Epigenetic Factors in Neurodegeneration

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Abstract As the world's population ages, the incidence of neurodegenerative disease is increasing. Unfortunately, identification of the underlying cause for most neurodegenerative disorders remains elusive, hindering therapeutic design. Many contributing factors have been identified, including aging, environment, oxidative stress, as well as epigenetics. This review profiles key regulatory epigenetic factors and their associated contribution to neurodegenerative disease. While characterization of the neurodegenerative epigenome is incomplete, a growing body of research supports altered DNA methylation and dysregulated histone modification as contributing factors. Furthermore, histone deacetylases demonstrate a promising role as therapeutic targets in neurodegenerative mouse models. What remains to be determined is how to effectively study the at-risk cellular populations in humans.

Keywords Alzheimer's disease · Parkinson's disease · Amyotrophic lateral sclerosis · Huntington's disease · Spinocerebellar ataxia · Neurodegeneration · DNA methylation · DNA demethylation · CpG dinucleotide DNA methyltransferases · 5-Hydroxymethylcytosine · Histone acetyltransferase · Histone deacetyltransferases · HDAC inhibitors · Epigenetics · Sirtuins · Aging · Neurons · Cell death · Brain · Cerebellum · Purkinje cell · Hippocampus · Therapeutics

Introduction

Neurodegenerative diseases (ND) are increasingly prevalent in the aging population, consuming resources of health care

systems worldwide. These devastating disorders deprive an individual of their independence, quality of life and dignity. Currently, affected individuals face a lack of effective treatment and no known cure. The most common neurodegenerative disease is Alzheimer's disease (AD), followed by Parkinson's disease (PD).

At the most rudimentary level, neurodegeneration is the progressive loss of neuronal cell function followed by neuronal cell death. While genetic mutations have been identified in these disorders and other neurodegenerative diseases, for the majority of individuals with AD or PD, the exact cause is unknown. Aging is the most reliable risk factor, influenced by environmental factors, genetic risk, and oxidative stress [1, 2]. Epigenetic factors regulating chromatin structure and transcriptional activity have also been implicated in the pathogenesis of neurodegenerative disorders [3, 4, 5].

The classic definition of epigenetics, attributed to Conrad Waddington, is the heritable change in cell phenotype that is independent of changes in genomic DNA sequence. A more modern interpretation of epigenetics often includes all mechanisms that control gene activity and regulation [5]. Epigenetic dysregulation leads to a variety of developmental defects and disorders and is involved in a variety of cancers [6]. In contrast to cancer biology, the study of epigenetics in neurodegeneration is still a relatively young field of research, and we have yet to define the neurodegenerative epigenome. This review will highlight recent observations in two key areas of epigenetic regulation, DNA methylation and histone acetylation, and the therapeutic potential of these findings.

DNA Methylation

The birth of DNA methylation as a field of research occurred more than 35 years ago, when two papers proposed

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that cytosine methylation could regulate gene activity during development and differentiation [7, 8]. Here we are so many years later, only now beginning to understand how DNA methylation is connected to neurodegenerative disease. The role for DNA methylation in normal development, regulating genomic imprinting, dosage compensation, suppression of repetitive elements, and tissue-specific gene regulation is well documented [9]. Typically found in regulatory regions, including promoters, enhancers, locus control regions and imprinting domains, DNA methylation's link to gene silencing stems from inhibition of transcriptional machinery binding regulatory regions by the cytosine methyl-mark [10]. Seemingly contradictory, DNA methylation is found in the gene body of actively transcribed genes, where silencing transcriptional activity of *alu* sequences and transposons is the attributed mode of action [11, 12].

DNA Readers and Writers

DNA methyltransferases (DNMTs) are responsible for the writing, or addition, of a methyl-group to the 5 position of the cytosine pyrimidine ring. Methylated cytosines (5mC) are found in the context of a neighboring guanine, a pairing referred to as CpG dinucleotides [6]. The CpG dinucleotide is actually underrepresented in vertebrate genomes, because spontaneous deamination of 5-methylcytosine (5-mC) results in a C to T conversion. However, clusters of CpG dinucleotides are found in regions called CpG islands, representing regulatory regions that are rarely methylated [13].

