Obesity and Mood Disorders

Subjects: Others
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Obesity and mood disorders are considered as the most prevalent morbidities in many countries. We suppose that epigenetic mechanisms may induce higher rates of obesity in subjects who suffer from mood disorders. In this study, we focused on the potential roles of DNA methylation on mood disorders and obesity development.

Keywords: depression ; epigenetics ; mood disorders ; obesity.

1. Introduction

Obesity and mood disorders are considered as the most prevalent morbidities in developed and developing countries [1][2][3]. The worldwide prevalence of obesity has nearly tripled since 1975. In 2016, more than 650 million adults were obese and 38 million children under the age of 5 were overweight or obese in 2019 [4]. The prevalence of mood disorders differs based on sex and disease. For example, the prevalence of major depressive disorder (MDD) and anxiety are 17.4% and 18.2% in men, 22.7% and 23.6 in women, respectively [5].

A combination of genetics and environmental factors affect the incidence and development of obesity and mood disorders [6][7]. The type and amount of food consumed during depression appeared to be significantly correlated and could affect the weight in a long time [8]. It has been well-established that 12% of the responsible genes for obesity are shared with depression [9], and changes in the mutual pathways of the shared genes could lead to altering the pathological eating behavior in patients with mood disorders. In addition, antidepressant drugs can alter body mass indexes [10][11][12].

One of the possible biological changes that could be responsible for the co-occurrence of these disorders might be epigenetic changes [13][14]. Epigenetics could legitimize modifications in the chromatin level, which alters the expression of genes involved in obesity and mood disorder [15][16]. Epigenetics could explain complex interactions between the genome and the environment. Epigenetic modifications, such as DNA methylation and histone modification, alter DNA accessibility and chromatin structure, thereby regulating patterns of gene expression [17]. For example, increasing the methylation of DNA reduces the expression of genes, while decreasing methylation is associated with increased gene expression [18]. DNA methylation occurs in the whole genome but could play an important role in repressing gene transcription when affecting the gene promoter (especially in the CpG islands, shore, and shelves) [19]. The relationship between DNA methylation and obesity and mood disorders has been reported previously [20][21][22][23][24].

2. Discussion

Our results revealed three overlapped genes with different methylated patterns during obesity or mood disorders, which can assist us to understand better the molecular pathophysiology of these disorders. In the further step, we attempted to identify the possible pathways that could be involved in obesity and mood disorders through the overlap genes.

In the era of the increasing prevalence of obesity and mood disorders, especially in both developing and developed world, results from our systematic review suggest an interplay between genetic susceptibility, diet, epigenetics, metagenomics, and the environment [25][26].

Evidently, obesity was found to increase the risk of depression, and depression was found to be predictive of developing obesity. Remarkably, obese persons had a 55% increased risk of developing depression over time, whereas depressed persons had a 58% increased risk of becoming obese. Neuroendocrine disturbances may also lead to depression, which in turn would cause an increase in weight over time by dysregulated stress systems or through unhealthy lifestyles. It is also possible that obesity, by its adverse effects on self-image or somatic consequences, results in the development of depression over time [27]. So, scientists struggled to find responsible genes through genome-wide association studies (GWAS) to identify the risk associated with single nucleotide polymorphisms, which might also be responsible for the co-occurrence of two conditions.

In recent years, scientific documents proved that genes are not responsible for disease by themselves, and the interaction of genes and environment is better determinants for phenotypes. Accordingly, the latest researches are likely to focus on epigenome-wide association studies (EWAS). The advantages of EWAS is considering the interaction of both genes and environments. The information gained from GWAS and EWAS has potential applications in disease control and treatment. In this study, we merely focused on DNA methylation, which could cause alterations in gene expressions and changes in the pathophysiology of diseases. We found three overlapped genes between mood disorders and obesity "*TAPBP*, *SORBS2*, and *BDNF.*" As these genes were found through published results of EWAS, we will discuss canonical pathways that might be involved in co-occurrence mood disorders and obesity.

TAPBP: The *TAPBP* gene is located in chromosome 6 and encodes tapsin; a transmembrane glycoprotein that mediates the interaction between newly assembled major histocompatibility complex (MHC) class I molecules. MHC1 is a transporter associated with antigen processing (TAP), which is required for the transport of antigenic peptides across the ER membrane [28][29]. *TAPBP*-mutant mice have defects in the expression of MHC class I, antigen presentation, and immune responses. Remarkably, Cui et al. found that the expression levels of HLA-ABC were upregulated even in the *TAPBP* knock-out cells by the interferon treatment, and immune rejection was reduced in *TAPBP*-deficient hESC line. Potent inflammatory molecules such as eicosanoids are able to upregulate *TAPBP* [30][31].

