
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.


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
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.
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.

2015
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.
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.


A century after the discovery of acetylcholine (ACh), we recognize both ACh receptors, transporters, and synthesizing and degrading enzymes and regulators of their expression as contributors to cognition, metabolism, and immunity. Recent discoveries indicate that pre- and post-transcriptional ACh signaling 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.


Recent international terror outbreaks notably involve long-term mental health risks to the exposed population, but whether physical health risks are also anticipated has remained unknown. Here, we report fear of terror-induced annual increases in resting heart rate (pulse), a notable risk factor of all-cause mortality. Partial least squares analysis based on 325 measured parameters successfully predicted annual pulse increases, inverse to the expected age-related pulse decline, in approximately 4.1% of a cohort of 17,380 apparently healthy active Israeli adults. Nonbiased hierarchical regression analysis among 27 of those parameters identified pertinent fear of terror combined with the inflammatory biomarker C-reactive protein as prominent coregulators of the observed annual pulse increases. In comparison, basal pulse primarily depended on general physiological parameters and reduced cholinergic control over anxiety and inflammation, together indicating that consistent exposure to terror threats ignites fear-induced exacerbation of preexisting neuro-immune risks of all-cause mortality.

It is generally assumed that sociology affects scientific progress but specific examples of this assumption are hard to find. We examined this hypothesis by comparing the social network structure and its dynamics over the last 16 years, for two common human diseases; Alzheimer's disease, for which there has been very little therapeutic progress, and Lymphoma, were there has been significant therapeutic progress. We found that the Alzheimer's research community is more interlinked ('dense') and more 'cliquish' than that of Lymphoma and suggest that this could affect its scientific progress.

2014


MicroRNAs (miRNAs) have presumably contributed to the emergence of the novel expression patterns, higher brain functions and skills underlying human evolution. However, it is incompletely understood how new miRNAs have evolved in the human lineage since their initial emergence predictably entailed deleterious consequences due to their powerful multi-target effects. Here, we report genetic variation and conservation parameters for miRNAs and their predicted targets in the genomes of 1092 humans and 58 additional organisms. We show that miRNAs were evolutionarily more conserved than their predicted binding sites, which were inversely subject to the accumulation of single nucleotide variations over short evolutionary timescales. Moreover, the predictably 'younger' human-specific miRNAs presented lower genetic variation than other miRNAs; their targets displayed higher genetic variation compared to other miRNA targets in diverse human populations; and neuronal miRNAs showed yet lower levels of genetic variation and were found to target more protein-coding genes than non-neuronal miRNAs. Furthermore, enrichment analysis indicated that targets of human-specific miRNAs primarily perform neuronal functions. Specifically, the genomic regions harboring the vertebrate-conserved neuronal miRNA-132 presented considerably higher conservation scores than those of its target genes throughout evolution, whereas both the recently evolved human miRNA-941 and its acquired targets showed relatively low conservation. Our findings demonstrate inversely correlated genetic variation around miRNAs and their targets, consistent with theories of co-evolution of these elements and the predicted role attributed to miRNAs in recent human evolution.


The continuously prolonged human lifespan is accompanied by increase in neurodegenerative diseases incidence, calling for the development of inexpensive blood-based diagnostics. Analyzing blood cell transcripts by RNA-Seq is a robust means to identify novel biomarkers that rapidly becomes a commonplace. However, there is lack of tools to discover novel exons, junctions and splicing events and to precisely and sensitively assess differential splicing through RNA-Seq data analysis and across RNA-Seq platforms. Here, we present a new and comprehensive computational workflow for whole-transcriptome RNA-Seq analysis, using an updated version of the software AltAnalyze, to identify both known and novel high-confidence alternative splicing events, and to integrate them with both protein-domains and microRNA binding annotations. We applied the novel workflow on RNA-Seq data from Parkinson's disease (PD) patients' leukocytes pre- and post- Deep Brain Stimulation (DBS) treatment and compared to healthy controls. Disease-mediated changes included decreased usage of alternative promoters and N-termini, 5'-
end variations and mutually-exclusive exons. The PD regulated FUS and HNRNP A/B included prion-like domains regulated regions. We also present here a workflow to identify and analyze long non-coding RNAs (lncRNAs) via RNA-Seq data. We identified reduced lncRNA expression and selective PD-induced changes in 13 of over 6,000 detected leukocyte lncRNAs, four of which were inversely altered post-DBS. These included the U1 spliceosomal lncRNA and RP11-462G22.1, each entailing sequence complementarity to numerous microRNAs. Analysis of RNA-Seq from PD and unaffected controls brains revealed over 7,000 brain-expressed lncRNAs, of which 3,495 were co-expressed in the leukocytes including U1, which showed both leukocyte and brain increases. Furthermore, qRT-PCR validations confirmed these co-increases in PD leukocytes and two brain regions, the amygdala and substantia-nigra, compared to controls. This novel workflow allows deep multi-level inspection of RNA-Seq datasets and provides a comprehensive new resource for understanding disease transcriptome modifications in PD and other neurodegenerative diseases.


Selective serotonin reuptake inhibitors (SSRIs) show anti-inflammatory effects, suggesting a possible interaction with both Toll-like-receptor 4 (TLR4) responses and cholinergic signaling through as yet unclear molecular mechanism(s). Our results of structural modeling support the concept that the antidepressant fluoxetine physically interacts with the TLR4-myeloid differentiation factor-2 complex at the same site as bacterial lipopolysaccharide (LPS). We also demonstrate reduced LPS-induced pro-inflammatory interleukin-6 and tumor necrosis factor alpha in human peripheral blood mononuclear cells preincubated with fluoxetine. Furthermore, we show that fluoxetine intercepts the LPS-induced decreases in intracellular acetylcholinesterase (AChE-S) and that AChE-S interacts with the nuclear factor kappa B (NFkB)-activating intracellular receptor for activated C kinase 1 (RACK1). This interaction may prevent NFkB activation by residual RACK1 and its interacting protein kinase PKC?II. Our findings attribute the anti-inflammatory properties of SSRI to surface membrane interference with leukocyte TLR4 activation accompanied by intracellular limitation of pathogen-inducible changes in AChE-S, RACK1, and PKC?II.


