Daniel Sapozhnikov[1]

[1]Department of Biology, Mc-Gill University, Montreal, QC, Canada

The Promise of Mindfulness-Based Interventions as Therapies to Prevent Cognitive Decline

Email Correspondence

daniel.sapozhnikov@mail.mcgill.ca

Abstract

Background: Alzheimer's disease (AD) is a neurodegenerative disorder that affects 5 million United States citizens. Many authors have proposed that mindfulness-based interventions (MBIs) have the potential to effectively prevent AD-associated pathology and symptomology. However, the fact that both meditation and AD are complex processes that involve a great number of biological pathways has made these phenomena particularly challenging to dissect. This review advocates the use of gene expression to investigate the mechanisms by which MBIs combat AD pathology.

Methods: Searches were performed using Thomson Reuters Web of Science. Ultimately, 85 journal articles were selected for their content as it pertains to the purpose of this review.

Summary: Peripheral blood mononuclear cells (PBMCs) may provide reliable measures of cerebral gene expression. Profiling their gene expression has demonstrated that MBIs may produce gene expression changes in many of the same pathways (inflammation, cellular stress, proliferation, synaptic function) and often in the opposite direction of disease-related deregulation. While AD is marked by shortened telomeres resulting in genetic turmoil, meditation has been documented to exhibit a positive effect on telomere maintenance. A comprehensive gene expression investigation is invaluable to reveal relevant molecular mechanisms and provide the foundation for exploring the interaction between MBI and AD.

Introduction

Alzheimer's disease (AD) is the sixth leading cause of death in the United States and affects more than 5 million citizens. By the year 2050, this number is expected to nearly triple to 13.8 million citizens. It is a particularly common disease in those of advanced age, with 11% of people age 65 and older and 32% of people 85 and older suffering from AD. Disease management carries heavy financial burden, with total costs of care expected to increase from a current annual $203 billion to $1.2 trillion by 2050. Unfortunately, these vast expenses do little for the patients, as AD cannot be treated, nor can its progression be slowed. The prevalence and associated expenses make AD uniquely damaging to society, but the neurodegenerative symptoms – of vastly unknown pathology – are the true detriment to quality of life. (1)

The promise of secondary prevention takes its roots in a 1988 postmortem examination of 137 nursing home residents that revealed 10 subjects whose cognition and functionality during life were unaffected despite mild AD pathology in the brain. Interestingly, these 10 subjects also had higher brain weights and greater neuron density, indicative of what is known as higher brain reserve. (2) Since these origins, the cognitive reserve hypothesis has evolved to encompass the fact that an individual with larger brain size and neuronal count has a reserve of brain matter that may protect the brain from neurodegenerative diseases by providing alternate physical pathways for effective neural signaling as other paths degenerate with disease. In fact, a meta-analysis of over 29,000 individuals showed that those with high cognitive reserve had a 46% reduced risk of developing dementia. (3) Further research has shown that increased cortical atrophy, higher levels of amyloid peptides in cerebrospinal fluid, and greater regional atrophy are necessary in order for individuals with higher cognitive reserve to express clinical symptoms of AD. (4)

At present, the main determinants used to predict cognitive reserve are education, occupation, and leisure time activities. (5) An activity aimed at building cognitive reserve that appears to be very promising is mindful meditation, or rather, the many varying forms of mindfulness-based intervention (MBI), which has been shown to invoke increases in volume in several regions of the brain and thickens the cerebral cortex. (6) Though far from being established therapies, MBIs are supported by a range of statistically significant data suggesting that they are effective in treating psychological disorders.

Purported Effects of MBIs on AD-Related Pathology

One brain region of interest on which MBIs have a neurotrophic effect is the hippocampus. In AD, the hippocampus atrophies even before subjects or their family members notice cognitive changes. (7) The decline in hippocampal volume is strongly correlated to AD and is especially linked to memory-loss symptoms. Remarkably, when two studies employed short, 8-week meditation periods, researchers found promising effects in the hippocampus. Hölzel demonstrated an increased left hippocampal volume in healthy subjects, while Wells described decreased hippocampal atrophy in patients with Mild Cognitive Impairment (MCI), a stage that is commonly considered to precede early AD. (8, 9) However, these particular studies had small sample sizes and were designed to detect structural differences, with less focus on the clinical diagnoses and cognitive changes that are relevant to AD improvement. Several other studies by Luders have demonstrated significantly larger right and left hippocampal volumes in long-term meditators as opposed

to normal controls. (10, 11) The importance of this recurring association is that meditation may build reserve and reduce atrophy – leading to less diminished cognition – in the area of the brain which is most damaged by AD. Therefore, it is very possible that meditation will at least prevent symptoms associated with decreased hippocampal function.