The important role of *TAPBP is* not recognized in the past in both obesity and mood disorders, and just in recent years. The results of EWAS-approved methylation in this gene could play a crucial role in these conditions. Murphy et al. identified epigenetic changes such as differentiated methylated regions (DMR) located in the third intron of the *TAPBP* gene that is related to the major depressive disorder and suicide [32]. Another study demonstrated hypermethylated CpG sites observed in the promoter region of *TAPBP* in obese and overweight subjects. These results confirmed by NEST cohort results revealed differentially methylated CpGs of *TAPBP* gene is related to the maternal pre-pregnancy obesity [33]. In vitro experiments revealed higher methylation levels of *TAPBP,* such as those found in above-mentioned studies might decrease tapsin via reduced transcriptional activity, leading to impaired immune responses and lower CD8 + T-cell responses [34][35][36]. In mice, tapsin is activated by the cytokines like IFN-γ and IFN-β, and to a lesser extent, TNF-α [36].

These results were very thought-provoking and cited several times by others and unlocked doors to the diagnosis of pathophysiology and new treatments.

TAPBP is linked to both mood disorders and obesity through the JNK pathway. This pathway plays a vital role in the inflammatory response and oxidative stress [34]. Briefly, stress-induced JNK activation occurs in the adipose and liver tissue of obese mice, whether obesity is induced by a high-fat diet or genetically through leptin deficiency (obese/obese mice). Insulin resistance in obese mice through ER stress-mediated JNK pathway is induced by the phosphorylation of insulin receptor substrate 1 (IRS1), which impairs insulin action and causes insulin resistance [35].

Interestingly, in the different tissues of obese subjects, inflammatory factors can be observed to cause continuous activation of JNK. The activated JNK acts on nuclear factor-κB (NF-κB) and activator protein-1 (AP-1) to produce more inflammatory factors, further reducing the sensitivity of insulin target cells toward insulin, finally forming a vicious circle and aggravating insulin resistance. Moreover, a network framed by PPARγ, NF-κB, and PTP1B signaling pathways crossing with the JNK signaling pathway plays a crucial role in regulating insulin resistance [28].

We assumed that a better understanding of the JNK signaling pathway and its relationship with PPARγ, NF-κB, PTP1B signaling pathways are necessary for a new drug targeting the treatment of obesity and mood disorders [28].

SORBS2: The role of *SORBS2* gene in obesity and mood disorders has been discovered recently by different genome-wide methylation studies [37]. This gene located on the 4q35. 1 encodes the Arg protein tyrosine kinase binding protein 2 (ArgBP2). *SORBS2* is an RNA-binding protein, which is involved in the regulation of RNA metabolism [38]. *SORBS2* is involved in several biological pathways. Sorbin, the product of *SORBS2,* is an ArgBP2 protein and SH3 domain-containing protein 2 and might be involved in insulin-mediated translocation of GLUT4 and thereby might affect energy storage [39]. Previous research has highlighted the role of this functional protein in disease states [40][41][42][43]. Downregulation of this gene was reported to be associated with mood disorders [44]. Linear regression analyses revealed a strong association of methylation with BMI for *SORBS2* in abdominal omental visceral adipose tissue [45]. There is enough data to provide functional evidence that promoter methylation in *SORBS2* directly influences gene activity and thus contributes to the abiogenesis. We suggest that *SORBS2* is related to obesity through the innate immunity and inflammation response by the Notch signaling pathway that plays a major role in adipogenic differentiation [46]. Increased Notch signaling in mice blocked the expansion of white adipose tissue, ectopic fat accumulation, and insulin resistance [47].

The genetic deletion of Sorbin in mice leads to mood disorders by a reduction in the average number of spines per dendrite [41]. Additionally, to the grapevine, *SORBS2* is related to mood disorders through two different pathways; actin-related proteins and the Notch signaling pathway [48][49]. Notch signaling is important in regulating neural cell proliferation, differentiation, and neural cellular growth, and is considered as a contributor in adaptive and innate immune responses. Active Notch signaling has been observed under a variety of inflammatory conditions such as atherosclerosis [47][50]. Interestingly, prototypical proinflammatory cytokines positively regulate Notch signaling and its target gene expression. For example, TNF induces expression of Notch1, Notch4 [51]. In addition, IL-1β induces Notch target genes, and Interferon-γ (IFNγ) functions as a negative regulator of Notch pathway activation [52].

BDNF: This gene is located in the 11p14.1 and encodes a member of the nerve growth factor family of proteins [53]. Alternative splicing results in multiple transcripts, at least one of which encodes a preproprotein that is proteolytically processed to generate the mature protein. Binding of this protein to its cognate receptor promotes neuronal survival in the adult brain. *BDNF* gene structure is complex, regulated by nine functional promoters. Each promoter regulates the expression of this gene [54]. *BDNF* encompasses several biological pathways and has a complex regulation; the exact roles of *BDNF* and its transcripts are not fully understood. BDNF insufficiency or missense mutations in its receptor, TrkB, are associated with weight gain and obesity in humans and mouse models [55][56]. In line with these observations, both exogenous *BDNF* administration and *BDNF* gene transfer in mouse model support the concept of the BDNF deficit in the brain induces a metabotropic impairment leading to obesity. Essentially, it has been established that the hypothalamic reduction of *BDNF* modulates energy homeostasis affecting food intake and promoting an anorectic signal [57].

