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The histone code in dementia: Transcriptional and chromatin plasticity fades away

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Abstract

With the aging of the population, Alzheimer's disease and other forms of dementia represent major challenges for health care systems globally. To date, the molecular mechanisms underlying the pathophysiology of dementia remain elusive, with a consequent negative impact in developing efficient disease modifiers. New exciting findings suggest that modulation of the histone code may influence transcriptional networks at the root of neuronal plasticity and cognitive performance. Although most of the current conclusions require further mechanistic evidence, it appears that chromatin perturbations actually correlate with Alzheimer's disease onset and progression. Thus, a better understanding of the epigenetic contribution to normal brain function and dementia pathogenesis may help to identify new epigenetic targets for the inhibition of disease trajectories associated with cognitive decline.

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Introduction

Dementia is an umbrella term describing neuropathologically distinct chronic brain disorders having in common a progressive decline of acquired cognitive functions that inevitably lead to memory loss, problem-solving difficulties, disorientation, mood swings, and language and communication deterioration [1,2]. Based on the current World Health Organization projections, approximately 50 million people have dementia worldwide, with a prevalence of 5–8% in the population aged 60–69 and of more than 33% in individuals aged 85 and older [2,3]. Because aging is one of the major risk factors [4,5], it is expected that dementia prevalence will further increase in the next decades because of the growing life expectancy in high-income as well as low- to middle-income countries around the globe. In affected people, the gradual progression of neurodegeneration and consequent brain atrophy are two common hallmarks associated with the onset of clinical symptoms that include the progressive loss of cognitive functions as well as other neurological impairments [6,7]. Alzheimer's disease (AD) is the most common form of dementia and accounts for almost 60–70% of all dementia cases [8,9]. Among the most prominent subclinical symptoms, patients often exhibit mild cognitive impairment and memory loss. Despite the enormous investment in preclinical and clinical investigations, molecular and cellular events underlying AD pathogenesis remain elusive. Postmortem evidence indicates tissue-specific spreading of neuropathological hallmarks across functionally connected brain areas [10–12]. In this regard, vast literature has reported deposition of parenchymal amyloid β (Aβ) peptide–containing plaques that anticipate the formation of intracellular neurofibrillary tangles primarily consisting of microtubule-associated protein tau [13–15]. Besides AD, there are other forms of dementia affecting millions of people globally. Vascular dementia, for instance, accounts for 10% of cases and is caused by cerebrovascular diseases associated with ischemic or hemorrhagic infarcts [16,17]. Frontotemporal dementia (e.g. Pick's disease) features neurological symptoms predominantly caused by the degeneration of the frontal and temporal lobes and is accompanied by intracellular aggregates of different protein species. Dementia with Lewy bodies is a less common form and may be considered a mixed condition since it shares many clinical features with Parkinson's disease. Other less common causes of dementia include inherited genetic disorders, head injuries, and infections (e.g. HIV). Despite the growing number of cases and urgently needed drug therapeutics, disease-modifying interventions are not available. Currently available treatments provide limited symptomatic effects but do not slow disease progression [9,18,19]. The complex etiology of the different forms

of dementia represents an obvious limiting factor in developing effective clinical approaches that may help to delay and ameliorate cognitive dysfunction linked to brain disorders. While several disease-causing mutations have been described in familial AD and frontotemporal dementia [13,20,21], less is known about the molecular mechanisms underlying idiopathic cases. Because genetic factors cannot fully explain the vast majority of dementia cases, it has been postulated that progressive alterations of the epigenome may contribute to diminishing cognitive abilities with advancing age, thereby contributing to the transition from a healthy state to advanced disease (see Figure 1). Under such a scenario, comorbidities as well as environmental conditions, lifestyle and genetic risk factors may interactively exceed a critical threshold beyond which a compensation of age-related decline in neural functions is no longer possible, ultimately resulting in the development of sporadic forms of dementia [22–24].