Meditation may also prevent AD symptomology by other means. Although there is conflicting research amongst individual studies, meta-analyses and reviews suggest that depression is a risk factor for developing AD later in life, and one study reached the conclusion that MCI patients with depression have more than twice the risk of developing AD. (12-14) Depression occurs in approximately 20-30% of patients with AD, but it is unclear whether it is a risk factor for the disease, whether it is a symptom of neurodegeneration, or whether it is simply a reaction to cognitive decline. (15) No matter the case, MBIs are highly effective in decreasing the likelihood of depressive relapse. (16) Meditation has also been shown to counteract many other risk factors for AD, including high cholesterol, hypertension, stress, and cerebral hypoperfusion. (17-19)

Recent research has focused on the important role played by glucose in AD development, with a multitude of studies implicating defective glucose metabolism in patients with AD, plaque development, and decreased cognitive abilities. Several key findings are that higher blood glucose levels are a risk factor for AD; that AD patients have defective insulin signaling; and that insulin has been linked to neuroprotective factors that improve attention, memory, and cognition. More importantly, intranasal insulin therapy in patients with MCI and AD has produced cognitive improvements, possibly because the metabolism of the hippocampus is dependent on insulin for proper function. (20-22) At the same time, meditation upregulates insulin secretion, and as such, demonstrates the potential for decreasing cognitive decline. (23)

Ultimately, the aforementioned mechanisms are only a subset of the many ways that meditation can potentially mediate decreased cognitive decline and even improve cognitive function. For further reference, there are several recent review articles that further discuss the plethora of evidence to support this hypothesis. (24, 25) Of particular note is a review by Larouche et al. that identifies six main AD-related targets of MBIs: stress hormones, cytokines, serotonin, oxidation, white matter hyperintensities, insulin, and IGF-1. (26)

Research on MBIs in the context of AD is limited by few clinical studies and small sample sizes. However, the existing research does suggest that there is promise in the possibility that meditation can be an effective non-pharmacological invention. Several MBIs have been linked to slowed age-related atrophy of the brain, although these studies did not address the effects of neurodegenerative diseases. (6) Studies on the effect of Kirtan Kirya meditation on neurodegenerative diseases have documented many improved cognitive parameters in patients with cognitive decline, MCI, and AD. (19) A study by Well and colleagues also examined an MBI (MBSR) as a potential preventative measure for dementia-related cognitive decline. The preliminary study demonstrated the potential for reduced hippocampal atrophy and improved functional connectivity in patients with MCI, yet it had too small a sample size for significance, was not structured to detect clinical differences in cognition, lacked a long-term follow up, and had an inadequate control group. (9)

The Power of Gene Expression Profiling

Less than twenty studies address overlap between MBIs and neurodegenerative diseases, and to date, none have addressed the topic with the complexity that is necessary to understand this potential interaction. While clinically relevant measurements of the effectiveness of MBIs on AD progression – such as fMRIs that measure cerebral size and tests that estimate various cognitive abilities – are unarguably pertinent in evaluating the relevant outcomes of MBIs, these measures do nothing to elucidate the mechanisms by which the two phenomena interact. Both meditation and AD involve physiological changes in an immense number of biochemical pathways, which complicates analyses of AD pathogenesis and MBIs. (27) With microarray profiling, it is possible quantitate the expression of many genes in parallel and identify differentially expressed genes across diverging conditions. (28, 29) Thus, this technology may allow us to obtain a better understanding of convoluted molecular mechanisms.

In an effort to produce accurate gene expression profiles, it may be most relevant to investigate expression in cells of the CNS, and preferably those affected by AD pathology. Unfortunately, such analyses cannot be performed on the living, and post-mortem modifications of proteins and RNA degradation may perturb the resulting data. Still, there have been many studies investigating gene expression in human brains exhibiting a range of pathology, from MCI to severe AD. Such studies have reaffirmed the idea that AD is a systemic disease by finding significant differences in gene expression in a multitude of pathways. Those that were often down-regulated include general genomic transcription levels, transcription factors and associated signaling molecules, neurotrophic factors, signal transduction pathways, energy metabolism, synaptic vesicle pathways, calcium binding, and cytoskeletal formation. Those pathways that were consistently up-regulated were apoptotic signaling, pro-inflammatory signaling, cell adhesion, cell proliferation, protein synthesis, and lipid metabolism. (23, 30-37) However, many of these studies have had poor statistical power due mainly to small sample sizes. A recent study selectively reaffirmed decreased expression across a large number of genes involved in synaptic trafficking in MCI and AD patients as compared to healthy controls, with no significant difference between the two diseased states. (38) Further recent microarray studies have supported altered synaptic vesicle trafficking, as well as altered calcium signaling, cellular signaling, protein synthesis, metabolism, apoptosis, proliferation, transcription factor activity, inflammation, and neuronal proteins, among other differences that are concordant with the earlier gene expression analyses. (39-43) However, these were all post-mortem analyses of the brain and may contain gene expression data that is inconsistent with that of the living.