There are several pieces of evidence about the role of BDNF in brain function and mood disorders [58][59][60]. Previous studies indicated that the positive correlation between brain and circulating BDNF suggests that BDNF levels in the blood reflect the levels occurring in the central nervous system. Thus, circulating BDNF has been proposed as a potential biomarker for neuropsychiatric disorders and neurodegenerative diseases [61][62][63][64][65][66].

BDNF is one of the major neurotrophic factors, plays an important role in the maintenance and survival of neurons and in synaptic plasticity. Several lines of evidence suggest that BDNF is involved in depression and plays an important role in the maintenance and survival of neurons and in synaptic plasticity. Recent documents demonstrated that the expression of *BDNF* is decreased in depressed patients [67]. BDNF has a multifaceted role from its neurotrophic activity to inflammation, metabolism, and cardiovascular diseases [68][69][70].

Methylation of the *BDNF* gene was analyzed at CpG sites in upstream of exon I. It is also possible that the hypomethylation promotor is located in exon I, which could cause altered *BDNF* expression, leading to abnormal eating behaviors [71][72]. Gardner et al. displayed different methylation in the promoter of *BDNF* related to obesity [71]. Interestingly, three of the obesity-associated CpGs were located within two of the numerous promoters of *BDNF*, and differential *BDNF* transcripts are expressed at different time points and in different cellular compartments [73][74]. Carriers of the risk allele at rs10767664 had higher methylation in the pII promoter of *BDNF*, and lower methylation in the pVI promoter of *BDNF* [75]. Januar et al. have revealed that late-life depression is associated with elevated *BDNF* methylation of specific CpG sites within promoters I and IV, with all associations remaining after adjustment for a range of covariates [76].

Furthermore, recent studies reported an increased *BDNF* methylation is associated with depression in animal models [77] and in humans [78]. Decreased BDNF may relate to the reduced function of the *BDNF* gene in promoting neural growth and repair in depression. Thus, among depressive patients, those with a higher *BDNF* methylation status are at a greater risk of suicidal behavior [79]. Hypermethylation in Exon I, in the promoter region, reduced BDNF levels in the plasma and post-mortem hippocampus of depressed individuals [80][81][82][83]. Another post-stroke cohort indicated that higher *BDNF* promoter methylation status was independently associated with depressive symptoms over one year after the onset of stroke, although not associated with baseline depressive symptom severity [79][84][85]. The methylation state of CpG sites within mouse promoter/exon IV is correlated with the expression of BDNF in the developing mouse forebrain, and similar associations were found with chronic depression, and these effects were not driven by antidepressant treatment [61]. For example, Jin et al. using the Sequenom Mass Array platform, demonstrated in mice model that fluoxetine can downregulate the expression of BDNF by the methylation of 11 CpG sites in promoter IV [86].

Strangely, BDNF has leading biological roles in inflammation and apoptosis; consequently, it is a crucial neurotrophic factor for preserving normal nervous system function. Moreover, BDNF is an associated member of the neurotrophic factor family that is mainly secreted by neuron or glial cells [87].

Sources of chronic inflammation or non-resolving inflammation may originate from either pathophysiological (e.g., inflammatory diseases, immune-based disorders, T cell dysfunction) or non-pathological conditions, including aging and obesity. Interestingly, BDNF has main biological roles in inflammation and apoptosis; thus, it is a crucial neurotrophic

factor for preserving normal nervous system function [87].

Additionally, BDNF has a multifaceted role from its neurotrophic activity to inflammation, metabolism, and cardiovascular diseases. BDNF is considered as a potential modulator/mediator with anti-inflammatory effects [81].

BDNF-related neuroprotective effects are elicited by activation of extracellular signal-related kinase (ERK) and phosphatidylinositol 3-kinase (PI3K)/protein kinase B (AKT)-signaling pathways. Production of inflammatory cytokines can regulate by complex signaling pathways, especially nuclear factor-κb (NF-κB) and inflammatory response signal pathway (BDNF-TrkB-MEK-ERK-NF-κB pathway) [88][89][90].

3. Conclusions

While mechanisms linking both obesity and mood disorders to epigenetic response are still unknown, it is well-known that chronic inflammation induces a novel epigenetic program. As the results of gene enrichment pathways analysis exhibited that *TAPBP, BDNF,* and *SRBP2* are related together by inflammatory pathways, we hypothesis that hypermethylation in these genes might play a crucial role in the co-occurrence of obesity and mood disorders due to the inflammation process. Our results shed light on our understanding of such associations. Future studies should focus on the molecular pathophysiology of these disorders in the hope of opening new approaches for target treatment.

