Alzheimer's disease (AD) involves changes in both lipid and RNA metabolism, but it remained unknown if these differences associate with AD's cognition and/or post-mortem neuropathology indices. Here, we report RNA-sequencing evidence of inter-related associations between lipid processing, cognition level, and AD neuropathology. In two unrelated cohorts, we identified pathway-enriched facilitation of lipid processing and alternative splicing genes, including the neuronal-enriched NOVA1 and hnRNPA1. Specifically, this association emerged in temporal lobe tissue samples from donors where postmortem evidence demonstrated AD neuropathology, but who presented normal cognition proximate to death. The observed changes further associated with modified ATP synthesis and mitochondrial transcripts, indicating metabolic relevance; accordingly, mass-spectrometry-derived lipidomic profiles distinguished between individuals with and without cognitive impairment prior to death. In spite of the limited group sizes, tissues from persons with both cognitive impairment and AD pathology showed elevation in several drug-targeted genes of other brain, vascular and autoimmune disorders, accompanied by pathology-related increases in distinct lipid processing transcripts, and in the RNA metabolism genes hnRNPH2, TARDBP, CLP1 and EWSR1. To further detect 3'-polyadenylation variants, we employed multiple cDNA primer pairs. This identified variants that showed limited differences in scope and length between the tested cohorts, yet enabled superior clustering of demented and non-demented AD brains versus controls compared to total mRNA expression values. Our findings indicate inter-related cognition-associated differences in AD's lipid processing, alternative splicing and 3'-polyadenylation, calling for pursuing the underlying psychological and therapeutics implications.

MicroRNAs (miRNAs) are small non-coding RNA chains that can each interact with the 3'-untranslated region of multiple target transcripts in various organisms, humans included. MiRNAs tune entire biological pathways, spanning stress reactions, by regulating the stability and/or translation of their targets. MiRNA genes are often subject to co-evolutionary changes together with their target transcripts, which may be reflected by differences between paralog mouse and primate miRNA/mRNA pairs. However, whether such evolution occurred in stress-related miRNAs remained largely unknown. Here, we report that the stress-induced evolutionarily conserved miR-132-3p, its target transcripts and its regulated pathways provide an intriguing example to exceptionally robust conservation. Mice and human miR-132-3p share six experimentally validated targets and 18 predicted targets with a common miRNA response element. Enrichment analysis and mining in-house and web-available experimental data identified co-regulation by
miR-132 in mice and humans of stress-related, inflammatory, metabolic, and neuronal growth pathways. Our findings demonstrate pan-mammalian preservation of miR-132's neuronal roles, and call for further exploring the corresponding stress-related implications.


Abstract

Epilepsy is a common neurological disease, manifested in unprovoked recurrent seizures. Epileptogenesis may develop due to genetic or pharmacological origins or following injury, but it remains unclear how the unaffected brain escapes this susceptibility to seizures. Here, we report that dynamic changes in forebrain microRNA (miR)-211 in the mouse brain shift the threshold for spontaneous and pharmacologically induced seizures alongside changes in the cholinergic pathway genes, implicating this miR in the avoidance of seizures. We identified miR-211 as a putative attenuator of cholinergic-mediated seizures by intersecting forebrain miR profiles that were Argonaute precipitated, synaptic vesicle target enriched, or differentially expressed under pilocarpine-induced seizures, and validated TGFBR2 and the nicotinic antiinflammatory acetylcholine receptor nAChRa7 as murine and human miR-211 targets, respectively. To explore the link between miR-211 and epilepsy, we engineered dTg-211 mice with doxycycline-suppressible forebrain overexpression of miR-211. These mice reacted to doxycycline exposure by spontaneous electrocorticography-documented nonconvulsive seizures, accompanied by forebrain accumulation of the convulsive seizures mediating miR-134. RNA sequencing demonstrated in doxycycline-treated dTg-211 cortices overrepresentation of synaptic activity, Ca2+ transmembrane transport, TGFBR2 signaling, and cholinergic synapse pathways. Additionally, a cholinergic dysregulated mouse model overexpressing a miR refractory acetylcholinesterase-R splice variant showed a parallel propensity for convulsions, miR-211 decreases, and miR-134 elevation. Our findings demonstrate that in mice, dynamic miR-211 decreases induce hypersynchronization and nonconvulsive and convulsive seizures, accompanied by expression changes in cholinergic and TGFBR2 pathways as well as in miR-134. Realizing the importance of miR-211 dynamics opens new venues for translational diagnosis of and interference with epilepsy.


