Integrative Analysis of Key Candidate Genes and Signaling Pathways in Alzheimer’s disease Related to Chronic Periodontitis Based on Analysis of GEO Dataset and Text Mining

Zhengye Jiang  
First Hospital of Xiamen: The First Affiliated Hospital of Xiamen University  
https://orcid.org/0000-0001-5630-1476

Yanxi Shi  
The Second Hospital of Jiaxing: The Second Affiliated Hospital of Jiaxing University

Wenpeng Zhao  
First Hospital of Xiamen: The First Affiliated Hospital of Xiamen University

Bingchang Zhang  
First Hospital of Xiamen: The First Affiliated Hospital of Xiamen University

Yuanyuan Xie  
First Hospital of Xiamen: The First Affiliated Hospital of Xiamen University

Yaya Zhang  
First Hospital of Xiamen: The First Affiliated Hospital of Xiamen University

Zhanxiang Wang  
WangZX@xmu.edu.cn  
First Hospital of Xiamen: The First Affiliated Hospital of Xiamen University

Research

Keywords: Differentially Expressed Genes, Chronic periodontitis, Cognitive decline, Alzheimer disease, Mild cognitive impairment, Signaling pathway

DOI: https://doi.org/10.21203/rs.3.rs-358537/v1

License: This work is licensed under a Creative Commons Attribution 4.0 International License. Read Full License
Abstract

**Background:** Although chronic periodontitis has been confirmed to be related to Alzheimer’s disease, the pathogenesis between the two is unclear. Herein, we analyzed and screened out the prospective molecular marker.

**Methods:** To explore the candidate genes, as well as signaling cascades involved in Alzheimer’s disease and mild cognitive impairment (MCI) related to chronic periodontitis, we extracted the integrated differentially expressed genes (DEGs) from the intersection of genes from the Gene Expression Omnibus (GEO) cohorts and text mining, followed by enrichment of the matching cell signal cascade through DAVID analysis. Moreover, the MCODE of Cytoscape software was employed to uncover the protein-protein interaction (PPI) network and the matching hub gene.

**Results:** A total of 305 and 100 integrated human DEGs in AD and MCI group associated with chronic periodontitis were uncovered, respectively, that met the criteria of \(|\log_2 \text{changes}| \geq 2\), adjusted \(P < 0.01\). After PPI network construction, the top five hub genes associated with AD were extracted, including IL6, VEGFA, AKT1, MAPK3, and ALB, whereas those associated with MCI were EGFR, IL10, IGF1, BMP2, and LDLR.

**Conclusions:** The establishment of the above-mentioned candidate key genes, as well as the enriched signaling cascades provides promising molecular marker for chronic periodontitis-related cognitive decline, especially AD, which may help the diagnosis and treatment of AD patients in the future.

1. Introduction

Periodontitis constitutes a chronic inflammatory disease. During the development of periodontitis, associated complications such as alveolar bone destruction, as well as the loss of attachment of collagen fibers to periodontal ligament will occur, eventually leading to tooth loss[1]. A large number of recent reports have shown that chronic periodontitis comprises a risk factor for neurodegenerative diseases such as cognitive decline. Among them, in the study of Cestari et al., it was found that the levels of inflammatory cytokines in individuals with Alzheimer’s disease (AD) /Mild Cognitive Impairment (MCI) were remarkably correlated with periodontitis [2].

AD constitutes a progressive neurodegenerative disease. Its clinical indications primarily include cognitive decline, which eventually develops into AD. It has a place in diseases that threaten the lifespan of the elderly. A large number of previous studies have confirmed that immune factors, depression, genetic factors, etc. could be remarkably positively correlated with the incidence and development of AD[3-8]. Despite the huge advancements in AD research, the current AD treatments can only improve and relieve patient conditions to some level [9]. As the threat of AD to the elderly becomes greater and greater, it is imperative for us to establish the etiology, as well as the molecular features of AD disease. Therefore, we explore the molecular biomarkers by studying the correlation between chronic periodontitis and AD disease to provide evidence for early diagnosis, prevention, as well as the treatment of this disease.
At present, high-throughput sequencing techniques, such as molecular diagnosis, prognosis estimation, as well as drug target discovery, and, which can be employed to assess the gene expression differences, as well as the variable splicing variation, are gradually considered to have important clinical significance in disease research. The Integrated Gene Expression Database (GEO), a publicly available websites supported by the National Center for Biotechnology Information (NCBI), harbors dozens of basic experimental disease gene expression patterns and is extensively employed to explore key genes and prospective mechanisms of disease onset and development[10]. Though the pathogenesis of chronic periodontitis has been found to be related to AD recently, its pathogenesis, as well as the molecular mechanism remain unknown. Hence, we need to utilize the gene expression chip in the bulletin database and analyze its data through modern software to find new diagnostic markers and therapeutic targets[11].

In this study, we retrieved GSE5281 and GSE18309, the human AD and MCI gene expression patterns, respectively, from the GEO website. After that, R software (version 3.6.3) installed Limma package was utilized to screen the differentially expressed genes (DEGs)[12,13]. Text mining about chronic periodontitis was then carried out by the pubmed2ensembl online tool [14]. After the data obtained from microarray, as well as the text mining were intersected to obtain the common gene, GO enrichment and KEGG pathway assessment were performed on the obtained DEGs [15]. Finally, the protein-protein interaction (PPI) network was developed using the Search Tool for the Retrieval of Interacting Genes (STRING) and Cytoscape software to screen candidate hub genes, as well as the highly relevant functional modules.