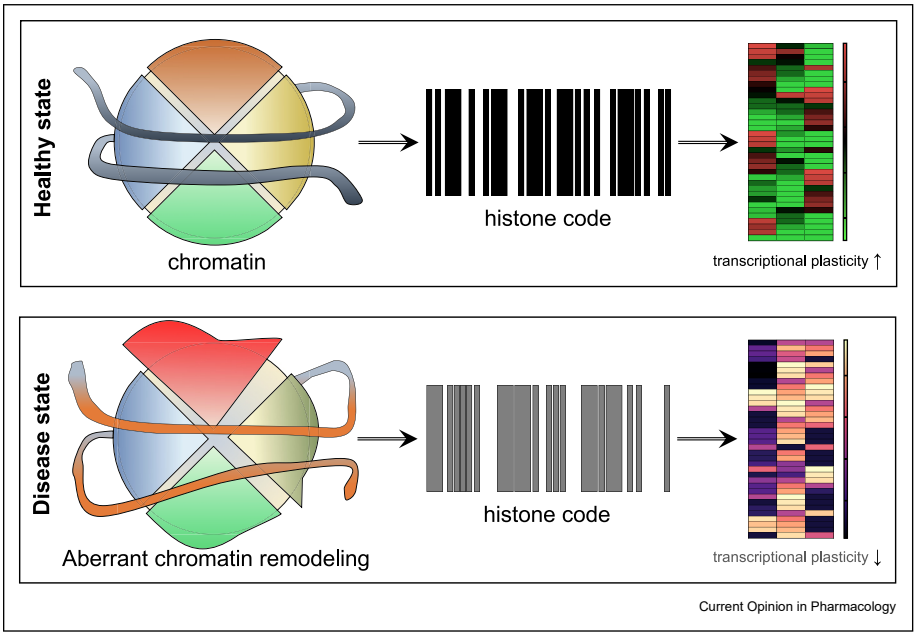
In this review, we will give a snapshot of recent reports that have been conducted primarily using human post-mortem samples, whereas we will omit the large number of studies obtained in experimental models. Because of text limitations, we will focus on the most recent evidence linking modulations of chromatin structure and function to cognitive decline associated with neurodegenerative diseases. Although the currently available experimental findings remain still limited and almost exclusively focused on AD, we envision a scenario whereby future investigations on epigenetic-dependent chromatin remodeling may help to elucidate mechanistic aspects involved in sporadic dementia and, eventually, other age-related idiopathic neurodegenerative diseases.

Main text

Neuro-epigenetics: histone code and cognitive function

Epigenetics refers to the reversible changes of transcriptional profiles resulting from biochemical modifications at the chromatin level that do not permanently mutate the DNA nucleotide sequence, but rather they transiently influence the chromatin state and the consequent accessibility to the genomic information within the nucleus. While many epigenetic traits can be transmitted across divisions in replicating cells, epigenetic changes can be both transient or long-lasting in postmitotic cells (e.g. neurons), thereby serving as memory barcodes of previous transcriptional events [25]. A large array of molecular factors and evolutionarily conserved multisubunit assemblies integrate environmental and internal cues into signals that influence the binding between DNA molecules, nucleosomal and linker histones, and scaffolding molecules involved in higher-order chromatin organization. In eukaryotic cells, the two most notable and studied epigenetic mechanisms are DNA methylation and histone post-translational modifications (PTMs). DNA methylation consists in the transfer of a methyl group from S-

Figure 1



The histone code underlies the transcriptional plasticity of cells. Nucleosomal and linker histones undergo post-translational modifications, resulting in patterns that define the accessibility of the genomic DNA. In normal physiological conditions (i.e. healthy state), intrinsic and environmental information is translated into a histone code that orchestrates the transcriptional profile of the cell. In contrast, aberrant chromatin remodeling can elicit a disease state that correlates with a histone code associated with diminished transcriptional plasticity.

adenosyl methionine to a cytosine pyrimidine ring preferentially at cytosine–guanine–enriched regions. Because of space limitations, we would recommend review articles that have extensively covered the importance of DNA methylation in human pathophysiology [26–28]. Instead, we will restrict our attention to nucleosomal histones and their PTMs [27,29,30] in their contribution to cognitive function and AD pathogenesis.