References

1. Popkin, B.M.; Adair, L.S.; Ng, S.W. Global nutrition transition and the pandemic of obesity in developing countries. Nutr. Rev. 2012, 70, 3–21.
2. Kelly, T.; Yang, W.; Chen, C.-S.; Reynolds, K.; He, J. Global burden of obesity in 2005 and projections to 2030. Int. J. Obes. 2008, 32, 1431–1437.
3. Kessler, R.C.; Aguilar-Gaxiola, S.; Alonso, J.; Chatterji, S.; Lee, S.; Ormel, J.; Üstün, T.B.; Wang, P.S. The global burden of mental disorders: An update from the WHO World Mental Health (WMH) surveys. Epidemiologia e Psichiatr. Soc. 2009, 18, 23–33.
4. WHO. Obesity and Overweight; WHO: Geneva, Switzerland, 2020.
5. Veisani, Y.; Mohamadian, F.; Delpisheh, A. Prevalence and comorbidity of common mental disorders and associations with suicidal ideation in the adult population. Epidemiol. Heal. 2017, 39, e2017031.
6. Palou, A.; Serra, F.; Bonet, M.; Picó, C. Obesity: Molecular bases of a multifactorial problem. Eur. J. Nutr. 2000, 39, 127–144.
7. Akiskal, H.S. New insights into the nature and heterogeneity of mood disorders. J. Clin. Psychiatry 1989, 50, 50.
8. Morris, W.N.; Reilly, N.P. Toward the self-regulation of mood: Theory and research. Motiv. Emot. 1987, 11, 215–249.
9. Afari, N.; Noonan, C.; Goldberg, J.; Roy-Byrne, P.; Schur, E.; Golnari, G.; Buchwald, D. Depression and obesity: Do shared genes explain the relationship? Depression Anxiety 2010, 27, 799–806.
10. Khan, A.; Schwartz, K.A.; Kolts, R.L.; Brown, W.A. BMI, sex, and antidepressant response. J. Affect. Disord. 2007, 99, 101–106.
11. Hinze-Selch, D.; Schuld, A.; Kraus, T.; Kühn, M.; Uhr, M.; Haack, M.; Pollmacher, T. Effects of Antidepressants on Weight and on the Plasma Levels of Leptin, TNF-α and Soluble TNF Receptors A Longitudinal Study in Patients Treated with Amitriptyline or Paroxetine. Neuropsychopharmacol 2000, 23, 13–19.
12. Gafoor, R.; Booth, H.P.; Gulliford, M.C. Antidepressant utilisation and incidence of weight gain during 10 years' follow-up: Population based cohort study. BMJ 2018, 361, k1951.
13. Van Dijk, S.J.; EpiSCOPE, M.O.; Molloy, P.L.; Varinli, H.; Morrison, J.L.; Muhlhausler, B.S. Epigenetics and human obesity. Int. J. Obes. 2014, 39, 85–97.
14. Fass, D.M.; Schroeder, F.A.; Perlis, R.H.; Haggarty, S.J. Epigenetic mechanisms in mood disorders: Targeting neuroplasticity. Neuroscience 2013, 264, 112–130.
15. Schones, D.E.; Leung, A.; Natarajan, R. Chromatin Modifications Associated with Diabetes and Obesity. Arter. Thromb. Vasc. Boil. 2015, 35, 1557–1561.
16. Saavedra, K.; Molina-Márquez, A.M.; Saavedra, N.; Zambrano, T.; Salazar, L.A. Epigenetic Modifications of Major Depressive Disorder. Int. J. Mol. Sci. 2016, 17, 1279.