alpha-Synuclein overexpression (ASOX) drives the formation of toxic aggregates in neurons vulnerable in Parkinson's disease (PD), including dopaminergic neurons of the substantia nigra (SN) and cholinergic neurons of the dorsal motor nucleus of the vagus (DMV). Just as these populations differ in when they exhibit alpha-synucleinopathies during PD pathogenesis, they could also differ in their physiological responses to ASOX. An ASOX-mediated hyperactivity of SN dopamine neurons, which was caused by oxidative dysfunction of Kv4.3 potassium channels, was recently identified in transgenic (A53T-SNCA) mice overexpressing mutated human alpha-synuclein. Noting that DMV neurons display extensive alpha-synucleinopathies earlier than SN dopamine neurons while exhibiting milder cell loss in PD, we aimed to define the electrophysiological properties of DMV neurons in A53T-SNCA mice. We found that DMV neurons maintain normal firing rates in response to ASOX. Moreover, Kv4.3 channels in DMV neurons exhibit no oxidative dysfunction in the A53T-SNCA mice, which could only be recapitulated in wild-type mice by glutathione dialysis. Two-photon imaging of redox-sensitive GFP corroborated the finding that mitochondrial oxidative stress was diminished in DMV neurons in the A53T-SNCA mice. This reduction in
oxidative stress resulted from a transcriptional downregulation of voltage-activated (Cav) calcium channels in DMV neurons, which led to a reduction in activity-dependent calcium influx via Cav channels. Thus, ASOX induces a homeostatic remodeling with improved redox signaling in DMV neurons, which could explain the differential vulnerability of SN dopamine and DMV neurons in PD and could promote neuroprotective strategies that emulate endogenous homeostatic responses to ASOX (e.g., stressless pacemaking) in DMV neurons. SIGNIFICANCE STATEMENT: Overexpression of mutant alpha-synuclein causes Parkinson's disease, presumably by driving neurodegeneration in vulnerable neuronal target populations. However, the extent of alpha-synuclein pathology (e.g., Lewy bodies) is not directly related to the degree of neurodegeneration across various vulnerable neuronal populations. Here, we show that, in contrast to dopamine neurons in the substantia nigra, vagal motoneurons do not enhance their excitability and oxidative load in response to chronic mutant alpha-synuclein overexpression. Rather, by downregulating their voltage-activated calcium channels, vagal motoneurons acquire a stressless form of pacemaking that diminishes mitochondrial and cytosolic oxidative stress. Emulating this endogenous adaptive response to alpha-synuclein overexpression could lead to novel strategies to protect dopamine neurons and perhaps delay the onset of Parkinson's disease.


MicroRNA (miR)-132 brain-to-body messages suppress inflammation by targeting acetylcholinesterase (AChE), but the target specificity of 3'-AChE splice variants and the signaling pathways involved remain unknown. Using surface plasmon resonance (SPR), we identified preferential miR-132 targeting of soluble AChE-R over synaptic-bound AChE-S, potentiating miR-132-mediated brain and body cholinergic suppression of pro-inflammatory cytokines. Inversely, bacterial lipopolysaccharide (LPS) reduced multiple miR-132 targets, suppressed AChE-S more than AChE-R and elevated inflammatory hallmarks. Furthermore, blockade of peripheral miR-132 by chemically protected AM132 antisense oligonucleotide elevated muscle AChE-R 10-fold over AChE-S, and cortical miRNA-sequencing demonstrated inverse brain changes by AM132 and LPS in immune-related miRs and neurotransmission and cholinergic signaling pathways. In neuromuscular junctions, AM132 co-elevated the nicotinic acetylcholine receptor and AChE, re-balancing neurotransmission and reaching mild muscle incoordination. Our findings demonstrate preferential miR-132-induced modulation of AChE-R which ignites bidirectional brain and body anti-inflammatory regulation, underscoring splice-variant miR-132 specificity as a new complexity level in inflammatory surveillance.

polymorphisms associated with schizophrenia, bipolar disorder and autism, suggesting interaction with mental diseases. Our findings indicate functional roles of duplicated PSG+MRE in brain development and cognition, supporting physiological impact of the reciprocal co-regulation of PSG+MRE with MRE-sharing coding transcripts in human brain neurons.