2. Methods

2.1 Data Abstraction

We abstracted the gene expression chip data GSE5281[16] and GSE18309 from the NCBI Gene Expression Comprehensive (GEO) web resource (https://www.ncbi.nlm.nih.gov/geo/) [10,17]. The GSE5281 cohort contains ten euthyroid and ten AD samples, while the GSE18309 dataset includes three normal control and three MCI samples.

2.2 Identification of DEGs

The core R package was used to process the downloaded matrix files. After normalization, the differences between ad or MCI and the control group were determined by truncation criteria ($|\log_2$ fold change (FC)| ≥ 2, adjusted $P < 0.05$), and selected the remarkable DEGs for downstream analyses [18].

2.3 Text mining

We carried out the text mining based on the pubmed2ensembl public tool (http://pubmed2ensembl.ls. manchester.ac.uk/). When manipulated, pubmed2ensembl retrieves all the gene names found in the existing literature relevant to the search topic. We searched for the concept of
chronic periodontitis. We then screened all the genes associated with the topic from the results. Finally, we used the gene set obtained by text mining and the previously obtained differential gene set for the next step of analysis after the intersection.

2.4 Gene Ontology Analysis of DEGs and KEGG pathway analysis

The obtained DEGs were imported to David V. 6.8 (https://david.ncifcrf.gov/). The GO annotation and KEGG pathway enrichment were carried out in the web resource, which provided a sequence of functional annotation tools for systematic analysis of biological significance of gene lists. The above gene tables were analyzed with P < 0.05 as the significant threshold.

2.5 Assessment of the PPI network of the DEGs

We used the STRING online search tool to analyze the protein-protein interaction (PPI) data encoded by DEGs [19], and only the combination score >0.6 was considered significant. Then, the PPI network was analyzed and visualized by using Cytoscape, and the first five hub genes were determined as per the connectivity between des. The standard default setting of the mcode parameter is except for k-core = 5. The function enrichment of DEGs of each module was analyzed by P < 0.05 as the cutoff standard.

3. Results

3.1 DEGs identification

Firstly, 5672 DEGs were selected from AD samples and normal controls in the GSE5281 data set through limma package screening of R software. Of these, 3804 upregulated genes and 1868 downregulated genes were selected. At the same time, 1596 differentially expressed genes, including 706 upregulated genes and 890 downregulated genes, were obtained by analyzing the MCI samples in the GSE18309 data set and the normal control group. Then, the overall distribution of the two data sets and the first 100 DEGs are represented by volcano map and heat map respectively (Fig. 1A-D). Using |log2 fold change (FC)| ≥ 2 criteria and adjusted P <0.05.

Through text mining, 1096 human genes associated with chronic periodontitis (S. s 1). After the DEGs in the microarray data were crossed, the intersection of selected genes was obtained, and 305 genes involved in AD group and 100 genes involved in MCI group were obtained (Fig. 2A-B).

3.2 Function and Signal Pathway Enrichment Analysis

After introducing the DEGs obtained above into DAVID, we subjected them to GO and KEGG enrichment analysis. The purpose of this study is to study the biological functions of DEGs integrated in AD and MCI associated with chronic periodontitis. In the GO analysis results, 519 biological process terms (BP), 67 cell component terms (CC), and 95 molecular function terms (MF) were uncovered in the DEGs integrated by AD. The P < 0.05 signified threshold significance. Overall, 39 genes were primarily abundant in BP term to “inflammatory response”, 95 genes are located in the “extracellular space” of CC term, and 226 genes
were abundant in the MF term “protein binding” as indicated in Fig. 3. For MCI, integrated DEGs were remarkably abundant in 325 GO terms consisting of 239 BP terms, 37 CC terms, as well as 49 MF terms. Besides, the genes were majorly abundant in the following terms: modulation of inflammatory response in BP, extracellular space in CC, as well as protein binding in MF, which constituted the top 3 GO annotation terms, in which the integrated genes were most remarkably enriched (Fig. 4).

The KEGG enrichment assessment demonstrated that the integrated DEGs were remarkably enriched in the KEGG cascade Proteoglycans in cancer, PI3K-Akt signaling cascade and Influenza A in AD group and Cytokine-cytokine receptor crosstalk, Type I diabetes mellitus and Inflammatory bowel disease in the MCI group (Fig. 3-4).

3.3 Module screening from the PPI network

Based on the 305 AD group genes and the 100 MCI group genes, the Cytoscape publicly available platform and the STRING resource were employed to develop the PPI network, perform module analysis, as well as visualization. Consequently, we developed a PPI network bearing 1494 crosstalk based on 247 integrated DEGs related to AD (Fig. 5A). Moreover, we developed a PPI network in the MCI group containing 64 integrated DEGs (Fig. 6A). Based on the degree value, the top five hub genes extracted from the AD group consisted of IL6 (Interleukin-6), MAPK3 (Mitogen-activated protein kinase 3), VEGFA (Vascular endothelial growth factor A), AKT1 (Threonine kinase 1), and ALB (Albumin). On the contrary, in the MCI group, the top five hub genes were EGFR (Epidermal growth factor receptor), IL10 (Interleukin-10), IGF1 (Insulin-like growth factor I), BMP2 (Bone morphogenetic protein 2), and LDLR (Low-density lipoprotein receptor) (Table 1).

We employed the MCODE algorithm to determine highly interconnected subnets, which are frequently protein complexes, as well as components of cascades as per the topological structure. We selected the two most important modules from AD group and MCI group respectively for further analysis (Fig 5B-C, Fig 6B-C). Additional functional enrichment assessment of the established modules demonstrated that genes in the AD module were majorly abundant in the GO terms of “inflammatory response”, “extracellular space”, “heparin binding”, as well as KEGG cascade of “PI3K-Akt signaling pathway” (Fig 7A-B). Genes in the module of MCI primarily were abundant in the GO terms of “inflammatory response”, “extracellular space”, “chemokine activity” and KEGG pathway of “Proteoglycans in cancer” (Fig 8A-B).