Histone H3 and its PTMs associated with AD

Histone H3 is one of the four core histones forming the nucleosome. As a fundamental unit of the chromatin, the nucleosome consists of 147 bp of DNA wrapped around two copies of each histone H2A, H2B, H3, and H4. The histone H3 family includes three main members, plus additional tissue-specific and species-specific variants [31,32]. The two canonical histones H3.1 and H3.2 are highly expressed during the S phase, and their deposition is primarily coupled to DNA replication. Conversely, histone H3.3 is a replication-independent variant that is expressed and deposited throughout the cell cycle. Canonical and replication-independent H3 variants differ by a few amino acids that critically contribute to the specific binding to dedicated histone chaperones [31,32]. Furthermore, serine 31 is only found in H3.3 and is target of phosphorylation in the context of stimulus-dependent transcription, with implications for H3.3-specific binding of the H3K36me3 reader ZMYND11 [33,34]. Over time, histone H3.3 replaces canonical histones and accumulates almost at saturation in postmitotic cells [35,36]. In this context, histone H3.3 plays a critical role in cellular plasticity on stimulation, as shown by mechanistic studies that clearly defined the link between H3.3 turnover/deposition and altered gene transcription [36,37]. Because of this unique biological aspect, the histone H3.3 variant contributes to cognitive performance and other higher brain functions [36,38–42], with potential implications for the development of age-related cognitive decline associated with dementia. Analogous to other histones, H3 can undergo PTMs on residues at the N- and C-terminal tails, although accumulating lines of evidence suggest that some amino acid side chains within the globular domain (i.e. proline 38 to glycine 132) can also be covalently modified [43,44]. Within certain chromatin territories, these PTMs may represent a code that defines the deposition or removal of other epigenetic marks by distinct histone-modifying machineries [27,29]. In accordance with the composition and combination of each alphabet letter of this unique language, PTMs may influence histone binding to the DNA and to other chromatin factors, thereby creating liquid droplet–like compartments through phase separation that orchestrate chromatin structure transitions and DNA accessibility [45–47]. Thus, histone PTMs can promote chromatin relaxation and consequent gene transcription or can induce chromatin condensation usually associated with transcriptional inhibition. In the context of AD and cognition, the most described PTMs are the acetylation (ac) and methylation (met) at various lysine (K) residues in H3 tails. As recently shown in a longitudinal study followed by postmortem neuropathological analysis of prefrontal cortices of cognitively healthy individuals and subjects affected by AD [48], increasing tau-containing neurofibrillary tangle burden, but not Aβ load, is associated with a larger number of genomic regions featuring H3K9ac enrichment. These H3K9ac domains include active transcription start sites as well as enhancers, suggesting a positive correlation between H3K9ac deposition and transcriptional activity of targeted genes. Conceivably, tau could mediate alterations in chromatin structure with consequent transcriptional activation of regions that are normally epigenetically silenced, which may affect neuronal homeostasis and function. In line with this scenario, it was shown that AD samples with widespread neocortical pathology (i.e. Braak stage V–VI) exhibit higher H3K27ac and H3K9ac levels than controls (i.e. Braak stage I, with tau neurofibrillary tangles in the entorhinal cortex) [49]. Using postmortem human brain tissues from lateral temporal lobes, genome-wide chromatin immunoprecipitation analyses showed a considerable loss of H3K122ac and H3K4me1 marks in AD tissues. These epigenetic changes correlate with an enrichment of transcriptional patterns associated with pro-disease pathways, including inflammation and cell death, that are potentially dependent on the histone acetyl transferases CBP/p300 and SAGA complex [49]. Although acetylation changes have been recently described, it is important to emphasize that other epigenetic aspects have not been rigorously investigated, and these may also be relevant in AD pathogenesis. In this regard, a small study in postmortem temporal cortices showed an association between H3K9me3 and abnormal heterochromatin structure in patients with sporadic AD compared with controls [50]. Interestingly, H3K9me3 occupancy of genomic regions inversely correlates with gene expression levels in patients with AD [50]. Of note, H3K9me3 is enriched at promoters of genes that are involved in synaptic function, neuronal differentiation, and cytoskeletal organization. Thus, this line of evidence suggests that H3K9me3 deposition may be part of a regulatory circuit that negatively affects neuronal plasticity and tissue maintenance, thereby contributing to age-related cognitive decline linked to AD.

Histone H4 and post-translational acetylation

The histone H4 binds H3 and forms H3–H4 dimers that are later incorporated in the nucleosomal histone octamers. Apart from a human truncated C-terminal variant (i.e. H4G), all metazoans primarily express evolutionarily conserved histone H4 molecules.