Acetylcholine signaling is essential for cognitive functioning and blocks inflammation. To maintain homeostasis, cholinergic signaling is subjected to multi-leveled and bidirectional regulation by both proteins and non-coding microRNAs ("CholinomiRs"). CholinomiRs coordinate the cognitive and inflammatory aspects of cholinergic signaling by targeting major cholinergic transcripts including the acetylcholine hydrolyzing enzyme acetylcholinesterase (AChE). Notably, AChE inhibitors are the only currently approved line of treatment for Alzheimer's disease patients. Since cholinergic signaling blocks neuroinflammation which is inherent to Alzheimer's disease, genomic changes modifying AChE's properties and its susceptibility to inhibitors and/or to CholinomiRs regulation may affect the levels and properties of inflammasome components such as NLRP3. This calls for genomic-based medicine approaches based on genotyping of both coding and non-coding single nucleotide polymorphisms (SNPs) in the genes involved in cholinergic signaling. An example is a SNP in a recognition element for the primate-specific microRNA-608 within the 3' untranslated region of the AChE transcript. Carriers of the minor allele of that SNP present massively elevated brain AChE levels, increased trait anxiety and inflammation, accompanied by perturbed CholinomiR-608 regulatory networks and elevated prefrontal activity under exposure to stressful insults. Several additional SNPs in the AChE and other cholinergic genes await further studies, and might likewise involve different CholinomiRs and pathways including those modulating the initiation and progression of neurodegenerative diseases. CholinomiRs regulation of the cholinergic system thus merits in-depth interrogation and is likely to lead to personalized medicine approaches for achieving better homeostasis in health and disease. This is an article for the special issue XVth International Symposium on Cholinergic Mechanisms.


OBJECTIVE: Both non-alcoholic fatty liver disease (NAFLD) and the multitarget complexity of microRNA (miR) suppression have recently raised much interest, but the in vivo impact and context-dependence of hepatic miR-target interactions are incompletely understood. Assessing the relative in vivo contributions of specific targets to miR-mediated phenotypes is pivotal for investigating metabolic processes. DESIGN: We quantified fatty liver parameters and the levels of miR-132 and its targets in novel transgenic mice overexpressing miR-132, in liver tissues from patients with NAFLD, and in diverse mouse models of hepatic steatosis. We tested the causal nature of miR-132 excess in these phenotypes by injecting diet-induced obese mice with antisense oligonucleotide suppressors of miR-132 or its target genes, and measured changes in metabolic parameters and transcripts. RESULTS: Transgenic mice overexpressing miR-132 showed a severe fatty liver phenotype and increased body weight, serum low-density lipoprotein/very low-density lipoprotein (LDL/VLDL) and liver triglycerides, accompanied by decreases in validated miR-132 targets and increases in lipogenesis and lipid accumulation-related transcripts. Likewise, liver samples from both patients with NAFLD and mouse models of hepatic steatosis or non-alcoholic steatohepatitis (NASH) displayed dramatic increases in miR-132 and varying decreases in miR-132 targets compared with controls. Furthermore, injecting diet-induced obese mice with anti-miR-132
oligonucleotides, but not suppressing its individual targets, reversed the hepatic miR-132 excess and hyperlipidemic phenotype. CONCLUSIONS: Our findings identify miR-132 as a key regulator of hepatic lipid homeostasis, functioning in a context-dependent fashion via suppression of multiple targets and with cumulative synergistic effects. This indicates reduction of miR-132 levels as a possible treatment of hepatic steatosis.


