Histone Deacetylases

Subjects: Pharmacology & Pharmacy

Contributor: Hong-Yeoul Ryu

Histone acetylation status is considered a potential diagnostic biomarker for depression, while inhibitors of histone deacetylases (HDACs) have garnered interest as novel therapeutics.

Keywords: histone deacetylase (HDAC) ; depression ; biomarker ; anti-depressant therapy

1. Introduction

Depression is characterized by recurrent episodes of sadness and despondency (depressed mood) frequently accompanied by anhedonia, loss of appetite, reduced concentration and energy, excessive guilt, and recurrent suicidal ideation [1]. Despite treatment, more than 50% of patients experience recurrent episodes and approximately 80% of those with a history of two episodes experience another relapse [2]. Both the incidence and prevalence of depression are increasing, and depression is now a major global healthcare burden and cause of lost economic productivity [3]. Current treatment guidelines recommend modulators of monoaminergic transmission such as monoamine oxidase (MAO) inhibitors and specific serotonin reuptake inhibitors (SSRIs) as first-line therapy based on the theory that depression arises from abnormal monoaminergic transmission. However, despite the availability of many monoamine modulators, approximately 50% of patients are unresponsive to these treatments [4].

Indeed, the clinical diagnosis and treatment of depression based on the Diagnostic and Statistical Manual of Mental Disorders (DSM) or the wide-ranging International Statistical Classification of Diseases and Related Health Problems (ICD) have focused on observable behaviors (signs) and self-reported feelings and thoughts (symptoms). Classifying mental disorders according to clinical signs and symptoms has led to a limitation in reflecting the underlying pathophysiology, and to heterogeneity within groups diagnosed with the same psychiatric disease [5]. Thus, attempts have emerged to suggest the novel classification of mental disorders that reflects biological mechanisms, such as Research Domain Criteria (RDoC) and biological classification of mental disorders (BeCOME) study [6][7]. Furthermore, many studies have aimed to identify the pathomechanism of depression to overcome the limitations of other existing tools for its diagnosis and treatment.

In addition to the well-known monoaminergic neurotransmitter dysfunction, altered hypothalamic-pituitary-adrenal (HPA) axis activity, dysfunctional brain network activity, impaired neurotrophic factor signaling, and neuroinflammation have been implicated in depression and studied for potential diagnostic biomarkers and therapeutic targets [8][9][10]. Additionally, changes in brain structure [11][12], gastrointestinal factors [13][14], oxidative stress [15], and endocannabinoid system components [16] have also been implicated in depression [17]. In addition, correlation studies for the aforementioned biomarkers such as inflammatory factors and brain structural changes also have been conducted in depression [18][19]. Family, twin, and adoption studies suggest that genetic factors account for 30–40% of the variance in depression risk [20], but early genome-wide association studies (GWASs) failed to identify genetic variants strongly associated with depression, suggesting that genetic susceptibility is mediated by heterogeneous combinations of risk alleles [21][22][23]. However, recent GWASs have identified several genetic loci reproducibly associated with depression [24][25][26][27][28].

The remaining 60–70% of the variation in depression risk appears to be determined by environmental factors [29]. Environmental stressors such as physical, emotional, and sexual abuse, social rejection, and other early adverse experiences and stressful life events such as the death of a loved one, illness, injury, disability, and functional decline are demonstrated risk factors for depression [30][31][32]. Individual variations in susceptibility to such stimuli may be explained in part by genetic factors. Indeed, a gene-environment interaction model positing that penetrant and complex genetic predispositions interact with environmental factors to determine depression susceptibility is now widely accepted [33].

In this gene-environmental interaction model, epigenetic mechanisms act as a bridge between genes and environmental factors [34]. Epigenetics refers to “heritable, but reversible, regulation of various genomic functions mediated principally through changes in DNA methylation and chromatin structure” [35]. Thus, epigenetic mechanisms are the processes by

which various types of cells within the same organism acquire unique transcriptional properties and functions during development [36]. This dynamic and reversible process also contributes to the transcriptional plasticity manifested by the neurons and glia in the brain. Therefore, it is associated with learning and memory, age-related neurodegeneration, cognitive and behavioral effects of early experiences, repeated drug exposure, chronic stress, prolonged changes in nutritional status, and exposure to environmental toxins [37]. The functional analyses of DNA methylation quantitative trait locus (meQTL) and non-coding RNA (ncRNA) in depression-associated single nucleotide polymorphisms (SNPs) revealed that alterations in DNA methylation and ncRNAs interact with genetic factors in depression, which underscores the importance of epigenetic regulation for depression [38].