In 1996, it was noted that peripheral cells mimic many biological alterations that mark AD pathology. (44) Then in 2001, Tang and colleagues proposed the premise that distinct peripheral blood mononuclear cell (PBMC) expression patterns mirror differing neurological disease states, and used rat arrays with over 7000 genes to provide evidence for the hypothesized link. This team evaluated PBMC gene expression of rats that were subjected to ischemic strokes, hemorrhagic strokes, sham surgeries, kainite-induced seizures, and hypoxia or insulin-induced hypoglycemia, and concluded that these expression profiles are actually unique to each condition. Reporting gene expression changes in PBMCs after systemic hypoxia or hypoglycemia was not surprising since the cells are directly affected by the experimental conditions. However, changes in PBMC gene expression following non-systemic end-organ specific injury like brain ischemia, hemorrhage, or kainate-induced seizures was not self-explanatory, but confirmed the hypothesis that PBMC gene expression could be used as a fingerprint of cerebral neurological diseases. (45) Further study of PBMC gene expression patterns revealed consistency with distinct individual variations that were related to age, gender, the proportions of cell subtypes, and time of the day of sampling (46). Now, it is acknowledged that PBMCs can directly participate in the neurodegenerative processes and share many similarities with neurons in terms of biochemical machinery and AD-specific alterations. (47) Despite the fact that scientific research has yielded no validated peripheral markers for AD or any CNS-related events, PBMC gene expression analysis may be useful in understanding the multifactorial nature of neurological diseases, and especially those with systemic effects that extend past the central nervous system, such as AD.

There have been three studies that investigated the gene expression of PBMCs in AD patients. The first to address the issue was a study aimed to determine the gene expression profile of AD patients in comparison to age-matched controls in lymphocytes (a sub-category of PBMCs). RT-qPCR validation of microarray analyses excluded several genes – including those in the pathways of cellular and humoral immune responses and apoptosis – and determined that the α2C-adrenoreceptor and defensin genes – genes involved in blood pressure and inflammation – were the only truly down-regulated genes. (48) Another study in 2007 also aimed to profile mononuclear cell gene expression in mild AD patients, using microarray analysis followed by RT-qPCR. They discovered similar

results to neuronal gene expression analyses, with up-regulation of genes involved in apoptosis, cell development, cell metabolism, CNS-synapse, inflammation, lipid metabolism, protein synthesis, as well as down-regulation in many genes involved in anti-apoptosis, cell development, cell metabolism, synaptic processes, cytoskeleton form and function, DNA repair, inflammation, lipid metabolism, mitochondrial function, cellular trafficking, signal transduction, and transcription and translation. In fact, 28% of up-regulated genes and 16% of down-regulated genes were previously reported to have similar expression in the post-mortem expression analyses, all 3 of which were discussed previously. Comparison to more studies could result in more overlap. However, no genes were found to be in common with the aforementioned 2005 lymphocyte study, although similar pathways were affected. (49) The many correlations between this study and previous post-mortem studies strengthen the case of PBMCs as a "window" into the CNS. The third study, like the first, used lymphocytes for microarray expression analysis. While this study had the smallest sample sizes, it did make a distinction in order to compare AD and MCI to controls. The authors also found differences in expression of several of the same genes or genes in the same family as those that were differentially expressed in the previous monocyte study, including genes involved in cellular signaling and metabolism. They also found a significant differences in expression of members of the ABC transporter family (with roles in membrane transport, translation, and DNA repair) between normal patients, MCI patients, and AD patients. (50) Overall, the three studies in PBMCs have suggested expression differences in many similar functional categories of genes as the studies in CNS tissue and especially in the categories of inflammation and intracellular signaling. (39) Non-microarray, targeted studies of PBMCs have revealed further differential regulation in MCI and AD patients that include changes in expression of genes in cholesterol metabolism, inflammation (and specifically, NF-kB signaling), stress, proliferation, synaptic function, and iron homeostasis; the gene for transcription factor Sp1, which controls many AD-related proteins; and Scara1, an amyloid-beta receptor. (51-58)

Similar research has been conducted on the effects of MBIs on PMBC gene expression. The first study to do so analyzed practices that elicit the relaxation response (RR), which is particularly intriguing in that it does not delineate a specific form of meditation but rather allows for a variety of practices that induce similar physiological characteristics, mainly: decreased oxygen consumption, increased exhaled nitric oxide, and reduced physiological distress. (59, 60) This study compared the gene expression in long term practitioners (M) and 20 healthy controls (N1) who underwent eight weeks of RR training and were analyzed again (N2). In summary, the findings involved 1504 to 2209 differentially expressed genes in the 3 comparisons (N1 to N2, N1 to M, and N2 to M) with similar numbers of up-regulated and down-regulated genes. The differentially expressed genes were found to be involved in many recurring cellular pathways, including oxidative phosphorylation, ubiquitin-dependent protein catabolism, nuclear mRNA splicing, protein synthesis, cellular metabolism, NF-kB signaling, and the regulation of apoptosis. (61) Another study that also analyzed PBMC gene expression did so in response to Sudarshan Kriya, a yogic and meditative practice. However, instead of using microarrays, the study employed qRT-PCR techniques specifically focused on genes involved in oxidative stress, DNA damage, cell cycle control, aging and apoptosis. The study concluded that there were significant differences in gene expression of practitioners of several proteins that protect the cell from oxidative damage, and increases in inflammation- and apoptosis-related COX-2 and stress response gene HSP-70. The results also present increasing trends in telomerase reverse transcriptase and BCL-2, which are related to cellular aging and anti-apoptosis, respectively. (62) It is of note to mention a third study that has some similar findings despite being performed on neutrophils (which are not PBMCs) and on the practice of Qigong. This study also found down-regulated genes in ubiquitin-dependent protein catabolism, cellular stress (with the exception of two up-regulated HSPs), and protein synthesis, as well as up-regulation of certain immunity-related genes. (63) From these experiments, it is quite clear that MBIs give rise to gene expression changes in many of the same pathways that are altered by AD. However, these studies all have their own downfalls, including small sample sizes, unaccounted variables, and a lack of RT-qPCR validation. (64)