In humans, there are 15 genes encoding H4, some of which are constitutively expressed. Although many PTMs at the histone H4 tail influence nucleosome stability and chromatin compaction [51], their epigenetic contribution to dementia, if any, has been scarcely documented. Recently, comparative analyses have been carried out using sections from lateral temporal lobes of young, as well as elderly, cognitively healthy individuals and subjects affected by AD [52]. Here, the authors showed that genome-wide H4K16ac profiles are enriched in aged individuals who are cognitively healthy, whereas H4K16ac chromatin immunoprecipitation peaks are significantly reduced in tissues from patients with AD. H4K16ac accumulation occurs at transcription start sites and less at intergenic regions (e.g. regulatory elements), with a strong correlation between H4K16ac enrichment and gene expression of nearby targeted loci [52]. Although these findings do not provide mechanistic evidence linking age-related H4K16ac changes and AD pathogenesis, they highlight epigenetic alterations that may influence the transcriptional regulation of genes associated with aging and AD. Further studies will help to dissect the regulatory molecular processes that are protective or predispose elderly subjects to progressive cognitive decline.

Histone H2A and γH2A.X

Histone H2A binding to H2B results in dimers that critically regulate the remodeling of nucleosomal DNA [32]. Compared with the other core histones, the H2A family has the largest number of variants, most of which differ from canonical H2A at their C-terminal tails. H2A.Z and H2A.X are constitutively expressed throughout the cell cycle, and their turnover has notable effects on gene expression programs underlying neuronal plasticity [53–55]. However, while H2A.Z is rapidly deposited around transcription start sites of actively transcribed genes in neurons of animals exposed to stimuli (e.g. behavioral paradigms) that favor memory consolidation [53,54], phospho-serine 139-H2A.X (herein referred as γH2A.X) decorates DNA double-strand breaks, including promoters of early-response genes involved in experience-driven transcriptional programs [55]. Given these premises, it is not surprising that H2A variants have been the subject of several investigations in the neuro-epigenetic field. In this regard, postmortem analyses of patients with mild cognitive impairment or AD showed an increased neuronal γH2A.X staining compared with cognitively normal controls [56]. As a plausible explanation, it may be that chronic network hyperexcitability can increase double-strand break formation within actively transcribed loci, which are potentially linked to alterations of chromatin structure [55]. Alternatively, increased γH2A.X levels may simply reflect a progressive accumulation of DNA damage due to the disease state. Future studies will help to shed light on the biological relevance of γH2A.X in AD and other forms of cognitive impairment.

Conclusions

A growing number of studies has implied that aberrant epigenetic processes may contribute to cognitive impairment and age-related neurodegenerative diseases. Based on the current knowledge, it is evident that we have barely scratched the surface of what promises to be an important area of biomedical investigation. Thus, more research is needed to dissect those molecular mechanisms underlying transcriptional and chromatin plasticity that inevitably fade away during dementia pathogenesis. Through preventing that these processes go awry, we may be able to develop novel venues for urgently needed therapeutics.

Conflict of interest statement

Nothing declared.

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References

Papers of particular interest, published within the period of review, have been highlighted as:

* of special interest
** of outstanding interest

1. DeTure MA, Dickson DW: **The neuropathological diagnosis of Alzheimer's disease**. *Mol Neurodegener* 2019, **14**:32.
2. Arvanitakis Z, Shah RC, Bennett DA: **Diagnosis and management of dementia: review**. *JAMA* 2019, **322**:1589–1599.
3. Organization) WWH: *Ageing and health*. 2018.
4. Hou Y, Dan X, Babbar M, Wei Y, Hasselbalch SG, Croteau DL, Bohr VA: **Ageing as a risk factor for neurodegenerative disease**. *Nat Rev Neurol* 2019, **15**:565–581.
5. Clegg A, Young J, Iliffe S, Rikkert MO, Rockwood K: **Frailty in elderly people**. *Lancet* 2013, **381**:752–762.
6. Partridge L, Deelen J, Slagboom PE: **Facing up to the global challenges of ageing**. *Nature* 2018, **561**:45–56.
7. Prince MJ, Wu F, Guo Y, Gutierrez Robledo LM, O'Donnell M, Sullivan R, Yusuf S: **The burden of disease in older people and implications for health policy and practice**. *Lancet* 2015, **385**:549–562.
8. Jack Jr CR, Holtzman DM, Sperling R: **Dementia is not synonymous with Alzheimer's disease**. *Sci Transl Med* 2019:11.
9. Long JM, Holtzman DM: **Alzheimer disease: an update on pathobiology and treatment strategies**. *Cell* 2019, **179**:312–339.
10. Braak H, Braak E: **Staging of Alzheimer's disease-related neurofibrillary changes**. *Neurobiol Aging* 1995, **16**:271–278. discussion 278–284.