2. Histone Acetylation

Dynamic acetylation and deacetylation of histone lysine (Lys) residues control the packaging of genomic DNA, thereby influencing DNA replication, transcription, DNA repair, and cell cycle progression [39]. Histone acetyltransferase enzymes (HATs) catalyze the transfer of acetyl groups from acetyl CoA to the ε-amino groups of Lys residues within histones [40], while histone deacetylases (HDACs) remove these acetyl groups [41]. Thus, the balance between HAT and HDAC activities determines the net histone acetylation status of the genome. By dynamically modulating the interaction between histones and DNA at the local level, histone acetylation regulates the accessibility of gene promoters to various binding factors such as transcription factors. In addition, acetylation/deacetylation of non-histone proteins modulated by HATs and HDACs also regulates diverse cellular functions [42].

3. Histone Deacetylase (HDAC) Families and Classes

Human HDACs are traditionally divided into two families, the Zn^{2+}-dependent amidohydrolases including class I, II, and IV HDACs and the NAD^{+}-dependent class III SIRT enzymes (Table 1). To date, 18 HDACs have been identified in humans and are grouped by sequence homology and domain organization [43]. Class I HDACs share structural homology with the yeast transcriptional regulator Rpd3 and typically act as the catalytic subunit within a complex of cognate corepressors to inhibit transcription in the cell nucleus [44]. HDAC1 and 2 are present in NuRD, Sin3, NODE, CoREST, and MiDAC complexes, while HDAC3 is a component of SMRT and NCoR corepressor complexes [45][46]. In contrast, HDAC8 can function independently without forming a multiprotein complex [47].

Table 1. HDAC classification.

Class	Protein (*S. cerevisiae*)	Protein (Human)	Subcellular Localization
Class I	**Rpd3**	**HDAC1**	**Nucleus**
		HDAC2	**Nucleus**
		HDAC3	**Nucleus**
		HDAC8	**Nucleus**
Class IIa	**Hda1**	**HDAC4**	**Nucleus/cytoplasm**
		HDAC5	**Nucleus/cytoplasm**
		HDAC7	**Nucleus/cytoplasm**
		HDAC9	**Nucleus/cytoplasm**
Class IIb	**Hda1**	**HDAC6**	**Cytoplasm**
		HDAC10	**Cytoplasm**
Class IV	**Hos3**	**HDAC11**	**Nucleus/cytoplasm**
Class III	**Sir2**	**SIRT1**	**Nucleus/cytoplasm**
		SIRT2	**Nucleus/cytoplasm**
		SIRT3	**Nucleus/mitochondria**
		SIRT4	**Mitochondria**
		SIRT5	**Mitochondria**
		SIRT6	**Nucleus**

Class	Protein (*S. cerevisiae*)	Protein (Human)	Subcellular Localization
		SIRT7	Nucleus

Class II HDACs are highly homologous to yeast Hda1 and are subdivided into two groups [48]. Class IIa HDACs 4, 5, 7, and 9 each have a single catalytic domain and a unique adaptor domain including a transcription factor MEF2-binding motif [49], while class IIb HDACs 6 and 10 contain two catalytic domains, a ubiquitin-binding zinc finger domain and a leucine-rich repeat domain [50][51][52][53][54]. In contrast to class I HDACs, which are exclusively localized in the nucleus, class II enzymes can shuttle between the cytoplasm and nucleus in response to various regulatory cues [49].

HDAC11, a homolog of yeast Hos3, is the only member of Class IV [55]. It is primarily expressed in the brain, skeletal muscle, heart, testis, and kidney, suggesting specific functions in development, inflammation, metabolism [55].