There are, however, several more recent studies that have provided

further insight into altered gene expression induced by meditative and yogic practices. A second study from the same RR researchers proceeded to further analyze the subject. Although focusing on temporal transcriptional changes associated with a single RR practice session after either long-term practice or an 8-week session, functional analysis revealed the potential impact of meditation on several pathways. The results demonstrated upregulated genes involved in telomere maintenance (which will be discussed in further detail below), calcium signaling, transcriptional regulation, insulin, and energy metabolism – which, as the authors propose, may aid in protection against aging and oxidation – and down-regulated genes in the apoptosis pathway, stress response pathway, and inflammatory pathways, including NF-kB and associated molecules. (23) Another study that examined effects from only daily sessions of Sudarshan Kriya rather than longer-term practices reported significant rapid gene expression changes even from these single sessions. However, with several different approaches to gene ontology analysis, they were unable to identify any specific pathways that were affected. (65) Yet another study established decreased expression of pro-inflammatory genes and histone-deacetylases (HDACs, which generally repress transcription) based on custom pathway RT-qPCR of PBMC RNA of expert meditators after a day of intensive meditation. (66) Taken together, the two previously mentioned studies indicate that single daily sessions would most likely not be sufficient to combat AD pathology, and therefore serve to justify a longer intervention.

Only two studies have employed MBIs strictly as interventions – both lasting 8 weeks – and used PBMC gene expression as an outcome measure. One promising study demonstrated how 8 weeks of Kirtan Kriya Meditation reversed the pattern of up-regulated NF-kB-related inflammatory gene expression and decreased immunity gene expression observable in the PBMCs of dementia caregivers. (67) Even more relevant is one study that employed an 8 week MBSR intervention and discovered decreased expression of pro-inflammatory genes (including NF-kB) and correlated the reduction in inflammatory gene expression with a reduction in loneliness. (68) Despite being limited by small sample sizes, these studies demonstrate potential for meditation to combat at least some of the pathology of AD at the level of gene expression. There have been no published studies investigating the effects of MBIs on MCI or AD patients that have measured gene expression.

Telomeres

The effects of meditation and the pathology of AD converge on telomere maintenance. Telomeres are gene-poor, repetitive DNA regions that span 10-15 kb in humans. Active telomerase is crucial to maintain telomere length, and in turn, length is necessary to maintain cell viability; shortening beyond a critical length triggers a DNA damage response that results in cell cycle arrest or apoptosis. Telomere shortening is thought to contribute to the pathologies of degenerative diseases that often occur with age. (69, 70)

One of the first studies on AD and telomere length concluded that the PBMCs of AD patients had shorter telomeres than those of age-matched controls, and that T-cell telomere length specifically was correlated with Mini-Mental State Examination (MMSE) scores. The study also found an inversion correlation of T-cell telomere length with serum levels of the pro-inflammatory cytokine TNFα, suggestive of the concept that decreased telomere length is conducive of the immune dysfunction that is characteristic of AD pathology. (71) A study several years later provided supporting evidence, again citing shorter telomere lengths in T-cells of patients with AD-type dementia. (72) A third study demonstrated decreased peripheral blood leukocyte (PBL) telomere length in AD patients with a higher mortality correlated with shorter telomere length. (73) Another study also reported decreased PBL telomere length in AD, but comparatively longer hippocampal telomere length, probably due to gliosis, a glial cell response to cerebral injury that involves up-regulated telomerase. When comparing telomere length in the cerebellum – a region that is incapable of gliosis – to PBL telomere length, a correlation was found. (74, 75) Of particular note is a later study that reported significantly shorter

telomere length in monocytes of AD patients compared to controls. (76) An important implication of this research is that longer telomere length is associated with more normal functioning. Indeed, longer telomere length has been shown to be linked to improved cognitive function in healthy and cognitively impaired subjects, thereby making telomere length a target for therapeutic medicines and practices. (73, 77-78)

As mentioned above, increased telomerase expression after MBIs has been noted in microarray analyses. (23) However, this measurement of RNA transcription alone is insufficient evidence of increased telomerase function nor of increased telomere length. To pursue the question, there have been four randomized control trials that tested the effect of meditation on telomerase activity in PBMCs. The studies had varied controls, sample sizes (39-63), hours of practice (11-57), methodology for outcome measures, populations (overweight, chronic fatigue, long-term meditators, dementia caretakers), and meditative practices; yet all studies reported increased telomerase activity in the meditative group. (79-82) Together, these four studies display a significant combined effect size of 0.46. (83) However, an important point is that increased telomerase activity does not necessarily translate increased telomere length, as telomerase must access the DNA in order to extend it. One trial investigated the effect of meditation on actual telomere length, and though restricted by a small sample size, it demonstrated an increasing trend in relative telomere length (RTL) and a significantly longer RTL in women. (84) No randomized controlled trials have examined the effect of meditation on telomere length or telomerase activity in MCI or AD patients.