Three mammalian DNA methyltransferases, DNMT1, 3a and 3b establish and/or maintain 5mC in the genome. The most abundant DNA methyltransferase, DNMT1, is primarily responsible for maintenance, or passive methylation, targeting hemimethylated CpG dinucleotides generated during replication [14]. Both DNMT3a and DNMT3b participate in maintenance methylation, but also are responsible for *de novo*, or active, methylation during embryogenesis [15]. Methylated CpGs are read by conserved members of the methyl-CpG binding domain family of proteins, MBD1, MBD2, MBD3, and MeCP2, which recruit histone-modifying enzymes to facilitate repressive chromatin structure [6].

DNA methylation is traditionally seen as a highly stable mark, barring the observation of genome wide demethylation in early development [10]. It is now recognized that gene-specific demethylation is an active event in somatic cells, as demonstrated by synaptic plasticity in the adult hippocampus [16]. DNA demethylation is still a quite controversial and largely unresolved area of research. Numerous mechanisms have been proposed, including, but not limited, to enzymatic removal of 5mC, base excision repair, and oxidative demethylation [17].

The role of DNMTs and MBDs in post-mitotic neurons is not well characterized, although DNMTs are demonstrated to function in synaptic plasticity, the cellular mechanism for storage of memory [18]. In this role, DNMT activity is linked to dynamic regulation of promoter methylation in the adult hippocampus, an unexpected result for terminally differentiated cells, which typically demonstrate lower DNMT expression and activity. What are the implications of DNMT activity in post-mitotic neurons? Overexpression of DNMT3a, but not DNMT1, induces apoptosis in differentiated neurons [19]. More specifically, motor neuron apoptosis was associated with increases in DNMT activity. In this study, analysis of post-mortem human brain tissue demonstrates that both DNMT protein expression and 5mC are unregulated in individuals with amyotrophic lateral sclerosis (ALS) [19]. This work suggests aberrant DNA methylation is relevant to human ALS pathology.

In the above study, overexpression of DNMT1 does not induce an apoptotic phenotype in motor neurons; however, two recent exome sequencing projects link mutations in the human DNMT1 gene with human neurodegenerative disease. Families with mutations in exon 20 of DNMT1 develop a hereditary sensory neuropathy with dementia and hearing loss (HSAN1)[20••]. DNMT1 mutations in exon 21 are associated with cerebellar ataxia, deafness and narcolepsy (ADCA-DN) [21•]. How do the mutations produce differing disease pathology? The mutations at exon 20 contribute to premature degradation of mutant DNMT1 proteins, while mutations at exon 21 disrupt a DNA-binding recognition site and could possibly disrupt secondary protein complex interactions. For both mutations, the consequence is reduced global DNA methylation, coupled with several distinct localized regions of hypermethylation. Klein et al. equate the similarity of this methylation pattern to the “neoplastic” epigenome [22]. The authors note that none of the HSAN kindred had a cancer history, and suggest that global hypomethylation results in a loss of cell cycle arrest, which has detrimental consequence in postmitotic neurons. This is not a novel observation, as re-expression of various cell cycle proteins has been reported in AD and other ND disorders [23•, 24]. These studies implicate impaired regulation of global gene promoter methylation as a mechanism of neurodegeneration.

Methyl-DNA Derivatives

Advances in genome-wide mapping demonstrate that 5-mC is not the only DNA mark [25]. Recently, three additional marks, 5-hydroxymethylcytosine (5hmC), 5-formylcytosine (5fC), and 5-carboxylcytosine (5-caC), have been characterized in murine ES cells and tissues (see Table 1) [26, 27]. These marks are regulated by the ten-eleven translocation

Table 1 DNA Modification

Cytosine Modification	Nomenclature	Writer	Reader	Function
5-methylcytosine	5mC	DNMT1, 3a, 3b	MBD domain	Gene Silencing
5-hydroxymethylcytosine	5hmC	Tet1-3	unknown	unknown
5-formylcytosine	5fC	Tet1-3	unknown	unknown
5-carboxylcytosine	5caC	Tet1-3	unknown	unknown

(TET 1-3) family of proteins, which hydrolyze the conversion of 5mC to 5hmC. Further iterative oxidation of 5hmC by TET family members results in oxidative derivatives, 5fC and 5caC, suggesting TET family members participate in active demethylation [28].