Alzheimer's disease is a devastating neurodegenerative disorder affecting a significant portion of the world's rapidly growing aging population. In spite of its prevalence, the etiology of the disease is still poorly understood, and effective therapy is all but unavailable. Over the past decade, noncoding RNA, including microRNA (miRNA), has emerged as a major class of regulatory molecules involved in virtually all physiological and disease states. The specificity provided by miRNA sequence complementarity, together with the ability of these molecules to regulate complex networks of genes, has made them exciting novel targets for therapeutic agents. In this chapter, we review recent progress on understanding the role of noncoding RNA in Alzheimer's disease (AD). The majority of available work has focused on miRNA, and we review the many studies implicating specific miRNAs in the development of the disease. More recently, several studies have tied other RNA classes to the disorder, including long noncoding RNA, circular RNA, and Y RNAs, and we review this fascinating field as well. Finally, we explore the potential promise of these findings for future therapeutic applications.


Maternal care is an indispensable behavioral component necessary for survival and reproductive success in mammals, and postpartum maternal behavior is mediated by an incompletely understood complex interplay of signals including effects of epigenetic regulation. We approached this issue using our recently established mice with targeted deletion of heterochromatin protein 1 binding protein 3 (HP1BP3), which we found to be a novel epigenetic repressor with critical roles in postnatal growth. Here, we report a dramatic reduction in the survival of pups born to Hp1bp3(-/-) deficient mouse dams, which could be rescued by co-fostering with wild-type dams. Hp1bp3(-/-) females failed to retrieve both their own pups and foster pups in a pup retrieval test, and showed reduced anxiety-like behavior in the open-field and elevated-plus-maze tests. In contrast, Hp1bp3(-/-) females showed no deficits in behaviors often associated with impaired maternal care, including social behavior, depression, motor coordination and olfactory capability; and maintained unchanged anxiety-associated hallmarks such as cholinergic status and brain miRNA profiles. Collectively, our results suggest a novel role for HP1BP3 in regulating maternal and anxiety-related behavior in mice and call for exploring ways to manipulate this epigenetic process.


Anxiety-related and metabolic disorders are under intense research focus. Anxiety-induced microRNAs (miRNAs) are emerging as regulators that are not only capable of suppressing inflammation but can also...
 induce metabolic syndrome-related processes. We summarize here evidence linking miRNA pathways which share regulatory networks in metabolic and anxiety-related conditions. In particular, miRNAs involved in these disorders include regulators of acetylcholine signaling in the nervous system and their accompanying molecular machinery. These have been associated with anxiety-prone states in individuals, while also acting as inflammatory suppressors. In peripheral tissues, altered miRNA pathways can lead to dysregulated metabolism. Common pathways in metabolic and anxiety-related phenomena might offer an opportunity to reclassify 'healthy' and 'unhealthy', as well as metabolic and anxiety-prone biological states, and inform putative strategies to treat these disorders.


Circular RNAs (circRNAs) are highly abundant and evolutionarily conserved non-coding RNAs produced by circularization of specific exons. Since their re-discovery as potential regulators of gene expression, thousands of circRNAs were detected in different tissues and cell types across most organisms. Accumulating data suggest key roles for them in the central nervous system. Neuronal-expressed RNAs are diverted to yield highly enriched CircRNAs in human, mouse, pig and flies, with many of them enriched in neuronal tissues. CircRNA levels are dynamically modulated in neurons, both during differentiation and following bursts of electrical activity, and accumulate with age, and many of them are enriched in synapses. Together, available data suggest that circRNAs have important roles in synaptic plasticity and neuronal function. This review covers current advances in the field and lays out hypotheses regarding functions of circRNAs in the brain as well as their putative involvement in initiation and progression of neurodegenerative processes.