Concluding Remarks

It is necessary to first validate the yet-unverified principle that MBIs may prevent the progression of AD pathology before delving into intricate dissections of the relevant molecular interactions. Furthermore, the time period of intervention must be refined; is prevention best accomplished with lifelong commitment to an MBI, or can it be employed as a short therapy when the disease is already visible; and if so, at what stages will it be effective? These questions can best be addressed by large, highly controlled studies which measure clinically relevant symptoms of AD progression, such as cognitive decline and cortical atrophy. It is important to note that while gene expression may identify candidate interfaces of AD-MBI interaction, it only creates the foundation for functional experiments to clarify and explain the overlapping pathways. Furthermore, a necessary supplement to these investigations would be to isolate the epigenetic mechanisms that are at the root of the changes in gene expression.

AD and meditation are two complicated processes that involve changes in a great multitude of unique and overlapping pathways. As science continues to push forward the frontiers of high throughput information processing, the veiled particulars may emerge to provide a clearer understanding of their interaction. However, the genetic and molecular information of the present day stands in strong support of the hypothesis that meditation may be an effective means for the prevention of AD progression. The scientific world awaits a comprehensive gene expression study that can form the basis for a new age of effective, noninvasive dementia treatment.

References

1. Alzheimer's Association. 2013 Alzheimer's disease facts and figures. Alzheimer's & dementia: the journal of the Alzheimer's Association. 2013; 9(2), 208.
2. Katzman R, Terry R, DeTeresa R, Brown T, Davies P, et al. Clinical, pathological, and neurochemical changes in dementia: A subgroup with preserved mental status and numerous neocortical plaques. Ann Neurol. 1988; 23: 138–144.
3. Valenzuela MJ, Sachdev P. Brain reserve and dementia: a systematic review. Psychol. Med. 2006; 36, 441-454.
4. Tucker AM, Stern Y. Cognitive Reserve in Aging. Current Alzheimer Research. 2011; 8(3).
5. Reed BR, Dowling M, Tomaszewski Farias S, Sonnen J., Strauss M, et al. Cognitive activities during adulthood are more important than education in building reserve. J. Int. Neuropsychol. Soc. 2011; 17(4): 615-624.
6. Luders E. Exploring age-related brain degeneration in meditation practitioners. Annals of the New York Academy of Sciences. 2014; 1307: 82–88.
7. Fox NC, Warrington EK, Freeborough PA, Hartikainen P, Kennedy AM, et al. Presymptomatic hippocampal atrophy in Alzheimer's disease A longitudinal MRI study. Brain. 1996; 119(6), 2001-2007.
8. Hölzel BK, Carmody J, Vangel M, Congleton C, Yerramsetti SM, et al. Mindfulness practice leads to increases in regional brain gray matter density, Psychiatry Research: Neuroimaging. 2011; 191(1): 36-43.
9. Wells RE, Yeh GY, Kerr CE, Wolkin J, Davis RB, et al. Meditation's impact on default mode network and hippocampus in mild cognitive impairment: A pilot study. Neuroscience Letters. 2013; 556, 15-19.
10. Luders E, Toga AW, Lepore N, Gaser C. The underlying anatomical correlates of long-term meditation: larger hippocampal and frontal volumes of gray matter. Neuroimage. 2009; 45(3), 672-678.
11. Luders E, Thompson PM, Kurth F, Hong JY, Phillips OR, et al. Global and regional alterations of hippocampal anatomy in long-term meditation practitioners. Human brain mapping. 2013; 34(12), 3369-3375.
12. Ownby RL, Crocco E, Acevedo A, John V, Loewenstein D. Depression and risk for Alzheimer disease: systematic review, meta-analysis, and metaregression analysis. Archives of general psychiatry. 2006; 63(5), 530-538.
13. Green RC, Cupples LA, Kurz A, Auerbach S, Go R, et al. Depression as a risk factor for Alzheimer disease: the MIRAGE Study. Archives of neurology. 2003; 60(5), 753-759.
14. Modrego PJ, Ferrández J. Depression in patients with mild cognitive impairment increases the risk of developing dementia of Alzheimer type: a prospective cohort study. Archives of Neurology. 2004; 61(8), 1290-1293.
15. Tsuno N, Homma A. What is the association between depression and Alzheimer's disease? Expert. Rev. Neurother. 2009; 9:1667–76.
16. Segal ZV, Williams JMG, Teasdale, JD. Mindfulness-based cognitive therapy for depression. New York: Guilford Press; 2012.
17. Toledo JB, Toledo E, Weiner MW, Jack Jr CR, Jagust W, et al. Cardiovascular risk factors, cortisol, and amyloid-β deposition in Alzheimer's Disease Neuroimaging Initiative. Alzheimer's & Dementia. 2012; 8(6), 483-489.
18. Roher AE, Debbins JP, Malek-Ahmadi M, Chen K, Pipe JG, et al. Cerebral blood flow in Alzheimer's disease. Vascular health and risk management. 2011; 8, 599-611.
19. Marciniak R, Sheardova K, Čermáková P, Hudeček D, Šumec R, et al. Effect of meditation on cognitive functions in context of aging and neurodegenerative diseases. Frontiers in Behavioral Neuroscience. 2014; 8.
20. Crane PK, Walker R, Hubbard RA, Li G, Nathan DM, et al. Glucose levels and risk of dementia. New England Journal of Medicine. 2013; 369(6), 540-548.
21. Hölscher C. First clinical data of the neuroprotective effects of nasal insulin application in patients with Alzheimer's disease. Alzheimer's & Dementia. 2014; 10(1), S33-S37.
22. McNay EC, Ong CT, McCrimmon RJ, Cresswell J, Bogan JS, et al. Hippocampal memory processes are modulated by insulin and high-fat-induced insulin resistance. Neurobiology of learning and memory. 2010; 93(4), 546-553.
23. Bhasin MK, Dusek JA, Chang BH, Joseph MG, Denninger JW, et al. Relaxation response induces temporal transcriptome changes in energy metabolism, insulin secretion and inflammatory pathways. PloS one. 2013; 8(5), e62817.
24. Gard T, Hölzel BK, Lazar SW. The potential effects of meditation on age-related cognitive decline: a systematic review. Annals of the New York Academy of Sciences. 2014; 1307(1), 89-103.
25. Innes KE, Selfe TK. Meditation as a therapeutic intervention for adults at risk for Alzheimer's disease–potential benefits and underlying mechanisms. Frontiers in psychiatry. 2014; 5.
26. Larouche E, Hudon C, Goulet S. Potential benefits of mindfulness-based interventions in mild cognitive impairment and Alzheimer's disease: An interdisciplinary perspective. Behavioural Brain Research. 2015; 276, 199-212.
27. Blalock EM, Geddes JW, Chen KC, Porter NM, Markesbery WR, et al. Incipient Alzheimer's disease: microarray correlation analyses reveal major transcriptional and tumor suppressor responses.Proceedings of the National Academy of Sciences of the United States of America. 2004; 101(7), 2173-2178.
28. Schena M, Shalon D, Davis RW, Brown PO. Quantitative monitoring of gene expression patterns with a complementary DNA microarray. Science. 1995; 270(5235), 467-470.
29. Pan W. A comparative review of statistical methods for discovering differentially expressed genes in replicated microarray experiments. Bioinformatics. 2002; 18(4), 546-554.
30. Colangelo V, Schurr J, Ball MJ, Pelaez RP, Bazan NG, et al. Gene expression profiling of 12633 genes in Alzheimer hippocampal CA1: Transcription and neurotrophic factor down-regulation and up-regulation of apoptotic and pro-inflammatory signaling. Journal of neuroscience research. 2002; 70(3), 462-473.
31. Loring JF, Wen X, Lee JM, Seilhamer J, Somogyi R. A gene expression profile of Alzheimer's disease. DNA and cell biology. 2001; 20(11), 683-695.
32. Ginsberg SD, Hemby SE, Lee VM, Eberwine JH, Trojanowski JQ. Expression profile of transcripts in Alzheimer's disease tangle-bearing CA1 neurons. Annals of neurology. 2000; 48(1), 77-87.