Discussion

In many epidemiological studies, chronic periodontitis may be the result of the gradual deterioration of neuronal function during aging. Therefore, a new potential treatment method for preventing the progression of AD has emerged, that is, delaying or preventing chronic inflammatory diseases. However, at present, the pathogenesis and effective treatment of chronic periodontitis for cognitive decline remain unclear. Hence, it is imperative to explore the molecular mechanism of the cognitive decline after chronic periodontitis to determine efficient biomarkers and effective approaches for the diagnosis, monitoring, as well as treatment of patients.
Herein, 305 genes in the AD and 100 genes in MCI linked to chronic periodontitis were uncovered for functional analysis using the GO, as well as the KEGG enrichment assessments. The data from the GO annotation suggested that the uncovered DEGs primarily participated in protein docking, apoptosis, as well as immune modulation. It is critical to point out that MAPK3 constitutes a prevalent gene in most of the rich KEGG pathways in AD. Additionally, the MAPK3 gene comprised one of the hub genes uncovered by the PPI network. MAPK3 referred to as the mitogen-activated protein kinase 3, is a MAP kinase family member and participates in an extensive array of biological processes, including cell proliferation, as well as angiogenesis. MAPK3 may serve as the intrafollicular mediators that trigger the expansion of the cumulus cell-oocyte complex (COC), as well as the maturation of the oocytes [20-22]. The extracellular, as well as intracellular mitogenic stimuli activate the MAPK3 cascade, which has pivotal functions in cellular differentiation, proliferation and survival [23]. The study of colorectal cancer by Schmitz et al. showed that the expression of MAPK3 is related to poor prognosis [24].

At the same time, IL10 is a common gene in most of the rich KEGG pathways in MCI, and also one of the hub genes uncovered in PPI network. Interleukin-10 (IL-10) is a key immunomodulatory cytokine, which is involved in the inflammatory response [25-27]. Among them, the research results of Guillot-Sestier et al. propose that the re-balancing of innate immunity via blocking of the IL-10 anti-inflammatory response may be linked to the treatment of AD [28]. Similarly, many studies have shown abnormal increases in IL-10 signaling in the brains of AD patients. Numerous results confirm and extend other studies that have reported elevated IL-10 levels in serum, as well as the brain extracts from individuals with AD [29-31].

Through the establishment of the PPI network, the functional enrichment assessment of the greatly integrated modules demonstrated that the AD module genes were majorly abundant in the KEGG PI3K-Akt signaling cascade term. Phosphatidylinositol 3-kinase (PI3K) is involved in the formation of phosphatidylinositol 3, 4, 5-trisphosphate, a second messenger, which is crucial in the Akt (protein kinase B) translocation. The activation of the Akt participates in important cellular roles, including cell survival, as well as cell proliferation. The PI3K-Akt cascade is related to the progression of numerous diseases, e.g., cancer, autoimmunity, as well as diabetes mellitus [32]. Moreover, five hub genes with the highest degree of connectivity were separately identified from the AD and MCI. The top five hub genes linked to AD are IL6, VEGFA, AKT1, MAPK3, and ALB, whereas those associated with MCI are EGFR, IL10, IGF1, BMP2, and LDLR.

VEGFA is a growth factor released by tumor cells. It participates in tumorigenesis and development. It can trigger the germination of existing vascular endothelial cells to form a new vascular system [33]. It is reported that VEGFA is abnormally regulated in various cancers and promote tumor progression [34]. According to reports, a variety of miRNAs inhibits tumor growth, angiogenesis, as well as metastasis by suppressing the expression of its target gene VEGFA [35,36]. In addition to its widely described growth factor function, VEGFA also acts as a neurotrophic factor [37-39], and interestingly, VEGFA also serves a critical role in hippocampal neurogenesis [40,41]. Recent studies have found that considerable evidence suggests that insufficient neuroprotection of VEGFA can lead to neurodegenerative diseases [42-44].
IL-6 constitutes a pleiotropic pro-inflammatory cytokine. The deregulation of IL-6 is linked to chronic inflammation, as well as multifactorial auto-immune disorders. The study of Gurel et al. found that IL6 is involved in iron homeostasis and inflammation, and IL6 was found to be elevated in the hippocampus of 5XFAD mice [45]. A large number of studies have found that IL-6 increases with age and is associated with loss of motor function [46-48]. Meanwhile, in many mental diseases, such as obsessive-compulsive disorder, acute psychosis, schizophrenia, panic disorder, as well as post-traumatic stress disorder (PTSD), IL-6 expression has been found to be significantly increased [49-54].

AKT1 comprises a redox-sensitive protein and its kinase activity is modulated by the redox milieu [55,56]. The results of Karege et al. [57] showed that the polymorphism of the AKT1 gene seems to have an impact on mental symptoms such as schizophrenia. Devaney et al. [58] documented that AKT1 is a risk factor of metabolic syndrome, as well as insulin resistance. Interestingly, a large number of studies have found that abnormalities in Akt1 signal have been observed in the brain tissues and animal models of AD patients [59-63].

EGFR functioning as a protein tyrosine kinase receptor, not only serves important functions in cell differentiation, cell growth, as well as tissue development and function, serving as an integrator at the convergence of the extracellular growth and survival signals, which are transformed into intracellular outputs [64,65]. In addition, EGFGR serves a vital role in the development of human cell transformation and cancer [64,65]. The function of EGFR is obviously related to a series of neurometabolic disorders, such as diabetes, AD, as well as aging [64,66].