BACKGROUND: Treatment of active ulcerative colitis is associated with incomplete efficacy, adverse events, and loss of response. Toll-like receptor-9 mediates innate and adaptive immune response toward intestinal microorganisms. The oral synthetic oligonucleotide toll-like receptor-9 modulator has demonstrated anti-inflammatory properties in colitis murine models and a satisfactory safety profile in humans. AIM: To evaluate the efficacy and safety of BL-7040 (a Toll-like receptor-9 modulator) in patients with moderately active ulcerative colitis. METHODS: Moderately active ulcerative colitis patients were included in this multicenter, open-label phase IIa trial. Concomitant mesalamine and steroids at a stable dose were allowed. Clinical outcome was evaluated using the Mayo score, histology, and mucosal cytokine levels. Side effects were registered. RESULTS: Sixteen out of 22 patients completed a 5-week treatment course and 2-week follow-up. Six patients discontinued the study, three of them due to adverse events. Clinical remission was observed in two patients (12.5 %), and clinical response as well as mucosal healing were achieved in half (50 %) of the patients, while all others remained stable. Furthermore, mucosal neutrophil (p = 0.002) and mucosal interleukin-6 levels (p = 0.046) were significantly reduced in responders compared to non-responders. Toll-like receptor-9 was well tolerated with only one unrelated to study drug serious adverse event (hemoglobin decrease) and 29 mild-to-moderate adverse events. CONCLUSIONS: Oral administration of the Toll-like receptor-9 agonist BL-7040 appeared efficacious, safe and well tolerated in patients with moderately active ulcerative colitis.

Trauma causes variable risk of posttraumatic stress symptoms (PTSS) owing to yet-unknown genome-neuronal interactions. Here, we report co-intensified amygdala and ventromedial prefrontal cortex (vmPFC) emotional responses that may overcome PTSS in individuals with the single-nucleotide polymorphism (SNP) rs17228616 in the acetylcholinesterase (AChE) gene. We have recently shown that in individuals with the minor rs17228616 allele, this SNP interrupts AChE suppression by microRNA (miRNA)-608, leading to cortical elevation of brain AChE and reduced cortisol and the miRNA-608 target GABAergic modulator CDC42, all stress-associated. To examine whether this SNP has effects on PTSS and threat-related brain circuits, we exposed 76 healthy Israel Defense Forces soldiers who experienced chronic military stress to a functional magnetic resonance imaging task of emotional and neutral visual stimuli. Minor allele individuals predictably reacted to emotional stimuli by hyperactivated amygdala, a hallmark of PTSS and a predisposing factor of posttraumatic stress disorder (PTSD). Despite this, minor allele individuals showed no difference in PTSS levels. Mediation analyses indicated that the potentiated amygdala reactivity in minor allele soldiers promoted enhanced vmPFC recruitment that was associated with their limited PTSS. Furthermore, we found interrelated expression levels of several miRNA-608 targets including CD44, CDC42 and interleukin 6 in human amygdala samples (N=7). Our findings suggest that miRNA-608/AChE interaction is involved in the threat circuitry and PTSS and support a model where greater vmPFC regulatory activity compensates for amygdala hyperactivation in minor allele individuals to neutralize their PTSS susceptibility.


The relationship between long-term cholinergic dysfunction and risk of developing dementia is poorly understood. Here we used mice with deletion of the vesicular acetylcholine transporter (VACHT) in the forebrain to model cholinergic abnormalities observed in dementia. Whole-genome RNA sequencing of hippocampal samples revealed that cholinergic failure causes changes in RNA metabolism. Remarkably, key transcripts related to Alzheimer’s disease are affected. BACE1, for instance, shows abnormal splicing caused by decreased expression of the splicing regulator hnRNPA2/B1. Resulting BACE1 overexpression leads to increased APP processing and accumulation of soluble Abeta1-42. This is accompanied by age-related increases in GSK3 activation, tau hyperphosphorylation, caspase-3 activation, decreased synaptic markers, increased neuronal death, and deteriorating cognition. Pharmacological inhibition of GSK3 hyperactivation reversed deficits in synaptic markers and tau hyperphosphorylation induced by cholinergic dysfunction, indicating a key role for GSK3 in some of these pathological changes. Interestingly, in human brains there was a high correlation between decreased levels of VACHT and hnRNPA2/B1 levels with increased tau hyperphosphorylation. These results suggest that changes in RNA processing caused by cholinergic loss can facilitate Alzheimer’s-like pathology in mice, providing a mechanism by which decreased cholinergic tone may increase risk of dementia.