33. Mufson EJ, Counts SE, Ginsberg SD. Gene expression profiles of cholinergic nucleus basalis neurons in Alzheimer's disease. Neurochemical research. 2002; 27(10), 1035-1048.

34. Yao PJ, Zhu M, Pyun EI, Brooks AI, Therianos S, et al. Defects in expression of genes related to synaptic vesicle trafficking in frontal cortex of Alzheimer's disease. Neurobiology of disease. 2003; 12(2), 97-109.

35. Pasinetti GM. Use of cDNA microarray in the search for molecular markers involved in the onset of Alzheimer's disease dementia. Journal of neuroscience research. 2001; 65(6), 471-476.

36. Marcotte ER, Srivastava LK, Quirion R. cDNA microarray and proteomic approaches in the study of brain diseases: focus on schizophrenia and Alzheimer's disease. Pharmacology & therapeutics. 2003; 100(1), 63-74.

37. Blalock EM, Chen KC, Stromberg AJ, Norris CM, Kadish I, et al. Harnessing the power of gene microarrays for the study of brain aging and Alzheimer's disease: statistical reliability and functional correlation. Ageing research reviews. 2005; 4(4), 481-512.

38. Counts SE, Alldred MJ, Che S, Ginsberg SD, Mufson EJ. Synaptic gene dysregulation within hippocampal CA1 pyramidal neurons in mild cognitive impairment. Neuropharmacology. 2014; 79, 172-179.

39. Cooper-Knock J, Kirby J, Ferraiuolo L, Heath PR, Rattray M, et al. Gene expression profiling in human neurodegenerative disease. Nature Reviews Neurology. 2012; 8(9), 518-530.

40. Saetre P, Jazin E, Emilsson L. Age-related changes in gene expression are accelerated in Alzheimer's disease. Synapse. 2011; 65(9), 971-974.

41. Berchtold NC, Sabbagh MN, Beach TG, Kim RC, Cribbs DH, et al. Brain gene expression patterns differentiate mild cognitive impairment from normal aged and Alzheimer's disease. Neurobiology of aging. 2014; 35(9), 1961-1972.