ALB (albumin) constitutes a multifunctional plasma protein found in large Numbers in human blood [67]. In addition, albumin is also involved in stabilizing colloidal osmotic pressure, removing free radicals and protecting nerve cells, and is significantly related to systemic nutritional status and inflammation [68]. The study of Lei et al. found that albumin concentration can be used as an independent prognostic factor for patients with endometrial cancer [69].

The IGF1 signaling pathway is ubiquitous in the aging process, so it is called the somatotropic axis [70,71]. Similarly, low levels of serum IGF1 can reduce the incidence of cognitive impairment in women after the age of 10 [72].

Low-density lipoprotein receptor (LDLR) can regulate the level of peripheral and central nervous system (CNS) lipoproteins, so it is known as an important receptor that inhibits amyloid deposition [73,74]. Yao et al. found that polyphenol-mediated regulation of LDLR expression may be a safe and effective treatment for AD disease, which can accelerate the clearance rate of AD [75].

Conclusions

By employing a sequence of bioinformatics tools for gene expression profiling, we established the core function of candidate key genes, including MAPK3 and IL10, and the enriched signaling cascades constituting the PI3K-Akt axis in the molecular modulation network of cognitive decline via integrated
bioinformatic analysis. This provided the prospective targets for the future diagnosis, as well as clinical treatment of AD. However, in vitro, as well as in vivo studies should be conducted to verify our findings.

Declarations

Compliance with ethical standards

Competing of interests
The authors declare that they have no competing interests.

Ethical approval

This article does not contain any studies with human participants or animals performed by any of the authors.

Consent to participate

Not applicable.

Consent for publication

All authors consent to the publication of this study.

Availability of data and material

All data is available under reasonable request.

Code availability

Not applicable.

Authors’ contributions

ZJ, BZ, YZ and YS conceived and designed this study. ZJ wrote this manuscript. ZW revised this manuscript. ZJ made these figures with the help of YS, YX, WZ, LW and GT.

Funding

This work was supported by the National Natural Science Foundation of China (82072777).

Acknowledgements

Thanks to Bin Zhao (Official Wechat Account: SCIPhD) of ShengXinZhuShou for English editing on the manuscript.

References
[1] A. Cekici, A. Kantarci, H. Hasturk, T.E. Van Dyke, Inflammatory and immune pathways in the pathogenesis of periodontal disease, Periodontology 2000 64 (2014) 57-80. 10.1111/prd.12002.

[2] J.A.F. Cestari, G.M.C. Fabri, J. Kalil, R. Nitini, W. Jacob, J.T.T. de Siqueira, S. Siqueira, Oral Infections and Cytokine Levels in Patients with Alzheimer's Disease and Mild Cognitive Impairment Compared with Controls (vol 52, pg 1479, 2016), Journal of Alzheimers Disease 54 (2016) 845-845. 10.3233/jad-169006.

[3] R. Cacabelos, A. Meyyazhagan, J.C. Carril, P. Cacabelos, O. Teijido, Pharmacogenetics of Vascular Risk Factors in Alzheimer's Disease, Journal of Personalized Medicine 8 (2018) Unsp 3. 10.3390/jpm8010003.

[4] A. Jayaraman, C.J. Pike, Alzheimer's Disease and Type 2 Diabetes: Multiple Mechanisms Contribute to Interactions, Current Diabetes Reports 14 (2014) 476. 10.1007/s11892-014-0476-2.

[5] C. Reitz, Genetic diagnosis and prognosis of Alzheimer's disease: challenges and opportunities, Expert Review of Molecular Diagnostics 15 (2015) 339-348. 10.1586/14737159.2015.1002469.

[6] D.S. Rivera, N.C. Inestrosa, F. Bozinovic, On cognitive ecology and the environmental factors that promote Alzheimer disease: lessons from Octodon degus (Rodentia: Octodontidae), Biological Research 49 (2016) 10. 10.1186/s40659-016-0074-7.

[7] A.M. Tolppanen, H. Taipale, S. Hartikainen, Head or brain injuries and Alzheimer's disease: A nested case-control register study, Alzheimers & dementia : the journal of the Alzheimer's Association 13 (2017) 1371-1379. 10.1016/j.jalz.2017.04.010.

[8] M. Vijayan, P.H. Reddy, Stroke, Vascular Dementia, and Alzheimer's Disease: Molecular Links, Journal of Alzheimers Disease 54 (2016) 427-443. 10.3233/jad-160527.

[9] W.V. Graham, A. Bonito-Oliva, T.P. Sakmar, Update on Alzheimer's Disease Therapy and Prevention Strategies, in: C.T. Caskey (Ed.) Annual Review of Medicine, Vol 682017, pp. 413-430.

[10] T. Barrett, S.E. Wilhite, P. Ledoux, C. Evangelista, I.F. Kim, M. Tomashovsky, K.A. Marshall, K.H. Phillippy, P.M. Sherman, M. Holko, A. Yefanov, H. Lee, N. Zhang, C.L. Robertson, N. Serova, S. Davis, A. Soboleva, NCBI GEO: archive for functional genomics data sets-update, Nucleic Acids Research 41 (2013) D991-D995. 10.1093/nar/gks1193.

[11] Y. Guo, Y. Bao, M. Ma, W. Yang, Identification of Key Candidate Genes and Pathways in Colorectal Cancer by Integrated Bioinformatical Analysis, International Journal of Molecular Sciences 18 (2017) 722. 10.3390/ijms18040722.

[12] G.K. Smyth, Limma: Linear models for microarray data, in: R. Gentleman, V.J. Carey, W. Huber, R.A. Irizarry, S. Dudoit (Eds.) Bioinformatics and Computational Biology Solution Using R and Bioconductor2005, pp. 397-420.
[13] J.S. Racine, RStudio: A Platform-Independent IDE for R and Sweave, Journal of Applied Econometrics 27 (2012) 167-172. 10.1002/jae.1278.