17. Alegría-Torres, J.A.; Baccarelli, A.A.; Bollati, V. Epigenetics and lifestyle. Epigenomics 2011, 3, 267–277.
18. Attwood, J.; Yung, R.; Richardson, B. DNA methylation and the regulation of gene transcription. Cell. Mol. Life Sci. 200 2, 59, 241–257.
19. Kouzmenko, A.; Ohtake, F.; Fujiki, R.; Kato, S. Hormonal gene regulation through DNA methylation and demethylation. Epigenomics 2010, 2, 765–774.
20. Sayols-Baixeras, S.; Subirana, I.; Fernández-Sanlés, A.; Sentí, M.; Lluís-Ganella, C.; Marrugat, J.; Elosua, R. DNA met hylation and obesity traits: An epigenome-wide association study. The REGICOR study. Epigenetics 2017, 12, 909–91 6.
21. Sonne, S.B.; Yadav, R.; Yin, G.; Dalgaard, M.D.; Myrmel, L.S.; Gupta, R.; Wang, J.; Madsen, L.; Kajimura, S.; Kristians en, K. Obesity is associated with depot-specific alterations in adipocyte DNA methylation and gene expression. Adipocy te 2017, 6, 124–133.
22. De Mello, V.D.; Pulkkinen, L.; Lalli, M.; Kolehmainen, M.; Pihlajamäki, J.; Uusitupa, M. DNA methylation in obesity and t ype 2 diabetes. Ann. Med. 2014, 46, 103–113.
23. Kader, F.; Ghai, M.; Maharaj, L. The effects of DNA methylation on human psychology. Behav. Brain Res. 2018, 346, 47 –65.
24. Chen, N.; Meng, L.; Pei, F.; Zheng, Y.; Leng, J. A review of DNA methylation in depression. J. Clin. Neurosci. 2017, 43, 39–46.
25. Chapman, D.P.; Perry, G.S. Peer reviewed: Depression as a major component of public health for older adults. Prev. C hron. Dis. 2008, 5, 1.
26. Nigatu, Y.T.; Reijneveld, S.A.; De Jonge, P.; Van Rossum, E.; Bültmann, U. The Combined Effects of Obesity, Abdomin al Obesity and Major Depression/Anxiety on Health-Related Quality of Life: The LifeLines Cohort Study. PLoS ONE 20 16, 11, e0148871.
27. Chen, K.-W.; Chen, L. Epigenetic Regulation of BDNF Gene during Development and Diseases. Int. J. Mol. Sci. 2017, 18, 571.
28. Mayer, W.E.; Klein, J. Is tapasin a modified Mhc class I molecule? Immunogenetics 2001, 53, 719–723.
29. Herberg, J.A.; Sgouros, J.; Jones, T.; Copeman, J.; Humphray, S.J.; Sheer, D. Genomic analysis of the Tapasin gene, l ocated close to the TAP loci in the MHC. Eur. J. Immunol. 1998, 28, 459–467.
30. Montfort, A.; Martin, P.G.; Levade, T.; Benoist, H.; Ségui, B. FAN (factor associated with neutral sphingomyelinase activ ation), a moonlighting protein in TNF-R1 signaling. J. Leukoc. Boil. 2010, 88, 897–903.
31. Cui, D.; Wang, J.; Zeng, Y.; Rao, L.; Chen, H.; Li, W.; Li, Y.; Li, H.; Cui, C.; Xiao, L. Generating hESCs with reduced im munogenicity by disrupting TAP1 or TAPBP. Biosci. Biotechnol. Biochem. 2016, 80, 1484–1491.
32. Murphy, T.M.; Crawford, B.; Dempster, E.L.; Hannon, E.; Burrage, J.; Turecki, G.; Kaminsky, Z.; Mill, J. Methylomic profi ling of cortex samples from completed suicide cases implicates a role for PSORS1C3 in major depression and suicide. Transl. Psychiatry 2017, 7, e989.
33. Martin, C.L.; Jima, D.; Sharp, G.C.; McCullough, L.E.; Park, S.S.; Gowdy, K.M.; Skaar, D.; Cowley, M.; Maguire, R.L.; F uemmeler, B.; et al. Maternal pre-pregnancy obesity, offspring cord blood DNA methylation, and offspring cardiometabo lic health in early childhood: An epigenome-wide association study. Epigenetics 2019, 14, 325–340.
34. Grootjans, J.; Kaser, A.; Kaufman, R.J.; Blumberg, R.S. The unfolded protein response in immunity and inflammation. Nat. Rev. Immunol. 2016, 16, 469–484.
35. Ozcan, U. Endoplasmic Reticulum Stress Links Obesity, Insulin Action, and Type 2 Diabetes. Science 2004, 306, 457– 461.
36. Abarca-Heidemann, K.; Friederichs, S.; Klamp, T.; Boehm, U.; Guethlein, L.A.; Ortmann, B. Regulation of the expressio n of mouse TAP-associated glycoprotein (tapasin) by cytokines. Immunol. Lett. 2002, 83, 197–207.
37. Zhu, Y.; Strachan, E.; Fowler, E.; Bacus, T.; Roy-Byrne, P.; Zhao, J. Genome-Wide profiling of DNA methylome and tran scriptome in peripheral blood monocytes for major depression: A Monozygotic Discordant Twin Study. Transl. Psychiatr y 2019, 9, 215.
38. Lukong, K.E.; Chang, K.-W.; Khandjian, E.W.; Richard, S. RNA-Binding proteins in human genetic disease. Trends Gen et. 2008, 24, 416–425.
39. Taniguchi, T.; Tanaka, S.; Ishii, A.; Watanabe, M.; Fujitani, N.; Sugeo, A. A brain-specific Grb2-associated regulator of e xtracellular signal-regulated kinase (Erk)/mitogen-activated protein kinase (MAPK)(GAREM) subtype, GAREM2, contrib utes to neurite outgrowth of neuroblastoma cells by regulating Erk signaling. J. Cell Sci. 2013, 288, 29934.

40. Wang, H.; Bei, Y.; Shen, S.; Huang, P.; Shi, J.; Zhang, J.; Sun, Q.; Chen, Y.; Yang, Y.; Xu, T.; et al. miR-21-3p controls s epsis-associated cardiac dysfunction via regulating SORBS2. J. Mol. Cell. Cardiol. 2016, 94, 43–53.

41. Zhang, Q.; Gao, X.; Li, C.; Feliciano, C.; Wang, N.; Zhou, D.; Mei, Y.; Monteiro, P.; Anand, M.; Itohara, S.; et al. Impaire d Dendritic Development and Memory in Sorbs2 Knock-Out Mice. J. Neurosci. 2016, 36, 2247–2260.

42. Lu, P.; Qiao, J.; He, W.; Wang, J.; Jia, Y.; Sun, Y.; Tang, S.; Fu, L.; Qin, Y. Genome-Wide Gene Expression Profile Analy ses Identify CTTN as a Potential Prognostic Marker in Esophageal Cancer. PLoS ONE 2014, 9, e88918.