11. Braak H, Braak E: **Neuropathological stageing of Alzheimer-related changes**. *Acta Neuropathol* 1991, **82**:239–259.

12. * Vogel JW, Young AL, Oxtoby NP, Smith R, Ossenkoppele R, Strandberg OT, La Joie R, Aksman LM, Grothe MJ, Iturria-Medina Y, *et al.*: **Four distinct trajectories of tau deposition identified in Alzheimer's disease**. *Nat Med* 2021, **27**:871–881.
This article describes the spatiotemporal accummulation of microtubule associated protein tau in AD. The conclusions are based on distinct clinical profiles and longitudinal investigations using PET scans from individuals of multiple cohorts.

13. De Strooper B, Karran E: **The cellular phase of alzheimer's disease**. *Cell* 2016, **164**:603–615.

14. Herrup K: **The case for rejecting the amyloid cascade hypothesis**. *Nat Neurosci* 2015, **18**:794–799.

15. * Wegmann S, Biernat J, Mandelkow E: **A current view on Tau protein phosphorylation in Alzheimer's disease**. *Curr Opin Neurobiol* 2021, **69**:131–138.
This review provides an updated overview of tau and tau-related diseases.

16. Wardlaw JM, Smith C, Dichgans M: **Small vessel disease: mechanisms and clinical implications**. *Lancet Neurol* 2019, **18**:684–696.

17. Sweeney MD, Sagare AP, Zlokovic BV: **Blood-brain barrier breakdown in Alzheimer disease and other neurodegenerative disorders**. *Nat Rev Neurol* 2018, **14**:133–150.

18. Cummings J, Lee G, Ritter A, Zhong K: **Alzheimer's disease drug development pipeline: 2018**. *Alzheimers Dement (N Y)* 2018:195–214.

19. Livingston G, Sommerlad A, Orgeta V, Costafreda SG, Huntley J, Ames D, Ballard C, Banerjee S, Burns A, Cohen-Mansfield J, *et al.*: **Dementia prevention, intervention, and care**. *Lancet* 2017, **390**:2673–2734.

20. Gao FB, Almeida S, Lopez-Gonzalez R: **Dysregulated molecular pathways in amyotrophic lateral sclerosis-frontotemporal dementia spectrum disorder**. *EMBO J* 2017, **36**:2931–2950.

21. Arendt T, Stieler JT, Holzer M: **Tau and tauopathies**. *Brain Res Bull* 2016, **126**:238–292.

22. Stern Y: **Cognitive reserve: implications for assessment and intervention**. *Folia Phoniatr Logop* 2013, **65**:49–54.

23. Stern Y, Arenaza-Urquijo EM, Bartres-Faz D, Belleville S, Cantilon M, Chetelat G, Ewers M, Franzmeier N, Kempermann G, Kremen WS, *et al.*: **Whitepaper: defining and investigating cognitive reserve, brain reserve, and brain maintenance**. *Alzheimers Dement* 2020, **16**:1305–1311.

24. Wilson RS, Yu L, Lamar M, Schneider JA, Boyle PA, Bennett DA: **Education and cognitive reserve in old age**. *Neurology* 2019, **92**:e1041–e1050.

25. Sweatt JD: **The emerging field of neuroepigenetics**. *Neuron* 2013, **80**:624–632.

26. Lyko F: **The DNA methyltransferase family: a versatile toolkit for epigenetic regulation**. *Nat Rev Genet* 2018, **19**:81–92.

27. Allis CD, Jenuwein T: **The molecular hallmarks of epigenetic control**. *Nat Rev Genet* 2016, **17**:487–500.

28. Jones MJ, Goodman SJ, Kobor MS: **DNA methylation and healthy human aging**. *Aging Cell* 2015, **14**:924–932.

29. Soshnev AA, Josefowicz SZ, Allis CD: **Greater than the sum of parts: complexity of the dynamic epigenome**. *Mol Cell* 2016, **62**:681–694.