Cholinergic vulnerability, characterized by loss of acetylcholine (ACh), is one of the hallmarks of Alzheimer’s disease (AD). Previous work has suggested that decreased ACh activity in AD may contribute to pathological changes through global alterations in alternative splicing. This occurs, at least partially, via the regulation of the expression of a critical protein family in RNA processing, heterogeneous nuclear ribonucleoprotein (hnRNP) A/B proteins. These proteins regulate several steps of RNA metabolism,
including alternative splicing, RNA trafficking, miRNA export, and gene expression, providing multilevel surveillance in RNA functions. To investigate the mechanism by which cholinergic tone regulates hnRNPA2/B1 expression, we used a combination of genetic mouse models and in vivo and in vitro techniques. Decreasing cholinergic tone reduced levels of hnRNPA2/B1, whereas increasing cholinergic signaling in vivo increased expression of hnRNPA2/B1. This effect was not due to decreased hnRNPA2/B1 mRNA expression, increased aggregation, or degradation of the protein, but rather to decreased mRNA translation by nonsense-mediated decay regulation of translation. Cell culture and knock-out mice experiments demonstrated that M1 muscarinic signaling is critical for cholinergic control of hnRNPA2/B1 protein levels. Our experiments suggest an intricate regulation of hnRNPA2/B1 levels by cholinergic activity that interferes with alternative splicing in targeted neurons mimicking deficits found in AD.

SIGNIFICANCE STATEMENT: In Alzheimer's disease, degeneration of basal forebrain cholinergic neurons is an early event. These neurons communicate with target cells and regulate their long-term activity by poorly understood mechanisms. Recently, the splicing factor hnRNPA2/B, which is decreased in Alzheimer's disease, was implicated as a potential mediator of long-term cholinergic regulation. Here, we demonstrate a mechanism by which cholinergic signaling controls the translation of hnRNPA2/B1 mRNA by activation of M1 muscarinic type receptors. Loss of cholinergic activity can have profound effects in target cells by modulating hnRNPA2/B1 levels.


Semiconductor-metal hybrid nanoparticles manifest efficient light-induced spatial charge separation at the semiconductor-metal interface, as demonstrated by their use for hydrogen generation via water splitting. Here, we pioneer a study of their functionality as efficient photocatalysts for the formation of reactive oxygen species. We observed enhanced photocatalytic activity forming hydrogen peroxide, superoxide, and hydroxyl radicals upon light excitation, which was significantly larger than that of the semiconductor nanocrystals, attributed to the charge separation and the catalytic function of the metal tip. We used this photocatalytic functionality for modulating the enzymatic activity of horseradish peroxidase as a model system, demonstrating the potential use of hybrid nanoparticles as active agents for controlling biological processes through illumination. The capability to produce reactive oxygen species by illumination on-demand enhances the available peroxidase-based tools for research and opens the path for studying biological processes at high spatiotemporal resolution, laying the foundation for developing novel therapeutic approaches.


Parkinson's disease (PD) involves motor symptoms reflecting the progressive degeneration of dopaminergic neurons in the substantia nigra. However, diagnosis is only enabled late in the disease, limiting treatment to palliative assistance. Here, we review recently generated transcriptional profiling datasets from blood and brain RNA of human PD cohorts and animal models that may offer unprecedented progress in PD research. Specifically, advanced analysis techniques demonstrated functionally inter-related underlying impairments of RNA metabolism and neuroimmune signalling processes. Identifying novel biomarkers in serum and nucleated blood cells, including protein networks and non-coding RNAs can drive discovery of the molecular mechanisms involved and reveal new targets for therapeutic intervention, posing a dual diagnosis/treatment opportunity for limiting the exacerbation of
neuroinflammatory events in PD.


Emerging evidence demonstrates association of depression with both immune malfunctioning and worsened course of diverse aging-related diseases, but there is no explanation for the pathway(s) controlling this dual association. Here, we report that in post-reproductive and evolutionarily 'blind' years, depression may weaken pathogen-host defense, compatible with the antagonistic pleiotropy hypothesis. In 15,532 healthy volunteers, depression scores associated with both inflammatory parameters and with increased circulation cholinesterase activities, implicating debilitated cholinergic blockade of inflammation as an underlying mechanism; furthermore, depression, inflammation and cholinesterase activities all increased with aging. In the entire cohort, combined increases in inflammation and the diabetic biomarker hemoglobin A1c associated with elevated depression. Moreover, metabolic syndrome patients with higher risk of diabetes showed increased cholinesterase levels and pulse values, and diabetics presented simultaneous increases in depression, inflammation and circulation cholinesterase activities, suggesting that cholinergic impairment precedes depression. Our findings indicate that dys-functioning cholinergic regulation weakens the otherwise protective link between depression and pathogen-host defense, with global implications for aging-related diseases.