42. Panigrahi PP, Singh TR. Computational studies on Alzheimer's disease associated pathways and regulatory patterns using microarray gene expression and network data: Revealed association with aging and other diseases. Journal of theoretical biology. 2013; 334, 109-121.

43. Avramopoulos D, Szymanski M, Wang R, Bassett S. Gene expression reveals overlap between normal aging and Alzheimer's disease genes. Neurobiology of aging. 2011; 32(12), 2319-e27.

44. Govoni S, Gasparini L, Racchi M, Trabucchi M. Peripheral cells as an investigational tool for Alzheimer's disease. Life sciences. 1996; 59(5), 461-468.

45. Tang Y, Lu A, Aronow BJ, Sharp FR. Blood genomic responses differ after stroke, seizures, hypoglycemia, and hypoxia: Blood genomic fingerprints of disease. Ann Neurol. 2001; 50: 699–707.

46. Whitney AR, Diehn M, Popper SJ, Alizadeh AA, Boldrick JC, et al. Individuality and variation in gene expression patterns in human blood. Proceedings of the National Academy of Sciences. 2003; 100(4), 1896-1901.

47. Arosio B, D'Addario C, Gussago C, Casati M, Tedone E, et al. Peripheral Blood Mononuclear Cells as a Laboratory to Study Dementia in the Elderly. BioMed research international. 2014.

48. Kalman J, Kitajka K, Pakaski M, Zvara A, Juhasz A, et al. Gene expression profile analysis of lymphocytes from Alzheimer's patients. Psychiatric genetics. 2005; 15(1), 1-6.

49. Maes OC, Xu S, Yu B, Chertkow HM, Wang E, et al. Transcriptional profiling of Alzheimer blood mononuclear cells by microarray. Neurobiology of aging. 2007; 28(12), 1795-1809.

50. Chen KD, Chang PT, Ping YH, Lee HC, Yeh CW, et al. Gene expression profiling of peripheral blood leukocytes identifies and validates ABCB1 as a novel biomarker for Alzheimer's disease. Neurobiology of disease. 2011; 43(3), 698-705.

51. Mandas A, Abete C, Putzu PF, la Colla P, Dessì S, et al. Changes in cholesterol metabolism-related gene expression in peripheral blood mononuclear cells from Alzheimer patients. Lipids Health Dis. 2012; 11, 39.

52. Zhang W, Wang LZ, Yu JT, Chi ZF, Tan L. Increased expressions of TLR2 and TLR4 on peripheral blood mononuclear cells from patients with Alzheimer's disease. Journal of the neurological sciences. 2012; 315(1), 67-71.

53. Ascolani A, Balestrieri E, Minutolo A, Mosti S, Spalletta G, et al. Dysregulated NF-κB Pathway in Peripheral Mononuclear Cells of Alzheimer's Disease Patients. Current Alzheimer Research. 2012; 9(1), 128-137.

54. Hu N, Tan MS, Sun L, Jiang T, Wang L., et al. Decreased expression of CD33 in peripheral mononuclear cells of Alzheimer's disease patients. Neuroscience letters. 2014; 563, 51-54.

55. Santos RR, Torres KC, Lima GS, Fiamoncini CM, Mapa FC, et al. Reduced frequency of T lymphocytes expressing CTLA-4 in frontotemporal dementia compared to Alzheimer's disease. Progress in Neuro-Psychopharmacology and Biological Psychiatry. 2014; 48, 1-5.

56. Crespo ÂC, Silva B, Marques L, Marcelino E, Maruta C, et al. Genetic and biochemical markers in patients with Alzheimer's disease support a concerted systemic iron homeostasis dysregulation. Neurobiology of aging. 2014; 35(4), 777-785.

57. Villa C, Ridolfi E, Fenoglio C, Ghezzi L, Vimercati R, et al. Expression of the transcription factor Sp1 and its regulatory hsa-miR-29b in peripheral blood mononuclear cells from patients with Alzheimer's disease. Journal of Alzheimer's Disease. 2013; 35(3), 487-494.

58. Frenkel D, Wilkinson K, Zhao L, Hickman SE, Means TK, et al. Scara1 deficiency impairs clearance of soluble amyloid-β by mononuclear phagocytes and accelerates Alzheimer's-like disease progression. Nature communications. 2013; 4.

59. Wallace RK, Benson H, Wilson AF. A wakeful hypometabolic physiologic state. Am J Physiol. 1971; 221(3), 795-799.

60. Benson H, Marzetta B, Rosner B, Klemchuk H. Decreased blood-pressure in pharmacologically treated hypertensive patients who regularly elicited the relaxation response. The Lancet. 1974; 303(7852), 289-291.

61. Dusek JA, Otu HH, Wohlhueter AL, Bhasin M, Zerbini LF, et al. Genomic counter-stress changes induced by the relaxation response. PloS one. 2008; 3(7), e2576.

62. Sharma H, Datta P, Singh A, Sen S, Bhardwaj NK, et al. Gene expression profiling in practitioners of Sudarshan Kriya. Journal of psychosomatic research. 2008; 64(2), 213-218.

63. Li QZ, Li P, Garcia GE, Johnson RJ, Feng L. Genomic profiling of neutrophil transcripts in Asian Qigong practitioners: a pilot study in gene regulation by mind-body interaction. Journal of Alternative & Complementary Medicine. 2005; 11(1), 29-39.