30. Zhang T, Cooper S, Brockdorff N: **The interplay of histone modifications - writers that read**. *EMBO Rep* 2015, **16**:1467–1481.

31. Bano D, Piazzesi A, Salomoni P, Nicotera P: **The histone variant H3.3 claims its place in the crowded scene of epigenetics**. *Aging (Albany NY)* 2017, **9**:602–614.

32. Talbert PB, Henikoff S: **Histone variants at a glance**. *J Cell Sci* 2021:134.

33. Armache A, Yang S, Martinez de Paz A, Robbins LE, Durmaz C, Cheong JQ, Ravishankar A, Daman AW, Ahimovic DJ, Klevorn T, *et al.*: **Histone H3.3 phosphorylation amplifies stimulation-induced transcription**. *Nature* 2020, **583**:852–857.

34. Wen H, Li Y, Xi Y, Jiang S, Stratton S, Peng D, Tanaka K, Ren Y, Xia Z, Wu J, *et al.*: **ZMYND11 links histone H3.3K36me3 to transcription elongation and tumour suppression**. *Nature* 2014, **508**:263–268.

35. Piazzesi A, Papic D, Bertan F, Salomoni P, Nicotera P, Bano D: **Replication-independent histone variant H3.3 controls animal lifespan through the regulation of pro-longevity transcriptional programs**. *Cell Rep* 2016, **17**:987–996.

36. Maze I, Wenderski W, Noh KM, Bagot RC, Tzavaras N, Purushothaman I, Elsasser SJ, Guo Y, Ionete C, Hurd YL, *et al.*: **Critical role of histone turnover in neuronal transcription and plasticity**. *Neuron* 2015, **87**:77–94.

37. Michod D, Bartesaghi S, Khelifi A, Bellodi C, Berliocchi L, Nicotera P, Salomoni P: **Calcium-dependent dephosphorylation of the histone chaperone DAXX regulates H3.3 loading and transcription upon neuronal activation**. *Neuron* 2012 Apr 12, **74**:122–135, https://doi.org/10.1016/j.neuron.2012.02.021.

38. Wenderski W, Maze I: **Histone turnover and chromatin accessibility: critical mediators of neurological development, plasticity, and disease**. *Bioessays* 2016, **38**:410–419.

39. Lepack AE, Bagot RC, Pena CJ, Loh YE, Farrelly LA, Lu Y, Powell SK, Lorsch ZS, Issler O, Cates HM, *et al.*: **Aberrant H3.3 dynamics in NAc promote vulnerability to depressive-like behavior**. *Proc Natl Acad Sci U S A* 2016.

40. Zovkic IB, Sweatt JD: **Memory-associated dynamic regulation of the "stable" core of the chromatin particle**. *Neuron* 2015, **87**:1–4.

41. Maze I, Noh KM, Soshnev AA, Allis CD: **Every amino acid matters: essential contributions of histone variants to mammalian development and disease**. *Nat Rev Genet* 2014, **15**:259–271.

42. * Lepack AE, Werner CT, Stewart AF, Fulton SL, Zhong P, Farrelly LA, Smith ACW, Ramakrishnan A, Lyu Y, Bastle RM, *et al.*: **Dopaminylation of histone H3 in ventral tegmental area regulates cocaine seeking**. *Science* 2020, **368**:197–201.
This works describes a new posttranslational modification of histone H3, its contribution to cocaine-mediated gene expression and the consequence on cocaine addiction. These findings expand the currently known array of PTMs on nucleosomal H3 histone and the mechanistically linked epigenetic processes.

43. Lawrence M, Daujat S, Schneider R: **Lateral thinking: how histone modifications regulate gene expression**. *Trends Genet* 2016, **32**:42–56.

44. Pradeepa MM, Grimes GR, Kumar Y, Olley G, Taylor GC, Schneider R, Bickmore WA: **Histone H3 globular domain acetylation identifies a new class of enhancers**. *Nat Genet* 2016, **48**:681–686.