[14] J. Baran, M. Gerner, M. Haeussler, G. Nenadic, C.M. Bergman, pubmed2ensembl: A Resource for Mining the Biological Literature on Genes, Plos One 6 (2011) e24716. 10.1371/journal.pone.0024716.

[15] D.W. Huang, B.T. Sherman, R.A. Lempicki, Systematic and integrative analysis of large gene lists using DAVID bioinformatics resources, Nature Protocols 4 (2009) 44-57. 10.1038/nprot.2008.211.

[16] C.M. Hooper, S.M. Hawes, U.R. Kees, N.G. Gottardo, PB. Dallas, Gene Expression Analyses of the Spatio-Temporal Relationships of Human Medulloblastoma Subgroups during Early Human Neurogenesis, Plos One 9 (2014) e112909. 10.1371/journal.pone.0112909.

[17] R. Edgar, M. Domrachev, A.E. Lash, Gene Expression Omnibus: NCBI gene expression and hybridization array data repository, Nucleic Acids Research 30 (2002) 207-210. 10.1093/nar/30.1.207.

[18] A. Reiner, D. Yekutieli, Y. Benjamini, Identifying differentially expressed genes using false discovery rate controlling procedures, Bioinformatics 19 (2003) 368-375. 10.1093/bioinformatics/btf877.

[19] A. Franceschini, D. Szklarczyk, S. Frankild, M. Kuhn, M. Simonovic, A. Roth, J. Lin, P. Minguez, P. Bork, C. von Mering, L.J. Jensen, STRING v9.1: protein-protein interaction networks, with increased coverage and integration, Nucleic Acids Research 41 (2013) D808-D815. 10.1093/nar/gks1094.

[20] M. Shimada, I. Hernandez-Gonzalez, I. Gonzalez-Robayna, J.A.S. Richards, Paracrine and autocrine regulation of epidermal growth factor-like factors in cumulus oocyte complexes and granulosa cells: Key roles for prostaglandin synthase 2 and progesterone receptor, Molecular Endocrinology 20 (2006) 1352-1365. 10.1210/me.2005-0504.

[21] M. Hsieh, D. Lee, S. Panigone, K. Homer, R. Chen, A. Theologis, D.C. Lee, D.W. Threadgill, M. Conti, Luteinizing hormone-dependent activation of the epidermal growth factor network is essential for ovulation, Molecular and Cellular Biology 27 (2007) 1914-1924. 10.1128/mcb.01919-06.

[22] J.Y. Park, Y.Q. Su, M. Ariga, E. Law, S.L.C. Jin, M. Conti, EGF-like growth factors as mediators of LH action in the ovolatory follicle, Science 303 (2004) 682-684. 10.1126/science.1092463.

[23] S. Schubbert, K. Shannon, G. Bollag, Hyperactive Ras in developmental disorders and cancer, Nature Reviews Cancer 7 (2007) 295-308. 10.1038/nrc2109.

[24] K.J. Schmitz, J. Wohlschlaeger, H. Alakus, J. Bohr, M.A. Stauder, K. Worm, G. Winde, K.W. Schmid, H.A. Baba, Activation of extracellular regulated kinases (ERK1/2) but not AKT predicts poor prognosis in colorectal carcinoma and is associated with k-ras mutations, Virchows Archiv 450 (2007) 151-159. 10.1007/s00428-006-0342-y.
[25] L.M. Williams, G. Ricchetti, U. Sarma, T. Smallie, B.M.J. Foxwell, Interleukin-10 suppression of myeloid cell activation - a continuing puzzle, Immunology 113 (2004) 281-292. 10.1111/j.1365-2567.2004.01988.x.

[26] K. Strle, J.H. Zhou, W.H. Shen, S.R. Broussard, R.W. Johnson, G.G. Freund, R. Dantzer, K.W. Kelley, Interleukin-10 in the brain, Crit Rev Immunol 21 (2001) 427-449.

[27] M.O. Li, R.A. Flavell, Contextual regulation of inflammation: A duet by transforming growth factor-beta and interleukin-10, Immunity 28 (2008) 468-476. 10.1016/j.immuni.2008.03.003.

[28] M.V. Guillot-Sestier, K.R. Doty, D. Gate, J. Rodriguez, Jr., B.P. Leung, K. Rezai-Zadeh, T. Town, Il10 deficiency rebalances innate immunity to mitigate Alzheimer-like pathology, Neuron 85 (2015) 534-548. 10.1016/j.neuron.2014.12.068.

[29] K.F. Loewenbrueck, J.T. Tigno-Aranjuez, B.O. Boehm, P.V. Lehmann, M. Tary-Lehmann, Th1 responses to beta-amyloid in young humans convert to regulatory IL-10 responses in Down syndrome and Alzheimer's disease, Neurobiology of Aging 31 (2010) 1732-1742. 10.1016/j.neurobiolaging.2008.09.007.

[30] D. Culpan, J.A. Prince, S. Matthews, L. Palmer, A. Hughes, S. Love, P.G. Kehoe, G.K. Wilcock, Neither sequence variation in the IL-10 gene promoter nor presence of IL-10 protein in the cerebral cortex is associated with Alzheimer's disease, Neuroscience Letters 408 (2006) 141-145. 10.1016/j.neulet.2006.08.068.

[31] P. Angelopoulos, H. Agouridaki, H. Vaiopoulos, E. Siskou, K. Doutsou, V. Costa, S.I. Baloyiannis, CYTOKINES IN ALZHEIMER'S DISEASE AND VASCULAR DEMENTIA, International Journal of Neuroscience 118 (2008) 1659-1672. 10.1080/00207450701392068.