43. Cheli, S.; Francois, S.; Bodega, B.; Ferrari, F.; Tenedini, E.; Roncaglia, E.; Ferrari, S.; Ginelli, E.; Meneveri, R. Expressi on Profiling of FSHD-1 and FSHD-2 Cells during Myogenic Differentiation Evidences Common and Distinctive Gene Dy sregulation Patterns. PLoS ONE 2011, 6, e20966.

44. McCarthy, M.J.; Leckband, S.G.; Kelsoe, J.R. Pharmacogenetics of lithium response in bipolar disorder. Pharmacogen omics 2010, 11, 1439–1465.

45. Keller, M.; Hopp, L.; Liu, X.; Wohland, T.; Rohde, K.; Cancello, R.; Klös, M.; Bacos, K.; Kern, M.; Eichelmann, F.; et al. Genome-wide DNA promoter methylation and transcriptome analysis in human adipose tissue unravels novel candidat e genes for obesity. Mol. Metab. 2017, 6, 86–100.

46. Ferrer-Lorente, R.; Bejar, M.T.; Badimon, L. Notch Signaling Pathway Activation in Normal and Hyperglycemic Rats Diff ers in the Stem Cells of Visceral and Subcutaneous Adipose Tissue. Stem Cells Dev. 2014, 23, 3034–3048.

47. Fung, E.; Tang, S.-M.T.; Canner, J.P.; Morishige, K.; Arboleda-Velasquez, J.F.; Cardoso, A.A.; Carlesso, N.; Aster, J.C.; Aikawa, E. Delta-Like 4 Induces Notch Signaling in Macrophages. Circulation 2007, 115, 2948–2956.

48. Cai, Z.; Zhao, B.; Deng, Y.; Shangguan, S.; Zhou, F.; Zhou, W.; Li, X.; Li, Y.; Chen, G. Notch signaling in cerebrovascul ar diseases (Review). Mol. Med. Rep. 2016, 14, 2883–2898.

49. Ahearn, E.P.; Speer, M.C.; Chen, Y.; Steffens, D.C.; Cassidy, F.; Van Meter, S.; Provenzale, J.M.; Weisler, R.H.; Krishna n, K.R.R. Investigation of Notch3 as a candidate gene for bipolar disorder using brain hyperintensities as an endophen otype. Am. J. Med. Genet. 2002, 114, 652–658.

50. Aoyama, T.; Takeshita, K.; Kikuchi, R.; Yamamoto, K.; Cheng, X.W.; Liao, J.K.; Murohara, T. γ-Secretase inhibitor reduc es diet-induced atherosclerosis in apolipoprotein E-deficient mice. Biochem. Biophys. Res. Commun. 2009, 383, 216–2 21.

51. Ando, K.; Kanazawa, S.; Tetsuka, T.; Ohta, S.; Jiang, X.; Tada, T.; Kobayashi, M.; Matsui, N.; Okamoto, T. Induction of Notch signaling by tumor necrosis factor in rheumatoid synovial fibroblasts. Oncogene 2003, 22, 7796–7803.

52. Hu, X.; Chung, A.Y.; Wu, I.; Foldi, J.; Chen, J.; Ji, J.D.; Tateya, T.; Kang, Y.J.; Han, J.; Gessler, M.; et al. Integrated Reg ulation of Toll-like Receptor Responses by Notch and Interferon-γ Pathways. Immunity 2008, 29, 691–703.

53. Hanson, I.M.; Seawright, A.; Van Heyningen, V. The human BDNF gene maps between FSHB and HVBS1 at the bound ary of 11p13–p14. Genomics 1992, 13, 1331–1333.

54. Pruunsild, P.; Kazantseva, A.; Aid, T.; Palm, K.; Timmusk, T. Dissecting the human BDNF locus: Bidirectional transcripti on, complex splicing, and multiple promoters. Genomics 2007, 90, 397–406.

55. Gray, J.; Yeo, G.S.H.; Cox, J.J.; Morton, J.; Adlam, A.; Keogh, J.M.; A Yanovski, J.; El Gharbawy, A.; Han, J.C.; Tung, Y. L.; et al. Hyperphagia, severe obesity, impaired cognitive function, and hyperactivity associated with functional loss of o ne copy of the brain-derived neurotrophic factor (BDNF) gene. Diabetes 2006, 55, 3366–3371.

56. Bonaccorso, S.; Sodhi, M.; Li, J.; Bobo, W.V.; Chen, Y.; Tumuklu, M.; Theleritis, C.; Jayathilake, K.; Meltzer, H.Y. The br ain-derived neurotrophic factor (BDNF) Val66Met polymorphism is associated with increased body mass index and insu lin resistance measures in bipolar disorder and schizophrenia. Bipolar. Disord. 2015, 17, 528–535.

57. Stanley, S.; Wynne, K.; McGowan, B.; Bloom, S.R. Hormonal Regulation of Food Intake. Physiol. Rev. 2005, 85, 1131–1158.