45. Wang L, Gao Y, Zheng X, Liu C, Dong S, Li R, Zhang G, Wei Y, Qu H, Li Y, *et al.*: **Histone modifications regulate chromatin compartmentalization by contributing to a phase separation mechanism**. *Mol Cell* 2019, **76**:646–659. e646.

46. Strickfaden H, Tolsma TO, Sharma A, Underhill DA, Hansen JC, Hendzel MJ: **Condensed chromatin behaves like a solid on the mesoscale in vitro and in living cells**. *Cell* 2020, **183**:1772–1784. e1713.

47. * Gibson BA, Doolittle LK, Schneider MWG, Jensen LE, Gamarra N, Henry L, Gerlich DW, Redding S, Rosen MK: **Organization of chromatin by intrinsic and regulated phase separation**. *Cell* 2019, **179**:470–484. e421.
This work describes how chromatin domains marked with H3K9me2 and H3K9me3 can create compartimentalization through phase separation mechanisms, with a consequent impact on DNA accessibility and gene expression.

48. ** Klein HU, McCabe C, Gjoneska E, Sullivan SE, Kaskow BJ, Tang A, Smith RV, Xu J, Pfenning AR, Bernstein BE, *et al.*: **Epigenome-wide study uncovers large-scale changes in**

histone acetylation driven by tau pathology in aging and Alzheimer's human brains. *Nat Neurosci* 2019, **22**:37–46.
This manuscript describes the genome-wide profile of H3K9ac in tau pathology. The paper discusses the implication of tau-related chromatin remodeling on the epigenome of human AD brain.

49. ** Nativio R, Lan Y, Donahue G, Sidoli S, Berson A, Srinivasan AR, Shcherbakova O, Amlie-Wolf A, Nie J, Cui X, *et al.*: **An integrated multi-omics approach identifies epigenetic alterations associated with Alzheimer's disease**. *Nat Genet* 2020, **52**:1024–1035.
This manuscript describes an unbiased proteomic screening and the subsequent identification of H3K27ac and H3K9ac as markers highly associated with AD and neurodegeneration.

50. Lee MY, Lee J, Hyeon SJ, Cho H, Hwang YJ, Shin JY, McKee AC, Kowall NW, Kim JI, Stein TD, *et al.*: **Epigenome signatures landscaped by histone H3K9me3 are associated with the synaptic dysfunction in Alzheimer's disease**. *Aging Cell* 2020, **19**:e13153.

51. Bowman GD, Poirier MG: **Post-translational modifications of histones that influence nucleosome dynamics**. *Chem Rev* 2015, **115**:2274–2295.

52. ** Nativio R, Donahue G, Berson A, Lan Y, Amlie-Wolf A, Tuzer F, Toledo JB, Gosai SJ, Gregory BD, Torres C, *et al.*: **Dysregulation of the epigenetic landscape of normal aging in Alzheimer's disease**. *Nat Neurosci* 2018, **21**:497–505.
This manuscript discusses the genomic enrichment of H4K16ac during aging. Moreover, it reports that H4K16ac profile is highly perturbed in AD.

53. Zovkic IB, Paulukaitis BS, Day JJ, Etikala DM, Sweatt JD: **Histone H2A.Z subunit exchange controls consolidation of recent and remote memory**. *Nature* 2014, **515**:582–586.

54. Stefanelli G, Azam AB, Walters BJ, Brimble MA, Gettens CP, Bouchard-Cannon P, Cheng HM, Davidoff AM, Narkaj K, Day JJ, *et al.*: **Learning and age-related changes in genome-wide H2A.Z binding in the mouse Hippocampus**. *Cell Rep* 2018, **22**:1124–1131.

55. Madabhushi R, Gao F, Pfenning AR, Pan L, Yamakawa S, Seo J, Rueda R, Phan TX, Yamakawa H, Pao PC, *et al.*: **Activity-Induced DNA breaks govern the expression of neuronal early-response genes**. *Cell* 2015, **161**:1592–1605.

56. * Shanbhag NM, Evans MD, Mao W, Nana AL, Seeley WW, Adame A, Rissman RA, Masliah E, Mucke L: **Early neuronal accumulation of DNA double strand breaks in Alzheimer's disease**. *Acta Neuropathol Commun* 2019, **7**:77.
This paper described the accumulation of γH2A.X in postmortem tissues from MCI or AD patients.