[32] M. Osaki, M. Oshimura, H. Ito, PI3K-Akt pathway: Its functions and alterations in human cancer, Apoptosis 9 (2004) 667-676. DOI 10.1023/B:APPT.0000045801.15585.dd.

[33] J. Folkman, Role of angiogenesis in tumor growth and metastasis, Semin Oncol 29 (2002) 15-18. 10.1053/sonc.2002.37263.

[34] J. Geng, X. Li, Z.M. Zhou, C.L. Wu, M. Dai, X.Y. Bai, EZH2 promotes tumor progression via regulating VEGF-A/AKT signaling in non-small cell lung cancer, Cancer Lett 359 (2015) 275-287. 10.1016/j.canlet.2015.01.031.

[35] H.B. Ma, J.S. Pan, L.X. Jin, J.F. Wu, Y.D. Ren, P.D. Chen, C.C. Xiao, J.H. Han, MicroRNA-17 similar to 92 inhibits colorectal cancer progression by targeting angiogenesis, Cancer Lett 376 (2016) 293-302. 10.1016/j.canlet.2016.04.011.

[36] L.P. Liu, N. Bi, L.H. Wu, X. Ding, Y. Men, W. Zhou, L. Li, W.M. Zhang, S.S. Shi, Y.M. Song, L.H. Wang, MicroRNA-29c functions as a tumor suppressor by targeting VEGFA in lung adenocarcinoma, Mol Cancer 16 (2017). ARTN 50
[37] O.O. Ogunshola, A. Antic, M.J. Donoghue, S.Y. Fan, H. Kim, W.B. Stewart, J.A. Madri, L.R. Ment, Paracrine and autocrine functions of neuronal vascular endothelial growth factor (VEGF) in the central nervous system, J Biol Chem 277 (2002) 11410-11415. 10.1074/jbc.M111085200.

[38] H. Matsuzaki, M. Tamatani, A. Yamaguchi, K. Namikawa, H. Kiyama, M.P. Vitek, N. Mitsuda, M. Tohyama, Vascular endothelial growth factor rescues hippocampal neurons from glutamate-induced toxicity: signal transduction cascades, Faseb J 15 (2001) 1218-1220.

[39] K.L. Jin, Y.H. Zhu, Y.J. Sun, X.O. Mao, L. Xie, D.A. Greenberg, Vascular endothelial growth factor (VEGF) stimulates neurogenesis in vitro and in vivo, P Natl Acad Sci USA 99 (2002) 11946-11950. 10.1073/pnas.182296499.

[40] T. Kiuchi, H. Lee, T. Mikami, REGULAR EXERCISE CURES DEPRESSION-LIKE BEHAVIOR VIA VEGF-Flk-1 SIGNALING IN CHRONICALLY STRESSED MICE, Neuroscience 207 (2012) 208-217. 10.1016/j.neuroscience.2012.01.023.

[41] K. Fabel, K. Fabel, B. Tam, D. Kaufer, A. Baiker, N. Simmons, C.J. Kuo, T.D. Palmer, VEGF is necessary for exercise-induced adult hippocampal neurogenesis, Eur J Neurosci 18 (2003) 2803-2812. 10.1111/j.1460-9568.2003.03041.x.

[42] S. Zacchigna, D. Lambrechts, P. Carmeliet, Neurovascular signalling defects in neurodegeneration, Nat Rev Neurosci 9 (2008) 169-181. 10.1038/nrn2336.

[43] E. Storkebaum, P. Carmeliet, VEGF: a critical player in neurodegeneration, J Clin Invest 113 (2004) 14-18. 10.1172/Jci200420682.

[44] D. Lambrechts, P. Carmeliet, VEGF at the neurovascular interface: Therapeutic implications for motor neuron disease, Bba-Mol Basis Dis 1762 (2006) 1109-1121. 10.1016/j.bbadis.2006.04.005.

[45] B. Gurel, M. Cansev, C. Sevinc, S. Kelestemur, B. Ocalan, A. Cakir, S. Aydin, N. Kahveci, M. Ozansoy, O. Taskapilioglu, I.H. Ulus, M.K. Basar, B. Sahin, M.B. Tuzuner, A.T. Baykal, Early Stage Alterations in CA1 Extracellular Region Proteins Indicate Dysregulation of IL6 and Iron Homeostasis in the 5XFAD Alzheimer's Disease Mouse Model, Journal of Alzheimers Disease 61 (2018) 1399-1409. 10.3233/jad-170329.

[46] C. Franceschi, M. Capri, D. Monti, S. Giunta, F. Olivier, F. Sevini, M.P. Panouraia, L. Invidia, L. Celani, M. Scurti, E. Cevenini, G.C. Castellani, S. Salvioli, Inflammaging and anti-inflammaging: A systemic perspective on aging and longevity emerged from studies in humans, Mechanisms of Ageing and Development 128 (2007) 92-105. 10.1016/j.mad.2006.11.016.

[47] C. Franceschi, Inflammaging as a major characteristic of old people: Can it be prevented or cured?, Nutrition Reviews 65 (2007) S173-S176. 10.1301/nr.2007.dec.S173-S176.
[48] C.A. Dinarello, Proinflammatory cytokines, Chest 118 (2000) 503-508. 10.1378/chest.118.2.503.

[49] D. Lindqvist, O.M. Wolkowitz, S. Mellon, R. Yehuda, J.D. Flory, C. Henn-Haase, L.M. Bierer, D. Abu-Amara, M. Coy, T.C. Neylan, L. Makotkine, V.I. Reus, X. Yan, N.M. Taylor, C.R. Marmar, F.S. Dhabhar, Proinflammatory milieu in combat-related PTSD is independent of depression and early life stress, Brain Behav Immun 42 (2014) 81-88. 10.1016/j.bbi.2014.06.003.