Class III HDACs are homologous to yeast Sir2. Like other HDACs, Class III members are involved in transcriptional silencing but have a deoxyhypusine synthase-like NAD/FAD-binding domain clearly distinct from the catalytic domains of other HDAC classes [56]. Seven Sir2-like proteins (SIRT1-7), referred to as sirtuins, have been identified in humans [57]. These sirtuins possess additional domain(s) such as a mono-ADP-ribosyltransferase domain. SIRT1 has the strongest histone deacetylase activity among sirtuins, while SIRT5 shows weak deacetylase activity but robust lysine desuccinylase and demalonylase activities [58]. These enzymes are differentially localized to the nucleus (SIRT1, 2, 3, 6, and 7), cytoplasm (SIRT1 and 2), and mitochondria (SIRT3, 4, and 5) [43].

References

1. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, 5th ed.; American Psychiatric Association: Arlington, VA, USA, 2013.
2. Burcusa, S.L.; Iacono, W.G. Risk for recurrence in depression. Clin. Psychol. Rev. 2007, 27, 959–985.
3. Liu, Q.; He, H.; Yang, J.; Feng, X.; Zhao, F.; Lyu, J. Changes in the global burden of depression from 1990 to 2017: Findings from the Global Burden of Disease study. J. Psychiatry Res. 2020, 126, 134–140.
4. Cipriani, A.; Furukawa, T.A.; Salanti, G.; Chaimani, A.; Atkinson, L.Z.; Ogawa, Y.; Levcht, S.; Ruhe, H.G.; Turner, E.H.; Higgins, J.P.T.; et al. Comparative efficacy and acceptability of 21 antidepressant drugs for the acute treatment of adults with major depressive disorder: A systematic review and network meta-analysis. Lancet 2018, 391, 1357–1366.
5. Calabro, M.; Fabbri, C.; Kasper, S.; Zohar, J.; Souery, D.; Montgomery, S.; Albani, D.; Forloni, G.; Ferentinos, P.; Rujescu, D.; et al. Research Domain Criteria (RDoC): A Perspective to Probe the Biological Background behind Treatment Efficacy in Depression. Curr. Med. Chem. 2021, 28, 1–23.
6. Insel, T.; Cuthbert, B.; Garvey, M.; Heinssen, R.; Pine, D.S.; Quinn, K.; Sanislow, C.; Wang, P. Research Domain Criteria (RDoC): Toward a New Classification Framework for Research on Mental Disorders. Am. J. Psychiatry 2010, 167, 748–751.
7. Bruckl, T.M.; Spoormaker, V.I.; Samann, P.G.; Brem, A.-K.; Henco, L.; Czamara, D.; Elbau, I.; Grandi, N.C.; Jollans, L.; Kuhnel, A.; et al. The biological classification of mental disorders (BeCOME) study: A protocol for an observational deep-phenotyping study for the identification of biological subtypes. BMC Psychiatry 2020, 20, 213.
8. Krishnan, V.; Nestler, E.J. The molecular neurobiology of depression. Nature 2008, 455, 894–902.
9. Hasler, G. Pathophysiology of depression: Do we have any solid evidence of interest to clinicians? World Psychiatry 2010, 9, 155–161.
10. Krishnan, V.; Nestler, E.J. Linking Molecules to Mood: New Insight Into the Biology of Depression. Am. J. Psychiatry 2010, 167, 1305–1320.
11. Schlaepfer, T.E.; Cohen, M.X.; Frick, C.; Kosel, M.M.; Brodesser, D.; Axmacher, N.; Joe, A.Y.; Kreft, M.; Lenartz, D.; Sturm, V. Deep Brain Stimulation to Reward Circuitry Alleviates Anhedonia in Refractory Major Depression. Neuropsychopharmacology 2007, 33, 368–377.
12. Price, J.L.; Drevets, W.C. Neural circuits underlying the pathophysiology of mood disorders. Trends Cogn. Sci. 2012, 16, 61–71.
13. Clapp, M.; Aurora, N.; Herrera, L.; Bhatia, M.; Wilen, E.; Wakefield, S. Gut Microbiota's Effect on Mental Health: The Gut-Brain Axis. Clin. Pract. 2017, 7, 131–136.
14. Wallace, C.J.K.; Milev, R. The effects of probiotics on depressive symptoms in humans: A systematic review. Ann. Gen. Psychiatry 2017, 16, 14.