The prognosis of neurodegenerative disorders is clinically challenging due to the inexistence of established biomarkers for predicting disease progression. Here, we performed an exploratory cross-sectional, case-control study aimed at determining whether gene expression differences in peripheral blood may be used as a signature of Parkinson's disease (PD) progression, thereby shedding light into potential molecular mechanisms underlying disease development. We compared transcriptional profiles in the blood from 34 PD patients who developed postural instability within ten years with those of 33 patients who did not develop postural instability within this time frame. Our study identified >200 differentially expressed genes between the two groups. The expression of several of the genes identified was previously found deregulated in animal models of PD and in PD patients. Relevant genes were selected for validation by real-time PCR in a subset of patients. The genes validated were linked to nucleic acid metabolism, mitochondria, immune response and intracellular-transport. Interestingly, we also found deregulation of these genes in a dopaminergic cell model of PD, a simple paradigm that can now be used to further dissect the role of these molecular players on dopaminergic cell loss. Altogether, our study provides preliminary evidence that expression changes in specific groups of genes and pathways, detected in peripheral blood samples, may be correlated with differential PD progression. Our exploratory study suggests that peripheral gene expression profiling may prove valuable for assisting in prediction of PD prognosis, and identifies novel culprits possibly involved in dopaminergic cell death. Given the exploratory nature of our study, further investigations using independent, well-characterized cohorts will be essential in order to validate our candidates as predictors of PD prognosis and to definitively confirm the value of gene expression analysis in aiding patient stratification and therapeutic intervention.

Neuro-inflammation, one of the pathogenic causes of neurodegenerative diseases, is regulated through the cholinergic anti-inflammatory pathway via the alpha7 nicotinic acetylcholine receptor (alpha7 nAChR). We previously showed that either bacterial lipopolysaccharide (LPS) or immunization with the alpha7(1-208) nAChR fragment decrease alpha7 nAChRs density in the mouse brain, exacerbating chronic inflammation, beta-amyloid accumulation and episodic memory decline, which mimic the early stages of Alzheimer’s disease (AD). To study the molecular mechanisms underlying the LPS and antibody effects in the brain, we employed an in vivo model of acute LPS-induced inflammation and an in vitro model of cultured glioblastoma U373 cells. Here, we report that LPS challenge decreased the levels of alpha7 nAChR RNA and protein and of acetylcholinesterase (AChE) RNA and activity in distinct mouse brain regions, sensitized brain mitochondria to the apoptogenic effect of Ca(2+) and modified brain microRNA profiles, including the cholinergic-regulatory CholinomiRs-132/212, in favor of anti-inflammatory and pro-apoptotic ones. Adding alpha7(1-208)-specific antibodies to the LPS challenge prevented elevation of both the anti-inflammatory and pro-apoptotic miRNAs while supporting the resistance of brain mitochondria to Ca(2+) and maintaining alpha7 nAChR/AChE decreases. In U373 cells, alpha7-specific antibodies and LPS both stimulated interleukin-6 production through the p38/Src-dependent pathway. Our findings demonstrate that acute LPS-induced inflammation induces the cholinergic anti-inflammatory pathway in the brain, that alpha7 nAChR down-regulation limits this pathway, and that alpha7-specific antibodies aggravate neuroinflammation by inducing the pro-inflammatory interleukin-6 and dampening anti-inflammatory miRNAs; however, these antibodies may protect brain mitochondria and decrease the levels of pro-apoptotic miRNAs, preventing LPS-induced neurodegeneration.