[50] L.P. Oganesyan, G.M. Mkrtchyan, S.H. Sukiasyan, A.S. Boyajyan, Classic and alternative complement cascades in post-traumatic stress disorder, Bull Exp Biol Med 148 (2009) 859-861. 10.1007/s10517-010-0836-0.

[51] S. Neelamekam, M. Nurjono, J. Lee, Regulation of interleukin-6 and leptin in schizophrenia patients: a preliminary analysis, Clin Psychopharmacol Neurosci 12 (2014) 209-214. 10.9758/cpn.2014.12.3.209.

[52] J. Mahadevan, A. Sundaresh, R.P. Rajkumar, A. Muthuramalingam, V. Menon, V.S. Negi, M.G. Sridhar, An exploratory study of immune markers in acute and transient psychosis, Asian J Psychiatr 25 (2017) 219-223. 10.1016/j.ajp.2016.11.010.

[53] E.A. Hoge, K. Brandstetter, S. Moshier, M.H. Pollack, K.K. Wong, N.M. Simon, Broad spectrum of cytokine abnormalities in panic disorder and posttraumatic stress disorder, Depress Anxiety 26 (2009) 447-455. 10.1002/da.20564.

[54] R. Ganguli, Z. Yang, G. Shurin, K.N. Chengappa, J.S. Brar, A.V. Gubbi, B.S. Rabin, Serum interleukin-6 concentration in schizophrenia: elevation associated with duration of illness, Psychiatry Res 51 (1994) 1-10. 10.1016/0165-1781(94)90042-6.

[55] L. Durgadoss, P. Nidadavolu, R.K. Valli, U. Saeed, M. Mishra, P. Seth, V. Ravindranath, Redox modification of Akt mediated by the dopaminergic neurotoxin MPTP, in mouse midbrain, leads to down-regulation of pAkt, Faseb J 26 (2012) 1473-1483. 10.1096/fj.11-194100.

[56] F. Ahmad, P. Nidadavolu, L. Durgadoss, V. Ravindranath, Critical cysteines in Akt1 regulate its activity and proteasomal degradation: implications for neurodegenerative diseases, Free Radical Bio Med 74 (2014) 118-128. 10.1016/j.freeradbiomed.2014.06.004.

[57] F. Karege, A. Meary, N. Perroud, S. Jamain, M. Leboyer, E. Ballmann, R. Fernandez, A. Malafosse, F. Schurhoff, Genetic overlap between schizophrenia and bipolar disorder: A study with AKT1 gene variants and clinical phenotypes, Schizophr Res 135 (2012) 8-14. 10.1016/j.schres.2011.12.015.

[58] J.M. Devaney, H. Gordish-Dressman, B.T. Harmon, M.K. Bradbury, S.A. Devaney, T.B. Harris, P.D. Thompson, P.M. Clarkson, T.B. Price, T.J. Angelopoulos, P.M. Gordon, N.M. Moyna, L.S. Pescatello, P.S. Visich, R.F. Zoeller, R.L. Seip, J. Seo, B.H. Kim, L.L. Tosi, M. Garcia, R.L. Li, J.M. Zmuda, M.J. Delmonico, R.S. Lindsay, B.V. Howard, W.E. Kraus, E.P. Hoffman, AKT1 polymorphisms are associated with risk for metabolic syndrome, Hum Genet 129 (2011) 129-139. 10.1007/s00439-010-0910-8.
[59] A. Tramutola, J.C. Triplett, F. Di Domenico, D.M. Niedowicz, M.P. Murphy, R. Coccia, M. Perluigi, D.A. Butterfield, Alteration of mTOR signaling occurs early in the progression of Alzheimer disease (AD): analysis of brain from subjects with pre-clinical AD, amnestic mild cognitive impairment and late-stage AD, J Neurochem 133 (2015) 739-749. 10.1111/jnc.13037.

[60] H. Sancheti, G. Akopian, F. Yin, R.D. Brinton, J.P. Walsh, E. Cadenas, Age-Dependent Modulation of Synaptic Plasticity and Insulin Mimetic Effect of Lipoic Acid on a Mouse Model of Alzheimer's Disease, Plos One 8 (2013) e69830. 10.1371/journal.pone.0069830.

[61] Y. Liu, F. Liu, I. Grundke-Iqbal, K. Iqbal, C.X. Gong, Deficient brain insulin signalling pathway in Alzheimer's disease and diabetes, Journal of Pathology 225 (2011) 54-62. 10.1002/path.2912.

[62] C. O' Neill, PI3-kinase/Akt/mTOR signaling: Impaired on/off switches in aging, cognitive decline and Alzheimer's disease, Experimental Gerontology 48 (2013) 647-653. 10.1016/j.exger.2013.02.025.

[63] F.-F. Liao, H. Xu, Insulin Signaling in Sporadic Alzheimer's Disease, Science Signaling 2 (2009) pe36. 10.1126/scisignal.274pe36.

[64] R. Avraham, Y. Yarden, Feedback regulation of EGFR signalling: decision making by early and delayed loops, Nat Rev Mol Cell Bio 12 (2011) 104-117. 10.1038/nrm3048.

[65] C. Berasain, M. Ujue Latasa, R. Urtasun, S. Goni, M. Elizalde, O. Garcia-Irigoyen, M. Azcona, J. Prieto, M.A. Avila, Epidermal Growth Factor Receptor (EGFR) Crosstalks in Liver Cancer, Cancers (Basel) 3 (2011) 2444-2461. 10.3390/cancers3022444.