15. Black, C.N.; Bot, M.; Scheffer, P.G.; Penninx, B.W.J.H. Oxidative stress in major depressive and anxiety disorders, and the association with antidepressant use; results from a large adult cohort. Psychol. Med. 2017, 47, 936–948.
16. Navarrete, F.; Garcia-Gutierrez, M.S.; Jurado-Barba, R.; Rubio, G.; Gasparyan, A.; Austrich-Olivares, A.; Manzanares, J. Endocannabinoid System Components as Potential Biomarkers in Psychiatry. Front. Psychiatry 2020, 11, 315.
17. Kennis, M.; Gerritsen, L.; Van Dalen, M.; Williams, A.; Cuijpers, P.; Bockting, C. Prospective biomarkers of major depressive disorder: A systematic review and meta-analysis. Mol. Psychiatry 2020, 25, 321–338.
18. Opel, N.; Cearns, M.; Clark, S.; Toben, C.; Grotegerd, D.; Heindel, W.; Kugel, H.; Teuber, A.; Minnerup, H.; Berger, K.; et al. Large-scale evidence for an association between low-grade peripheral inflammation and brain structural alterations in major depression in the BiDirect study. J. Psychiatry Neurosci. 2019, 44, 423–431.
19. Green, C.; Shen, X.; Stevenson, A.J.; Conole, E.L.; Harris, M.A.; Barbu, M.C.; Hawkins, E.L.; Adams, M.J.; Hillary, R.F.; Lawrie, S.M.; et al. Structural brain correlates of serum and epigenetic markers of inflammation in major depressive disorder. Brain Behav. Immun. 2021, 92, 39–48.
20. Sullivan, P.F.; Neale, M.C.; Kendler, K.S. Genetic Epidemiology of Major Depression: Review and Meta-Analysis. Am. J. Psychiatry 2000, 157, 1552–1562.
21. Bosker, F.J.; Hartman, C.A.; Nolte, I.M.; Prins, B.P.; Terpstra, P.; Posthuma, D.; van Veen, T.; Willemsen, G.; DeRijk, R.H.; de Geus, E.J.; et al. Poor replication of candidate genes for major depressive disorder using genome-wide association data. Mol. Psychiatry 2010, 16, 516–532.
22. Wray, N.R.; Pergadia, M.L.; Blackwood, D.H.R.; Penninx, B.W.J.H.; Gordon, S.D.; Nyholt, D.R.; Ripke, S.; MacIntyre, D.J.; McGhee, K.A.; Maclean, A.W.; et al. Genome-wide association study of major depressive disorder: New results, meta-analysis, and lessons learned. Mol. Psychiatry 2010, 17, 36–48.
23. Uher, R.; Investigators, G.; Investigators, M.; Investigators, S.D. Common Genetic Variation and Antidepressant Efficacy in Major Depressive Disorder: A Meta-Analysis of Three Genome-Wide Pharmacogenetic Studies. Am. J. Psychiatry 2013, 170, 207–217.