64. Saatcioglu F. Regulation of gene expression by yoga, meditation and related practices: a review of recent studies. Asian journal of psychiatry. 2013; 6(1), 74-77.

65. Qu S, Olafsrud SM, Meza-Zepeda LA, Saatcioglu, F. Rapid gene expression changes in peripheral blood lymphocytes upon practice of a comprehensive yoga program. PloS one. 2013; 8(4), e61910.

66. Kaliman P, Álvarez-López MJ, Cosín-Tomás M, Rosenkranz MA, Lutz A, et al. Rapid changes in histone deacetylases and inflammatory gene expression in expert meditators. Psychoneuroendocrinology. 2014; 40, 96-107.

67. Black DS, Cole SW, Irwin MR, Breen E, St Cyr NM, et al. Yogic meditation reverses NF-κB and IRF-related transcriptome dynamics in leukocytes of family dementia caregivers in a randomized controlled trial. Psychoneuroendocrinology. 2013; 38(3), 348-355.

68. Creswell JD, Irwin MR, Burklund LJ, Lieberman MD, Arevalo JM, et al. Mindfulness-based stress reduction training reduces loneliness and pro-inflammatory gene expression in older adults: a small randomized controlled trial. Brain, behavior, and immunity. 2012; 26(7), 1095-1101.

69. Baird DM, Kipling D. The extent and significance of telomere loss with age. Annals of the New York Academy of Sciences. 2004; 1019(1), 265-268.

70. Blasco MA. Telomeres and human disease: ageing, cancer and beyond. Nature Reviews Genetics. 2005; 6(8), 611-622.

71. Panossian LA, Porter VR, Valenzuela HF, Zhu X, Reback E, et al. Telomere shortening in T cells correlates with Alzheimer's disease status. Neurobiology of aging. 2003; 24(1), 77-84.

72. Jenkins EC, Velinov MT, Ye L, Gu H, Li S, et al. Telomere shortening in T lymphocytes of older individuals with Down syndrome and dementia. Neurobiology of aging. 2006; 27(7), 941-945.

73. Honig LS, Schupf N, Lee JH, Tang MX, Mayeux R. Shorter telomeres are associated with mortality in those with APOE 4 and dementia. Annals of neurology. 2006; 60(2), 181-187.

74. Thomas P, O'Callaghan NJ, Fenech M. Telomere length in white blood cells, buccal cells and brain tissue and its variation with ageing and Alzheimer's disease. Mechanisms of ageing and development. 2008; 129(4), 183-190.

75. Lukens JN, Van Deerlin V, Clark CM, Xie SX, Johnson FB. Comparisons of telomere lengths in peripheral blood and cerebellum in Alzheimer's disease. Alzheimer's & Dementia. 2009; 5(6), 463-469.

76. Hochstrasser T, Marksteiner J, Humpel C. Telomere length is age-dependent and reduced in monocytes of Alzheimer patients. Experimental gerontology. 2012; 47(2), 160-163.

77. Valdes AM, Deary IJ, Gardner J, Kimura M, Lu X, et al. Leukocyte telomere length is associated with cognitive performance in healthy women. Neurobiology of aging. 2010; 31(6), 986-992.

78. Yaffe K, Lindquist K, Kluse M, Cawthon R, Harris T, et al. Telomere length and cognitive function in community-dwelling elders: Findings from the Health ABC Study. Neurobiology of aging. 2011; 32(11), 2055-2060.

79. Jacobs TL, Epel ES, Lin J, Blackburn EH, Wolkowitz OM, et al. Intensive meditation training, immune cell telomerase activity, and psychological mediators. Psychoneuroendocrinology. 2011; 36(5), 664-681.

80. Ho RT, Chan JS, Wang CW, Lau BW, So KF, et al. A randomized controlled trial of qigong exercise on fatigue symptoms, functioning, and telomerase activity in persons with chronic fatigue or chronic fatigue syndrome. Annals of Behavioral Medicine. 2012; 44(2), 160-170.

81. Daubenmier J, Lin J, Blackburn E, Hecht FM, Kristeller J, et al. Changes in stress, eating, and metabolic factors are related to changes in telomerase activity in a randomized mindfulness intervention pilot study. Psychoneuroendocrinology. 2012; 37(7), 917-928.

82. Lavretsky H, Epel ES, Siddarth P, Nazarian N, Cyr NS, et al. A pilot study of yogic meditation for family dementia caregivers with depressive symptoms: effects on mental health, cognition, and telomerase activity. International journal of geriatric psychiatry. 2013; 28(1), 57-65.

83. Schutte NS, Malouff JM. A meta-analytic review of the effects of mindfulness

meditation on telomerase activity. Psychoneuroendocrinology. 2014; 42, 45-48.

84. Hoge EA, Chen MM, Orr E, Metcalf CA, Fischer LE, et al. Loving-Kindness Meditation practice associated with longer telomeres in women. Brain, behavior, and immunity. 2013; 32, 159-163.

85. Egger G, Liang G, Aparicio A, Jones PA. Epigenetics in human disease and prospects for epigenetic therapy. Nature. 2004; 429(6990), 457-463.