5hmC is not read by the same proteins that bind 5mC, namely, MBD1, 2, 4, and MeCP2. Also, 5hmC is poorly recognized by Dnmt1 [29], suggesting alternative binding proteins target 5hmC, contributing to a different biological function than 5mC. In the human brain, 5hmC is targeted to genes, including both promoter regions and gene bodies, but is selectively depleted from intergenic regions [30]. Several independent analysis of embryonic stem cells (ESCs) indicate that 5hmC can be found in promoters, exons and enhancers associated with transcriptional activity [31–33], while other studies indicate Tet1 and 5hmC are enriched in transcriptionally inactive regions in ESCs [17, 34]. Together, this suggests the 5hmC is involved in demarcation of developmentally poised regions.

In the adult animal, interrogation of the mouse dentate gyrus methylome reveals a relationship between dynamic DNA methylation and neuronal activity [28]. The pattern is particularly interesting, as activity-modified CpGs show a broad genomic distribution with significant enrichment in low-CpG density regions and an association with neuronal plasticity [32]. What has not yet been determined is whether density of stable versus dynamic DNA methylation is reflected by the combined effect of CpG density, DNA modification status and associated protein partner. Our understanding of DNA methylation, demethylation, and methyl-DNA derivatives, in neurodegenerative disease, while limited, is poised to expand exponentially due to advances in next generation sequencing. Technology, such as single-molecule, real-time (SMRT) DNA sequencing, demonstrates promising elucidation of these marks at a single-base resolution [35]. This opens a new door to therapeutic design, directed at these marks and the proteins that read and write 5hmC, 5fC and 5ca.

Histone Modification

Histone N-terminal tails carry a variety of reversible post-transcriptional marks, which Vincent Allfrey proposed to facilitate the transfer of genetic information from DNA to

RNA, nearly a half century ago. Over the decades, a wealth of information about the different types of histone marks and amino acid location, the protein complexes that modify or remodel these residues, the proteins that recognize the modifications, as well as the functional consequence of each type of mark, has emerged. The diversity of histone modifications conveys the depth of complexity by histone regulation. Lysine residues are most commonly modified, and are often acetylated, methylated, ubiquitinated, or sumoylated [6]. More recently, lysine butyrylation, crotonylation, and propionylation have been described. Other amino acid/modification pairings include ADP ribosylation, arginine methylation and deimination, serine/threonine phosphorylation and O-GlcNAcylation, tyrosine phosphorylation and hydroxylation [36]. A simplified view is that crosstalk between the pattern of modifications and the proteins that reads or writes the modifications leads to transcriptional competence or repression [36].

These patterns are not static. Rather, a host of protein complexes specific to reading or writing histone marks contribute to the dynamic chromatin landscape. Crosstalk on the histone tail establishes context, whereby a set of marks influences deposition, interpretation or removal of other histone modifications [37]. Furthermore, histone-modifying complexes target non-histone proteins, such as transcription factors and nuclear receptors, which facilitates gene expression [6]. The direct histone versus non-histone effects cannot always be uncoupled, suggesting that the actions are concerted, where the combined histone and non-histone proteins lead to a common endpoint, as demonstrated by the histone deacetylase complex activity in neurodegenerative disease. This section focuses on recent studies relative to the dynamic relationship between histone acetylation and deacetylation.

Histone Acetylation

Acetylation neutralizes lysine's positive charge, weakening the electrostatic interaction between histones and negatively charged DNA, and contributing to an opening of chromatin structure. Genome wide analysis demonstrates that histone acetylation is enriched at promoters and enhancers at transcriptionally active genes. Histone acetylation is read by proteins containing bromodomains and plant zinc finger

homeodomains (PHD). Histone acetylation status is regulated by two families of proteins, histone lysine acetyltransferases (HATs), and histone deacetylases (HDAC) [6, 38].

An interesting example of histone dysregulation associated with neurodegenerative disease is provided by SCA7, a progressive neurodegenerative disorder [39]. The causative mutation is a CAG repeat expansion in the first coding exon of the Ataxin-7 gene, which encodes a protein with longer stretches of glutamines, thus contributing to protein misfolding. Ataxin-7 is a member of the Spt3-Taf9-Ada-Gcn5-Acetyltransferase (STAGA) transcriptional co-activator complex, which contains multiple modules, including a Gcn5 module with histone acetyltransferase activity, and a USP22 containing module with histone H2B deubiquitinylation activity [40–42]. SCA7 transgenic and knock-in mouse models demonstrate a severe chromatin decondensation phenotype in rod photoreceptors [40]. Previously, the La Spada group characterized an SCA7 mouse model demonstrating that STAGA HAT activity is inhibited by a CAG repeat expansion [42]. The result is reduced total histone H3 acetylation at the promoter and enhancer regions, as well as downregulation of the Crx-target gene transcription [42–44].