Accumulating evidence suggests parasympathetic dysfunction and elevated inflammation as underlying processes in multiple peripheral and neurological diseases. Acetylcholine, the main parasympathetic neurotransmitter and inflammation regulator, is hydrolyzed by the two closely homologous enzymes, acetylcholinesterase and butyrylcholinesterase (AChE and BChE, respectively), which are also expressed in the serum. Here, we consider the potential value of both enzymes as possible biomarkers in diseases associated with parasympathetic malfunctioning. We cover the modulations of cholinesterase activities in inflammation-related events as well as by cholinesterase-targeted microRNAs. We further discuss epigenetic control over cholinesterase gene expression and the impact of single-nucleotide polymorphisms on the corresponding physiological and pathological processes. In particular, we focus on measurements of circulation cholinesterases as a readily quantifiable readout for changes in the sympathetic/parasympathetic balance and the implications of changes in this readout in health and disease. Taken together, this cumulative know-how calls for expanding the use of cholinesterase activity measurements for both basic research and as a clinical assessment tool.

MicroRNAs (miRNAs) can repress multiple targets, but how a single de-balanced interaction affects others remained unclear. We found that changing a single miRNA-target interaction can simultaneously affect multiple other miRNA-target interactions and modify physiological phenotype. We show that miR-608 targets acetylcholinesterase (AChE) and demonstrate weakened miR-608 interaction with the rs17228616 AChE allele having a single-nucleotide polymorphism (SNP) in the 3'-untranslated region (3'UTR). In cultured cells, this weakened interaction potentiated miR-608-mediated suppression of other targets, including CDC42 and interleukin-6 (IL6). Postmortem human cortices homozygote for the minor rs17228616 allele showed AChE elevation and CDC42/IL6 decreases compared with major allele homozygotes. Additionally, minor allele heterozygote and homozygote subjects showed reduced cortisol and elevated blood pressure, predicting risk of anxiety and hypertension. Parallel suppression of the conserved brain CDC42 activity by intracerebroventricular ML141 injection caused acute anxiety in mice. We demonstrate that SNPs in miRNA-binding regions could cause expanded downstream effects changing important biological pathways.


Parasympathetic activity influences long-term outcome in patients with cardiovascular disease, but the underlying mechanism(s) linking parasympathetic activity and the occurrence of major adverse cardiovascular events (MACEs) are incompletely understood. The aim of this pilot study was to evaluate the association between serum cholinesterase activities as parasympathetic biomarkers and the risk for the occurrence of MACEs. Cholinergic status was determined by measuring the cumulative capacity of serum acetylcholinesterase (AChE) and butyrylcholinesterase (BChE) to hydrolyze the AChE substrate acetylthiocholine. Cholinergic status was evaluated in randomly selected patients undergoing cardiac catheterization. The patients were divided into two groups of 100 patients in each group, with or without occurrence of MACEs during a follow-up period of 40 months. Cox regression models adjusted for potential clinical, metabolic and inflammatory confounders served to evaluate association with clinical outcome. We found that patients with MACE presented lower cholinergic status and AChE values at catheterization (1,127 ± 422 and 359 ± 153 nmol substrate hydrolyzed per minute per milliliter, respectively) than no-MACE patients (1,760 ± 546 and 508 ± 183 nmol substrate hydrolyzed per minute per milliliter, p


Neurodegenerative diseases in general and specifically late-onset Alzheimer's disease (LOAD) involve a genetically complex and largely obscure ensemble of causative and risk factors accompanied by complex feedback responses. The advent of "high-throughput" transcriptome investigation technologies such as microarray and deep sequencing is increasingly being combined with sophisticated statistical and bioinformatics analysis methods complemented by knowledge-based approaches such as Bayesian Networks or network and graph analyses. Together, such "integrative" studies are beginning to identify co-regulated gene networks linked with biological pathways and potentially modulating disease predisposition, outcome, and progression. Specifically, bioinformatics analyses of integrated microarray and genotyping
data in cases and controls reveal changes in gene expression of both protein-coding and small and long regulatory RNAs; highlight relevant quantitative transcriptional differences between LOAD and non-demented control brains and demonstrate reconfiguration of functionally meaningful molecular interaction structures in LOAD. These may be measured as changes in connectivity in "hub nodes" of relevant gene networks (Zhang et al., 2013). We illustrate here the open analytical questions in the transcriptome investigation of neurodegenerative disease studies, proposing "ad hoc" strategies for the evaluation of differential gene expression and hints for a simple analysis of the non-coding RNA (ncRNA) part of such datasets. We then survey the emerging role of long ncRNAs (IncRNAs) in the healthy and diseased brain transcriptome and describe the main current methods for computational modeling of gene networks. We propose accessible modular and pathway-oriented methods and guidelines for bioinformatics investigations of whole transcriptome next generation sequencing datasets. We finally present methods and databases for functional interpretations of IncRNAs and propose a simple heuristic approach to visualize and represent physical and functional interactions of the coding and non-coding components of the transcriptome. Integrating in a functional and integrated vision coding and ncRNA analyses is of utmost importance for current and future analyses of neurodegenerative transcriptomes.
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Weakened cholinergic blockade of inflammation associates with diabetes-related depression.

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