24. Cai, N.; Bigdeli, T.B.; Kretzschmar, W.; Li, Y.; Liang, J.; Song, L.; Hu, J.; Li, Q.; Jin, W.; Hu, Z.; et al. Sparse whole-genome sequencing identifies two loci for major depressive disorder. Nature 2015, 523, 588–591.
25. Okbay, A.; Baselmans, B.M.L.; De Neve, J.E.; Turley, P.; Nivard, M.G.; Fontana, M.A.; Meddens, S.F.W.; Linner, R.K.; Rietveld, C.A.; Derringer, J.; et al. Genetic variants associated with subjective well-being, depressive symptoms, and neuroticism identified through genome-wide analyses. Nat. Genet. 2016, 48, 624–633.
26. Hyde, C.L.; Nagle, M.W.; Tian, C.; Chen, X.; Paciga, S.A.; Wendland, J.R.; Tung, J.Y.; Hinds, D.A.; Perlis, R.H.; Winslow, A.R. Identification of 15 genetic loci associated with risk of major depression in individuals of European descent. Nat. Genet. 2016, 48, 1031–1036.
27. Lewis, C. Mega-Analysis of Genome-Wide Association Studies in Major Depressive Disorder: Mdd Working Group of the Psychiatric Genomics Consortium. Eur. Neuropsychopharm. 2017, 27, S119.
28. Howard, D.M.; Adams, M.J.; Shirali, M.; Clarke, T.K.; Marioni, R.E.; Davies, G.; Coleman, J.R.I.; Alloza, C.; Shen, X.Y.; Barbu, M.C.; et al. Genome-wide association study of depression phenotypes in UK Biobank identifies variants in excitatory synaptic pathways. Nat. Commun. 2018, 9, 1470.
29. Saveanu, R.V.; Nemeroff, C.B. Etiology of Depression: Genetic and Environmental Factors. Psychiatry Clin. N. Am. 2012, 35, 51–71.
30. Bruce, M.L. Psychosocial risk factors for depressive disorders in late life. Biol. Psychiatry 2002, 52, 175–184.
31. Cheptou, P.O.; Donohue, K. Epigenetics as a new avenue for the role of inbreeding depression in evolutionary ecology. Heredity 2013, 110, 205–206.
32. Shapero, B.G.; Black, S.K.; Liu, R.T.; Klugman, J.; Bender, R.E.; Abramson, L.Y.; Alloy, L.B. Stressful Life Events and Depression Symptoms: The Effect of Childhood Emotional Abuse on Stress Reactivity. J. Clin. Psychol. 2014, 70, 209–223.
33. Sun, H.; Kennedy, P.J.; Nestler, E.J. Epigenetics of the Depressed Brain: Role of Histone Acetylation and Methylation. Neuropsychopharmacology 2013, 38, 124–137.
34. Lin, E.; Tsai, S.-J. Epigenetics and Depression: An Update. Psychiatry Investig. 2019, 16, 654–661.
35. Mill, J.; Petronis, A. Molecular studies of major depressive disorder: The epigenetic perspective. Mol. Psychiatry 2007, 12, 799–814.
36. O'Donnell, K.J.; Meaney, M.J. Epigenetics, Development, and Psychopathology. Annu. Rev. Clin. Psychol. 2020, 16, 327–350.

