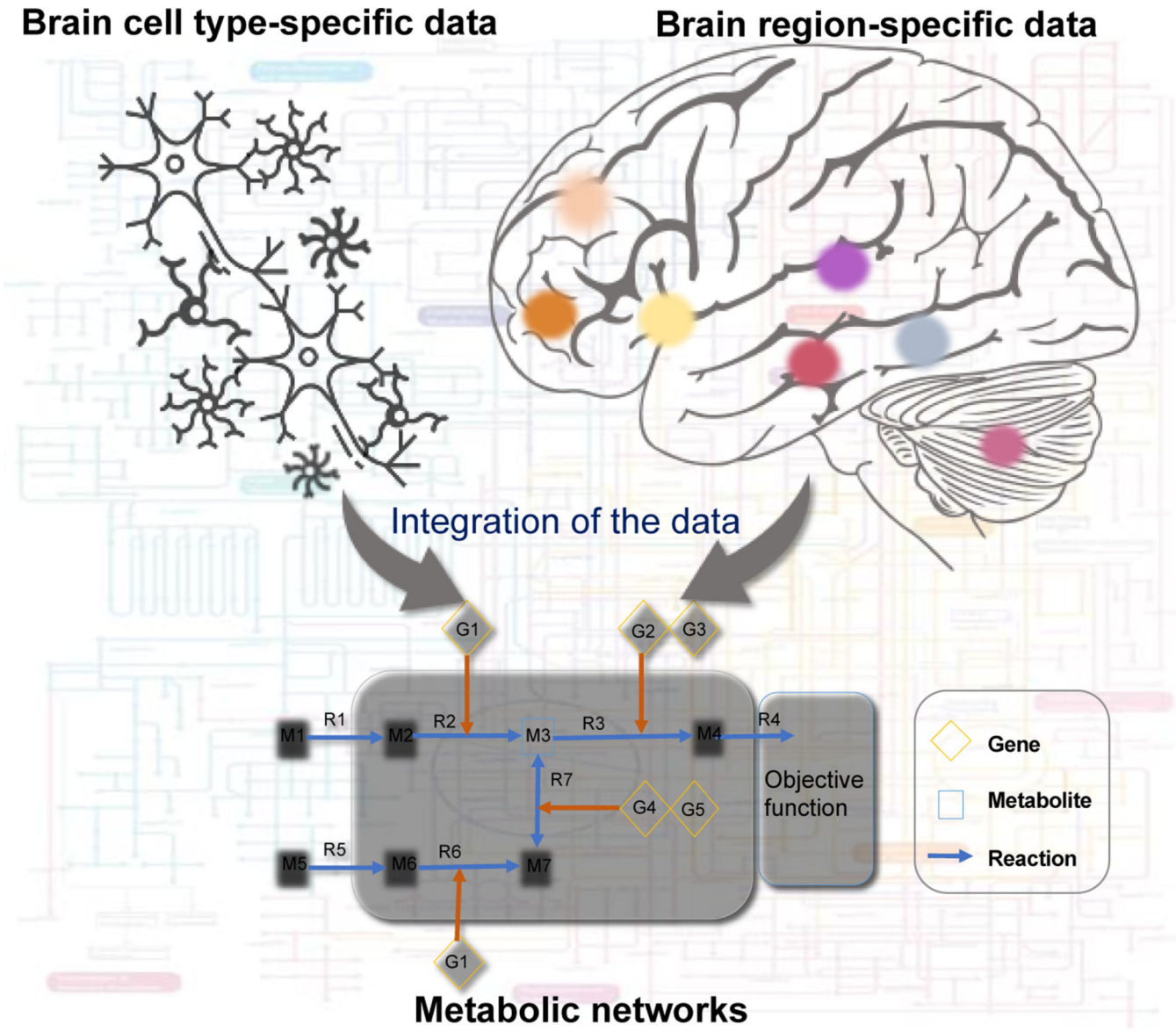

Figure 1:

A systems approach for investigating metabolic changes in the brain. Brain cell type-specific and region-specific data has been used to generate metabolic networks and identify metabolic dysregulation in NDDs.

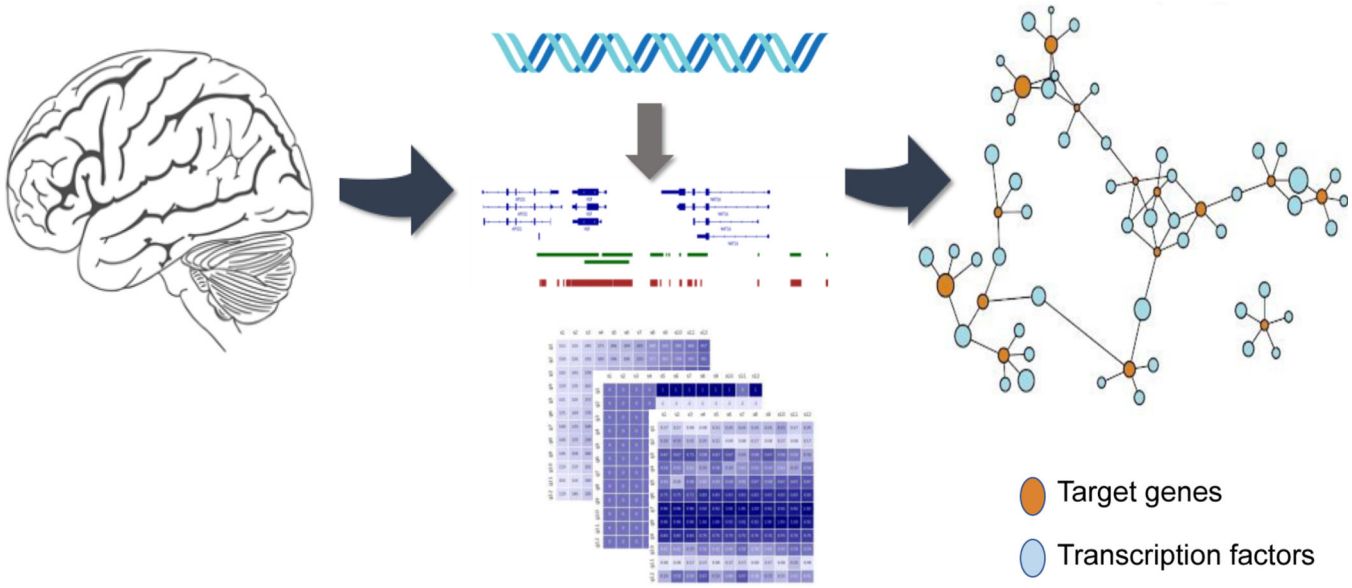

Figure 2:

Genome-scale TRN model of brain. Brain-specific DNase footprinting data and comprehensive TF-gene co-expression datasets have been used for generating the TRN model for identifying TF-target genes implicated in NDDs.