Recently, an additional study explored the relationship of Gcn5 HAT activity and expanded Ataxin-7 protein by crossing mice harboring Gcn5 mutations with SCA7 mice. Note, Gcn5 functions are essential for mouse embryo survival, and embryonic development, thus the mutation is a partial loss of Gcn5 function. Loss of Gcn5 function accelerates neuronal dysfunction and pathology in the cerebellum and retina of SCA7 mice [45]. This study strongly supports previous observations linking the presence of an expanded Ataxin-7 protein and a loss of STAGA-associated HAT activity. Thus, SCA7 provides a model disorder for the study of the relationship of direct epigenetic dysregulation on neurodegenerative disease progression.

Similar to Ataxin-7, a CAG repeat expansion in the Ataxin-1 gene is the causative mutation in SCA1, an inherited polyglutamine disorder characterized by Neurodegeneration of cerebellar Purkinje cells, brain stem and spinal cord. Ataxin-1 is found in a complex with histone acetyltransferase, tat-interacting protein 60 kDa (Tip60), and receptor-related orphan receptor alpha [46]. Partial loss of Tip60 (haploinsufficiency) slowed the progression of Atxn1-82Q-associated Purkinje cell atrophy, implicating that histone acetyltransferase activity plays a part in SCA1 pathogenesis [47].

Tip60 acetyltransferase activity is also linked with AD pathogenesis via an interaction with AD-associated amyloid precursor protein (APP) intracellular domain (AICD) [48]. A recent study by Pirooznia et al. examines the role of Tip60 acetyltransferase activity and APP induced apoptosis in a drosophila AD model [49]. In contrast to TIP60's neuroprotective role in SCA1, a loss of TIP60 mediates APP-induced

apoptosis in this *Drosophila* AD model. These results suggest that the context of HAT activity, rather than the protein itself, correlates with neuroprotection or neurotoxicity.

Histone Deacetylation

HDACs are responsible for removing lysine acetylation marks, thus returning a positive charge on the side chain. Four classes of HDACs encompass 18 known enzymes. Class I (HDACs 1–3 and 8), Class II (HDACs 4–7 and 9–10) and Class IV (HDAC 11) share a related zinc dependent catalytic mechanism, while Class III (Sirtuins 1–7) utilize a NAD⁺-dependent mechanism [6]. Similar to HATs, HDACs target both histone and non-histone proteins. Substrate specificity is influenced by the context of multiprotein complexes in which HDACs are found [38]. A growing body of work links HDAC activity with numerous degenerative diseases, and inhibition of HDAC activity is a promising therapeutic [3].

Two recent papers map HDAC2 cell-type expression in the murine brain, demonstrating expression in cholinergic, serotonergic and catecholaminergic neurons, as well as postsynaptic glutamatergic and GABAergic neurons. HDAC2 was seen in oligodendrocytes but not astrocytes or microglia [50]. Further analysis demonstrates that HDAC2 colocalizes with the insulin signaling pathway in postsynaptic glutamatergic neurons in the mouse hippocampus [51]. Independent analysis reveals increased HDAC2 levels in two mouse models of neurodegeneration and in AD patients, where it is responsible for reducing expression of genes associated with learning and memory [4•, 52]. Inhibition of HDAC2 by short-hairpin RNA mediated knockdown unlocks the repression of these genes, reinstating structural and synaptic plasticity, and reversing neurodegeneration-associated memory impairments [4•]. Combined, these studies demonstrate the cell type and associated gene targets of HDAC2 activity.

HDAC6's involvement in tau accumulation is revealed by the Petrucelli lab, who report that HDAC6 is regulated by ubiquitin ligase carboxy terminus of Hsp70-interacting protein (CHIP). In turn, HDAC6 regulates tau protein levels through regulation of Hsp90 acetylation. Decreased HDAC6 levels result in Hsp90 hyperacetylation, promoting protein degradation; thus, tau protein is cleared. The converse occurs when HDAC6 levels increase [53]. This suggests a non-histone protein role for HDAC6 that is relevant to tau accumulation in neurodegenerative diseases.