58. Ray, M.T.; Weickert, C.S.; Wyatt, E.; Webster, M.J. Decreased BDNF, trkB-TK+ and GAD67 mRNA expression in the hi ppocampus of individuals with schizophrenia and mood disorders. J. Psychiatry Neurosci. 2011, 36, 195–203.

59. Martinowich, K.; Manji, H.; Lu, B. New insights into BDNF function in depression and anxiety. Nat. Neurosci. 2007, 10, 1089–1093.

60. Jin, Y.; Sun, L.H.; Yang, W.; Cui, R.J.; Xu, S.B. The Role of BDNF in the Neuroimmune Axis Regulation of Mood Disord ers. Front. Neurol. 2019, 10.

61. Polyakova, M.; Stuke, K.; Schuemberg, K.; Mueller, K.; Schoenknecht, P.; Schroeter, M.L. BDNF as a biomarker for suc cessful treatment of mood disorders: A systematic & quantitative meta-analysis. J. Affect. Disord. 2015, 174, 432–440.

62. Fernandes, B.S.; Molendijk, M.L.; Köhler, C.A.; Soares, J.C.; Leite, C.M.G.S.; Machado-Vieira, R.; Ribeiro, T.L.; Silva, J.C.; Sales, P.M.G.; Quevedo, J.; et al. Peripheral brain-derived neurotrophic factor (BDNF) as a biomarker in bipolar di

sorder: A meta-analysis of 52 studies. BMC Med. 2015, 13, 289.

63. Sanada, K.; Zorrilla, I.; Iwata, Y.; Bermúdez-Ampudia, C.; Graff-Guerrero, A.; Martínez-Cengotitabengoa, M. The efficac y of non-pharmacological interventions on brain-derived neurotrophic factor in schizophrenia: A systematic review and meta-analysis. Int. J. Mol. Sci. 2016, 17, 1766.
64. Green, M.J.; Matheson, S.L.; Shepherd, A.; Weickert, C.S.; Carr, V.J. Brain-Derived neurotrophic factor levels in schizo phrenia: A systematic review with meta-analysis. Mol. Psychiatry 2010, 16, 960–972.
65. Cui, H.; Jin, Y.; Wang, J.; Weng, X.; Li, C. Serum brain-derived neurotrophic factor (BDNF) levels in schizophrenia: A sy stematic review. Shanghai Arch. Psychiatry 2012, 24, 250–261.
66. Fernandes, B.S.; Steiner, J.; Berk, M.; Molendijk, M.L.; Gonzàlez-Pinto, A.; Turck, C.W.; Nardin, P.; Gonçalves, C.-A. P eripheral brain-derived neurotrophic factor in schizophrenia and the role of antipsychotics: Meta-Analysis and implicatio ns. Mol. Psychiatry 2014, 20, 1108–1119.
67. Papathanassoglou, E.D.; Miltiadous, P.; Karanikola, M.N. May BDNF Be Implicated in the Exercise-Mediated Regulatio n of Inflammation? Critical Review and Synthesis of Evidence. Boil. Res. Nurs. 2014, 17, 521–539.
68. Zhang, J.-C.; Yao, W.; Hashimoto, K. Brain-Derived Neurotrophic Factor (BDNF)-TrkB Signaling in Inflammation-related Depression and Potential Therapeutic Targets. Curr. Neuropharmacol. 2016, 14, 721–731.
69. Chaldakov, G.N.; Fiore, M.; Stankulov, I.S.; Manni, L.; Hristova, M.G.; Antonelli, A.; Ghenev, P.I.; Aloe, L. Neurotrophin presence in human coronary atherosclerosis and metabolic syndrome: A role for NGF and BDNF in cardiovascular dise ase? In Progress in Brain Research; Elsevier BV: Amsterdam, The Netherlands, 2004; Volume 146, pp. 279–289.
70. Sandrini, L.; Di Minno, G.; Amadio, P.; Ieraci, A.; Tremoli, E.; Barbieri, S.S. Association between Obesity and Circulating Brain-Derived Neurotrophic Factor (BDNF) Levels: Systematic Review of Literature and Meta-Analysis. Int. J. Mol. Sci. 2018, 19, 2281.
71. Gardner, K.; Sapienza, C.; Fisher, J.J.P. Genetic and epigenetic associations to obesity-related appetite phenotypes a mong A frican–A merican children. Pediatric Obesity 2015, 10, 476–482.
72. Silviera, M.L.; Smith, B.P.; Powell, J.; Sapienza, C. Epigenetic differences in normal colon mucosa of cancer patients s uggest altered dietary metabolic pathways. Cancer Prev. Res. 2012, 5, 374–384.
73. Marosi, K.; Mattson, M.P. BDNF mediates adaptive brain and body responses to energetic challenges. Trends Endocrin ol. Metab. 2014, 25, 89–98.
74. Martínez-Levy, G.A.; Cruz-Fuentes, C.S. Genetic and Epigenetic Regulation of the Brain-Derived Neurotrophic Factor i n the Central Nervous System. Yale J. Boil. Med. 2014, 87, 173–186.
75. Keller, S.; Sarchiapone, M.; Zarrilli, F.; Videtic, A.; Ferraro, A.; Carli, V.; Sacchetti, S.; Lembo, F.; Angiolillo, A.; Jovanovi ć, N.; et al. Increased BDNF Promoter Methylation in the Wernicke Area of Suicide Subjects. Arch. Gen. Psychiatry 201 0, 67, 258–267.
76. Januar, V.; Ancelin, M.-L.; Ritchie, K.; Saffery, R.; Ryan, J. BDNF promoter methylation and genetic variation in late-life depression. Transl. Psychiatry 2015, 5, e619.
77. Tsankova, N.M.; Berton, O.; Renthal, W.; Kumar, A.; Neve, R.L.; Nestler, E.J. Sustained hippocampal chromatin regulati on in a mouse model of depression and antidepressant action. Nat. Neurosci. 2006, 9, 519–525.
78. Fuchikami, M.; Morinobu, S.; Segawa, M.; Okamoto, Y.; Yamawaki, S.; Ozaki, N.; Inoue, T.; Kusumi, I.; Koyama, T.; Tsu chiyama, K.; et al. DNA Methylation Profiles of the Brain-Derived Neurotrophic Factor (BDNF) Gene as a Potent Diagno stic Biomarker in Major Depression. PLoS ONE 2011, 6, e23881.
79. Kang, H.-J.; Kim, J.-M.; Lee, J.-Y.; Kim, S.-Y.; Bae, K.-Y.; Kim, S.-W.; Shin, I.-S.; Kim, H.-R.; Shin, M.-G.; Yoon, J.-S. BD NF promoter methylation and suicidal behavior in depressive patients. J. Affect. Disord. 2013, 151, 679–685.
80. Chiavetto, L.B.; Bagnardi, V.; Zanardini, R.; Molteni, R.; Nielsen, M.G.; Placentino, A.; Giovannini, C.; Rillosi, L.; Ventrig lia, M.; Riva, M.A.; et al. Serum and plasma BDNF levels in major depression: A replication study and meta-analyses. World J. Boil. Psychiatry 2010, 11, 763–773.
81. Kurita, M.; Nishino, S.; Kato, M.; Numata, Y.; Sato, T. Plasma Brain-Derived Neurotrophic Factor Levels Predict the Clin ical Outcome of Depression Treatment in a Naturalistic Study. PLoS ONE 2012, 7, e39212.
82. Lee, B.-H.; Kim, H.; Park, S.-H.; Kim, Y.-K. Decreased plasma BDNF level in depressive patients. J. Affect. Disord. 200 7, 101, 239–244.
83. Tripp, A.; Oh, H.; Guilloux, J.-P.; Martinowich, K.; Lewis, D.A.; Sibille, E. Brain-Derived Neurotrophic Factor Signaling a nd Subgenual Anterior Cingulate Cortex Dysfunction in Major Depressive Disorder. Am. J. Psychiatry 2012, 169, 1194–1202.