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Few studies so far examined alternative splicing alterations in blood cells of neurodegenerative disease patients, particularly Parkinson’s disease (PD). Prototype junction microarrays interrogate known human genome junctions and enable characterization of alternative splicing events; however, the analysis is not straightforward and different methods can be used to estimate junction-specific alternative splicing events (some of which can also be applied for analyzing RNA sequencing junction-level data). In this study, we characterized alternative splicing changes in blood leukocyte samples from Parkinson’s patients prior to, and following deep brain stimulation (DBS) treatment; both on stimulation and following 1 h off electrical stimulation. Here, we describe in detail analysis approaches for junction microarrays and provide suggestions for further analyses to delineate transcript level effects of the observed alterations as well as detection of microRNA binding sites and protein domains in the alternatively spliced target regions spanning across both untranslated and the coding regions of the targets. The raw expression data files are publically available in the Gene Expression Omnibus (GEO) database (accession number: GSE37591) and in Synapse, and can be re-analyzed. The results may be useful for designing of future experiments and cross correlations with other datasets from PD or patients having other neurodegenerative diseases.

Calcium influx elevates mitochondrial oxidant stress (mOS) in dorsal motor nucleus of the vagus (DMV) neurons that are prone to Lewy body pathologies in presymptomatic Parkinson's disease (PD) patients. In experimental PD models, treatment with isradipine, the dihydropyridine with the highest affinity to Cav1.3 channels, prevents subthreshold calcium influx via Cav1.3 channels into midbrain dopamine neurons and protects them from mOS. In DMV neurons, isradipine is also effective in reducing mOS despite overwhelming evidence that subthreshold calcium influx is negligible compared with spike-triggered influx. To solve this conundrum we combined slice electrophysiology, two-photon laser scanning microscopy, mRNA profiling, and computational modeling. We find that the unusually depolarized subthreshold voltage trajectory of DMV neurons is positioned between the relatively hyperpolarized activation curve of Cav1.3 channels and that of other high-voltage activated (HVA) calcium channels, thus creating a functional segregation between Cav1.3 and HVA calcium channels. The HVA channels flux the bulk of calcium during spikes but can only influence pacemaking through their coupling to calcium-activated potassium currents. In contrast, Cav1.3 currents, which we show to be more than an order-of-magnitude smaller than the HVA calcium currents, are able to introduce sufficient inward current to speed up firing. However, Kv4 channels that are constitutively open in the subthreshold range guarantee slow pacemaking, despite the depolarizing action of Cav1.3 and other pacemaking currents. We propose that the efficacy of isradipine in preventing mOS in DMV neurons arises from its mixed effect on Cav1.3 channels and on HVA Cav1.2 channels.


Recent evidence demonstrates the power of RNA sequencing (RNA-Seq) for identifying valuable and urgently needed blood biomarkers and advancing both early and accurate detection of neurological diseases, and in particular Parkinson's disease (PD). RNA sequencing technology enables non-biased, high throughput, probe-independent inspection of expression data and high coverage and both quantification of global transcript levels as well as the detection of expressed exons and junctions given a sufficient sequencing depth (coverage). However, the analysis of sequencing data frequently presents a bottleneck. Tools for quantification of alternative splicing from sequenced libraries hardly exist at the present time, and methods that support multiple sequencing platforms are especially lacking. Here, we describe in details a whole RNA-Seq transcriptome dataset produced from PD patient's blood leukocytes. The samples were taken prior to, and following deep brain stimulation (DBS) treatment while being on stimulation and following 1 h of complete electrical stimulation cessation and from healthy control volunteers. We describe in detail the methodology applied for analyzing the RNA-Seq data including differential expression of long noncoding RNAs (lncRNAs). We also provide details of the corresponding analysis of in-depth splice isoform data from junction and exon reads, with the use of the software AltAnalyze. Both the RNA-Seq raw (http://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE42608) and analyzed data (https://www.synapse.org/#!Synapse:syn2805267) may be found valuable towards detection of novel blood biomarkers for PD.

controllers coordinate the identity, functioning, dynamics, and brain-to-body communication of cholinergic cells. Checks and balances including epigenetic mechanisms, alternative splicing, and miRNAs may all expand or limit the diversity of these cholinergic components by consistently performing genome-related surveillance. This regulatory network enables homeostatic maintenance of brain-to-body ACh signaling as well as reactions to nicotine, Alzheimer's disease anticholinesterase therapeutics, and agricultural pesticides. Here I review recent reports on the functional implications of these controllers of cholinergic signaling in and out of the brain.

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