37. Meaney, M.J.; Ferguson-Smith, A.C. Epigenetic regulation of the neural transcriptome: The meaning of the marks. Nat. Neurosci. 2010, 13, 1313–1318.
38. Ciuculete, D.M.; Voisin, S.; Kular, L.; Jonsson, J.; Rask-Andersen, M.; Mwinyi, J.; Schioth, H.B. meQTL and ncRNA functional analyses of 102 GWAS-SNPs associated with depression implicate HACE1 and SHANK2 genes. Clin. Epigenetics 2020, 12, 99.
39. Wade, P.A.; Pruss, D.; Wolffe, A.P. Histone acetylation: Chromatin in action. Trends Biochem. Sci. 1997, 22, 128–132.
40. Roth, S.Y.; Denu, J.M.; Allis, C.D. Histone Acetyltransferases. Annu. Rev. Biochem. 2001, 70, 81–120.
41. Marks, P.A.; Miller, T.; Richon, V.M. Histone deacetylases. Curr. Opin. Pharmacol. 2003, 3, 344–351.
42. Narita, T.; Weinert, B.T.; Choudhary, C. Functions and mechanisms of non-histone protein acetylation. Nat. Rev. Mol. Cell Bio. 2019, 20, 156–174.
43. Seto, E.; Yoshida, M. Erasers of Histone Acetylation: The Histone Deacetylase Enzymes. Cold Spring Harb. Perspect. Biol. 2014, 6, a018713.
44. Taunton, J.; Hassig, C.A.; Schreiber, S.L. A Mammalian Histone Deacetylase Related to the Yeast Transcriptional Regulator Rpd3p. Science 1996, 272, 408–411.
45. Ayer, D.E. Histone deacetylases: Transcriptional repression with SINers and NuRDs. Trends Cell Biol. 1999, 9, 193–198.
46. Wen, Y.D.; Perissi, V.; Staszewski, L.M.; Yang, W.M.; Krones, A.; Glass, C.K.; Rosenfeld, M.G.; Seto, E. The histone deacetylase-3 complex contains nuclear receptor corepressors. Proc. Natl. Acad. Sci. USA 2000, 97, 7202–7207.
47. Hu, E.; Chen, Z.X.; Fredrickson, T.; Zhu, Y.; Kirkpatrick, R.; Zhang, G.-F.; Johanson, K.; Sung, C.-M.; Liu, R.G.; Winkler, J. Cloning and Characterization of a Novel Human Class I Histone Deacetylase That Functions as a Transcription Repressor. J. Biol. Chem. 2000, 275, 15254–15264.
48. Grozinger, C.M.; Hassig, C.A.; Schreiber, S.L. Three proteins define a class of human histone deacetylases related to yeast Hda1p. Proc. Natl. Acad. Sci. USA 1999, 96, 4868–4873.
49. Muslin, A.J.; Xing, H.M. 14-3-3 proteins: Regulation of subcellular localization by molecular interference. Cell. Signal 2000, 12, 703–709.
50. Grozinger, C.M.; Schreiber, S.L. Regulation of histone deacetylase 4 and 5 and transcriptional activity by 14-3-3-dependent cellular localization. Proc. Natl. Acad. Sci. USA 2000, 97, 7835–7840.
51. Wang, A.H.; Kruhlak, M.J.; Wu, J.; Bertos, N.R.; Vezmar, M.; Posner, B.I.; Bazett-Jones, D.P.; Yang, X.-J. Regulation of Histone Deacetylase 4 by Binding of 14-3-3 Proteins. Mol. Cell. Biol. 2000, 20, 6904–6912.
52. McKinsey, T.A.; Zhang, C.L.; Olson, E.N. Activation of the myocyte enhancer factor-2 transcription factor by calcium/calmodulin-dependent protein kinase-stimulated binding of 14-3-3 to histone deacetylase 5. Proc. Natl. Acad. Sci. USA 2000, 97, 14400–14405.
53. Kao, H.-Y.; Downes, M.; Ordentlich, P.; Evans, R.M. Isolation of a novel histone deacetylase reveals that class I and class II deacetylases promote SMRT-mediated repression. Gene Dev. 2000, 14, 55–66.
54. Zhang, H.; Okada, S.; Hatano, M.; Okabe, S.; Tokuhisa, T. A new functional domain of Bcl6 family that recruits histone deacetylases. Biochim. Biophys. Acta (BBA) Mol. Cell Res. 2001, 1540, 188–200.
55. Gao, L.; Cueto, M.A.; Asselbergs, F.; Atadja, P. Cloning and Functional Characterization of HDAC11, a Novel Member of the Human Histone Deacetylase Family. J. Biol. Chem. 2002, 277, 25748–25755.
56. Brachmann, C.B.; Sherman, J.M.; Devine, S.E.; Cameron, E.E.; Pillus, L.; Boeke, J.D. The SIR2 gene family, conserved from bacteria to humans, functions in silencing, cell-cycle progression, and chromosome stability. Genes Dev. 1995, 9, 2888–2902.
57. Frye, R.A. Characterization of Five Human cDNAs with Homology to the Yeast SIR2 Gene: Sir2-like Proteins (Sirtuins) Metabolize NAD and May Have Protein ADP-Ribosyltransferase Activity. Biochem. Biophys. Res. Commun. 1999, 260, 273–279.
58. Du, J.; Zhou, Y.; Su, X.; Yu, J.J.; Khan, S.; Jiang, H.; Kim, J.; Woo, J.; Choi, B.H.; He, B.; et al. Sirt5 Is a NAD-Dependent Protein Lysine Demalonylase and Desuccinylase. Science 2011, 334, 806–809.