84. Kim, J.-M.; Stewart, R.J.; Glozier, N.; Prince, M.; Kim, S.-W.; Yang, S.-J.; Shin, I.-S.; Yoon, J.-S. Physical health, depression and cognitive function as correlates of disability in an older Korean population. Int. J. Geriatr. Psychiatry 2005, 20, 160–167.
85. Kim, J.-M.; Stewart, R.J.; Kang, H.-J.; Kim, S.Y.; Kim, S.-W.; Shin, I.-S.; Park, M.-S.; Kim, H.-R.; Shin, M.-G.; Cho, K.-H.; et al. A longitudinal study of BDNF promoter methylation and genotype with poststroke depression. J. Affect. Disord. 2013, 149, 93–99.
86. Jin, H.-J.; Pei, L.; Li, Y.-N.; Zheng, H.; Yang, S.; Wan, Y.; Mao, L.; Xia, Y.-P.; He, Q.-W.; Li, M.; et al. Alleviative effects of fluoxetine on depressive-like behaviors by epigenetic regulation of BDNF gene transcription in mouse model of post-stroke depression. Sci. Rep. 2017, 7, 14926.
87. Bathina, S.; Das, U.N. Brain-Derived neurotrophic factor and its clinical implications. Arch. Med. Sci. 2015, 11, 1164–1178.
88. Crowder, R.J.; Freeman, R.S. Phosphatidylinositol 3-Kinase and Akt Protein Kinase Are Necessary and Sufficient for the Survival of Nerve Growth Factor-Dependent Sympathetic Neurons. J. Neurosci. 1998, 18, 2933–2943.
89. Han, B.H.; Holtzman, D.M. BDNF Protects the Neonatal Brain from Hypoxic-Ischemic Injury In Vivo via the ERK Pathway. J. Neurosci. 2000, 20, 5775–5781.
90. Makar, T.K.; Trisler, D.; Sura, K.; Sultana, S.; Patel, N.; Bever, C.T. Brain derived neurotrophic factor treatment reduces inflammation and apoptosis in experimental allergic encephalomyelitis. J. Neurol. Sci. 2008, 270, 70–76.