[66] S. Siddiqui, M. Fang, B. Ni, D.Y. Lu, B. Martin, S. Maudsley, Central Role of the EGF Receptor in Neurometabolic Aging, Int J Endocrinol (2012). Artn 739428 10.1155/2012/739428.

[67] A. Farrugia, Albumin usage in clinical medicine: tradition or therapeutic?, Transfus Med Rev 24 (2010) 53-63. 10.1016/j.tmrv.2009.09.005.

[68] M.P. Margarson, N. Soni, Serum albumin: touchstone or totem?, Anaesthesia 53 (1998) 789-803. 10.1046/j.1365-2044.1998.00438.x.

[69] J. Lei, Y. Wang, X.Q. Guo, S.P. Yan, D.M. Ma, P.R. Wang, B.J. Li, W.J. Du, R.X. Guo, Q.C. Kan, Low preoperative serum ALB level is independently associated with poor overall survival in endometrial cancer patients, Future Oncology 16 (2020) 307-316. 10.2217/fon-2019-0732.

[70] H.M. Brown-Borg, A. Bartke, GH and IGF1: Roles in Energy Metabolism of Long-Living GH Mutant Mice, J Gerontol a-Biol 67 (2012) 652-660. 10.1093/gerona/gls086.
[71] N. Barzilai, D.M. Huffman, R.H. Muzumdar, A. Bartke, The Critical Role of Metabolic Pathways in Aging, Diabetes 61 (2012) 1315-1322. 10.2337/db11-1300.

[72] L. Perice, N. Barzilai, J. Verghese, E.F. Weiss, R. Holtzer, P. Cohen, S. Milman, Lower circulating insulin-like growth factor-I is associated with better cognition in females with exceptional Longevity without compromise to muscle mass and function, Aging-Us 8 (2016) 2414-2424. 10.18632/aging.101063.

[73] L. Katsouri, S. Georgopoulos, Lack of LDL receptor enhances amyloid deposition and decreases glial response in an Alzheimer's disease mouse model, PLoS One 6 (2011) e21880. 10.1371/journal.pone.0021880.

[74] J.M. Basak, P.B. Verghese, H. Yoon, J. Kim, D.M. Holtzman, Low-density lipoprotein receptor represents an apolipoprotein E-independent pathway of Abeta uptake and degradation by astrocytes, J Biol Chem 287 (2012) 13959-13971. 10.1074/jbc.M111.288746.

[75] L. Yao, X. Gu, Q. Song, X. Wang, M. Huang, M. Hu, L. Hou, T. Kang, J. Chen, H. Chen, X. Gao, Nanoformulated alpha-mangostin ameliorates Alzheimer's disease neuropathology by elevating LDLR expression and accelerating amyloid-beta clearance, J Control Release 226 (2016) 1-14. 10.1016/j.jconrel.2016.01.055.

Tables

**Table 1.** Top five hub genes identified from the PPI networks

| Unstable angina related genes | Myocardial infarction related genes |
|------------------------------|-----------------------------------|
| **Gene** | **Node** | **Gene** | **Node** |
| IL6 | 91 | EGFR | 17 |
| VEGFA | 73 | IL10 | 16 |
| AKT1 | 69 | IGF1 | 15 |
| MAPK3 | 55 | BMP2 | 8 |
| ALB | 55 | LDLR | 7 |

Figures
Figure 1

Differentially expressed genes between Alzheimer disease/mild cognitive impairment and control groups. A, B Volcano plot and cluster heat map of the top 20 differentially expressed genes from GSE5281. C, D Volcano plot and cluster heat map of the top 20 differentially expressed genes from GSE18309. Red represents the upregulated genes based on |log2FC|>1 and P value < 0.05 and blue represents the downregulated genes based on the same statistical requirements.
Figure 2

Venn diagram of DEGs from microarray data and genes list from text mining. A Intersection of genes between DEGs generated from GSE5281 and chronic periodontitis gene list from text mining. B Intersection of genes between DEGs generated from GSE18309 and chronic periodontitis gene list from text mining. DEGs, differentially expressed genes.
Figure 3

GO term and KEGG pathway analysis for DEGs significantly associated with Alzheimer disease and chronic periodontitis. A Top 10 GO terms. Number of gene of GO analysis was acquired from DAVID functional annotation tool. p <0.05. (B) KEGG pathway.
Figure 4

GO term and KEGG pathway analysis for DEGs significantly associated with mild cognitive impairment and chronic periodontitis. A Top 10 GO terms. Number of gene of GO analysis was acquired from DAVID functional annotation tool. p < 0.05. (B) KEGG pathway.
Figure 5

A Based on the STRING online database, 247 genes/node were filtered into the DEG PPI network. B The most significant module 1 from the PPI network. C The second significant module 2 from the PPI network. The color of a node in the PPI network reflects the log (FC) value of the Z score of gene expression, and the size of node indicates the number of interacting proteins with the designated protein.
Figure 6

A Based on the STRING online database, 64 genes/node were filtered into the DEG PPI network. B The most significant module 1 from the PPI network. C The second significant module 2 from the PPI network. The color of a node in the PPI network reflects the log (FC) value of the Z score of gene expression, and the size of node indicates the number of interacting proteins with the designated protein.
Figure 7

Functional enrichment analysis of genes from the highly interconnected modules of Alzheimer disease. A Top 10 GO terms. Number of gene of GO analysis was acquired from DAVID functional annotation tool. p <0.05. (B) KEGG pathway.
Figure 8

Functional enrichment analysis of genes from the highly interconnected modules of mild cognitive impairment. A Top 10 GO terms. Number of gene of GO analysis was acquired from DAVID functional annotation tool. p < 0.05. (B) KEGG pathway.