Alzheimer’s disease affects roughly 30% of individuals over 80 years old, making it the most prevalent age-onset dementia. Disease first impairs memory, then cognition, progressively robbing its victims of their identity and autonomy. It is heartbreaking for those suffering, as well as their families and caretakers. The most common form of Alzheimer’s is sporadic late onset disease (LOAD). Though historical insight from early-onset genetic cases has greatly advanced disease understanding, it has not yet translated to clinical success. Thus, science is compelled to forge new approaches to discover key players and pathways with therapeutic promise. To this end, Wang et al. (2020) implement a powerful multi-omic approach, using validation in vitro and in vivo, to identify a compound with potential to improve neuronal dysfunction.

The etiology of LOAD is complex and multifactorial, including genetic susceptibility and risk factors, environmental effects, and lifestyle choices. A range of high-throughput sequencing technologies have been applied to such complex brain diseases for over a decade to identify key players and pathways. But these studies generate enormous datasets, with hundreds or even thousands of potential “hits,” making it a challenge to discern the most biologically salient findings. This challenge is amplified when working with precious human brain samples, where subject variation, brain region, disease stage, tissue quality, and technical noise can confound or obscure findings. Multi-omics approaches that integrate and analyze multiple data types (gene expression, GWAS, proteomics, clinical and histopathological staging, etc.) appear an emergent necessity for elucidating complex disease. Rigorous testing in model systems is then required to identify candidates with therapeutic promise.

Wang et al. previously generated a large dataset from >350 patients that captures a wide range of cognitive and pathological disease variables, from controls, to mild cognitive impairment, to LOAD (Wang et al., 2018). RNA-seq to identify disease-affected genes in specific brain regions was used to construct co-expression networks and define disease gene modules. In contrast to the authors’ previous work with these data that focused on immune modules, this study prioritized neuronal gene modules. Bayesian probabilistic causal networks were constructed, integrating expression quantitative trait loci (eQTLs) and transcription factor relationships, which identified 42 unique gene drivers in the top-ranked neural modules. To explore the biological potential of the analyses, they tested a key driver in top-ranked neuronal modules, ATP6V1A, a vacuolar or vesicular type ATPase. This gene was consistently downregulated in multiple brain regions in individuals with dementia, including those in early disease stages.

ATP6V1A is integral to two distinct vesicular processes: lysosomal acidification and synaptic vesicle loading. Wang et al. used in vitro and in vivo approaches to explore the potential impact of reduced neuronal ATP6V1A to disease. ATP6V1A reduction by CRISPRi in human induced pluripotent stem cell (hiPSC)-derived excitatory neurons led to reduced electrical activity without an effect on lysosomal acidity. Diminished neuronal activity was accompanied by reduction of synaptic vesicle markers SYN1 and vGLUT1, suggesting impairment is associated with pre-synaptic dysfunction. Neuronal excitability was further compromised by adding toxic amyloid-beta (Aß42) peptide, the hallmark aggregated protein of Alzheimer’s plaques.

Alzheimer’s disease is defined by memory and cognitive impairment, along with brain atrophy and degeneration. To probe functional consequences of reduced ATP6V1A, Wang et al. used the fly and genetically tested the impact of two orthologs of ATP6V1A. Reduced neuronal expression was sufficient to impair motor function. In the setting of added Aß42 expression, reduction of one ATP6V1A ortholog worsened motor dysfunction and neurodegeneration. These changes were accompanied by diminished mRNA of select synapse-related genes, implicating synaptic dysfunction as found in hiPSC-derived neurons and in disease models. Aß42 expression alone was also associated with reduced expression of the ATP6V1A orthologs in the fly brain.

To investigate the therapeutic potential of restoring ATP6V1A levels in disease, Wang et. al. implemented a bioinformatic drug repositioning approach (EMUDRA; Zhou et al., 2018), focusing on compounds to correct disease-gene signatures and increase expression of ATP6V1A. They tested several candidate histone deacetylase (HDAC) inhibitors.
In vitro testing on hiPSC-derived neurons showed one candidate, NCH-51, had efficacy to increase ATP6V1A mRNA and protein levels and, importantly, restore neural excitability. Feeding NCH-51 to flies mitigated Aβ42-associated neurodegeneration and partially increased mRNA levels of synapse-related genes. The levels of the toxic Aβ42 peptide were unaltered, suggesting NCH-51 promotes and restores neural activity rather than reduces toxic peptide.

The study by Wang et al. exemplifies the power and necessity of integrative multi-omics approaches to uncover drivers of complex brain disease. ATP6V1A was only one potentially important gene—additional genes were noted. Future mining of these data combined with high-throughput screens of hits could reveal additional manipulatable targets. Many therapeutic targets will likely need to be pursued in multiple model systems like human-derived iPS cells, fly, and mouse. Candidate genes and drugs may need to show spectacular success in models to hold promise for efficacy in patients, given the human complexity of genetics and environmental influences.

Challenges, puzzles, but also promises remain. Multi-omic studies are expensive and require many distinct fields of expertise, plus great computational power, bioinformatic prowess, and statistical rigor. Reproduction by multiple groups is not readily feasible. To expedite progress, the top results of such studies should be made widely accessible to the scientific community for further testing. Additional “omic” approaches, including epigenetics, single cell analyses, as well as incorporating the diversity of cell types in the brain (Lin et al., 2018; Mathys et al., 2019; Nativio et al., 2020; Zhao et al., 2020), will be required. Such approaches together with bioinformatic knowledge gained from integrated analyses as in Wang et al. will bring us closer toward the goals of a healthier human lifespan.

REFERENCES


Insights into the Irritating Mechanisms of TRPA1 Revealed by Cryo-EM

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TRPA1 is a promising target for the development of novel treatments for chronic pain. In this issue of Neuron, Liu et al. (2021) report a novel non-covalent TRPA1-biased agonist, GNE551, revealing a unique binding pocket by cryo-EM and activation properties that pave a path toward new avenues in the treatment of chronic pain.

“Pain is whatever the experiencing person says it is, existing whenever he says it does,” Margo McCaffery, a pioneer in pain management for nursing, said. Pain causes an unpleasant feeling to the experiencing person after nociceptive or psychogenic damage. While one of the primary physiological roles for pain sensation is to serve as a warning during harmful stimuli to avoid further damage, in many instances, the sensation of pain does not serve to benefit the individual and is something that should be ameliorated. This desire to control and inhibit pain has led to a massive development in analgesics and pain relief research typically dominated by opioid receptors and, by extension, has contributed to our