The Herrup group describes a complicated consequence of mutation of the *Atm* gene, the causative gene for the neurodegenerative disease ataxia telangiectasia. Here, they describe finding HDAC4 in the Purkinje cell nuclei of human ataxia telangiectasia samples, rather than in the

Purkinje cell cytoplasm, as normal [54]. Within the nucleus, HDAC4 binds chromatin, as well as myocyte enhancer factor 2A (MEF2A) and cAMP-responsive element binding protein (CREB), leading to histone deacetylation and altered neuronal gene expression. Blocking HDAC4 activity in *Atm* knockout mice only partially rescues neurodegeneration, as HDAC4 must also be in the cytoplasm for full rescue, which is achieved by phosphorylation of HDAC4. In *ATM*, PP2A activity is enhanced, leading to HDAC4 dephosphorylation and nuclear accumulation. The significance of their observation is that HDAC4 activity only partially contributes to ataxia telangiectasia; HDAC4 cellular location is also a contributing factor in disease pathology.

The Class III HDACs, represented by Sirtuins 1–7, are highly conserved NAD⁺ dependent enzymes that have been widely studied in the context of neurodegenerative disease [6]. Two recent exciting papers from overlapping research groups demonstrate a neuroprotective role for Sirt1 in mammalian Huntington's disease models. In the first paper, the researchers show an interaction between expanded HTT and Sirt1 that results in inhibition of Sirt1 deacetylase activity. The consequence is hyperacetylation of Sirt1 substrates, such as forkhead box O3A (Foxo3a), inhibiting cell survival [55•]. Overexpression of Sirt1 protects neurons from mutant HTT toxicity, accompanied with improved motor function, reduced brain atrophy and attenuated mutant HTT-associated metabolic abnormalities. In the HD mouse model, Sirt1 overexpression prevents the decline in brain-derived neurotrophic factor (BDNF) levels, and the signaling of its receptor, TrkB, restores dopamine and cAMP regulated phosphoprotein 32kDa (DARPP32) concentrations in the striatum [55•]. In the second paper, the researchers demonstrate that Sirt1-mediated neuroprotection from mutant huntingtin protein occurs through activation of the TORC1 and CREB transcriptional pathway. Sirt1 deacetylates and activates TORC1, and promotes TORC1 [56•]. The significance of these studies is the strong neuroprotection and reversal of disease pathogenesis by overexpression of SIRT1, which suggests that targeting Sirt1 to enhance its deacetylase activity is a worthwhile therapeutic approach.

HDAC Inhibitors as Therapeutics

Targeting HDACs with inhibitors is proving to be an exciting area of research in the neurodegenerative field. Blocking HDAC activity with inhibitors or short hairpin knockdown has successfully ameliorated several experimental models of neurodegenerative disease, including glaucomatous optic neuropathies [57]. Mithramycin A (MTM) is a gene-selective Sp1 inhibitor that has long been used as a chemotherapeutic agent, although it is also neuroprotective [58–60]. It binds to GC-rich DNA sequences, displacing the transcription factor Sp1 at

gene promoters of oncogenes. HDACi are small molecules that interfere with HDAC activity. Interestingly, protection from both MTM and HDACi is associated with inhibition of genes associated with cellular transformation, *Myc*, HDAC1, HDAC2 and HDAC3, as well as induction of the tumor suppressor p21^{waf1/cip1}, highlighting an overlap between cancer treatment and neurodegeneration. This observation is consistent with previously mentioned observations linking neuronal degeneration and re-entry into the cell cycle [20••].

The Gottesfeld lab reported that HDAC inhibitor 4b ameliorates the disease phenotype and transcriptional abnormalities in HD R6/2 mice and showed promising results in Friedreich's ataxia disease models [61–63]. The authors suggest that therapies aimed at modulating transcription could provide clinical benefits for HD patients, with minimal toxic effects. More recent work on HDAC inhibitor 4b defines what HDACs are targeted by the HD mouse model, HDAC1 and 3 [64•]. Namely, mutant *Htt* selectively causes HDACs 1 and 3 to accumulate in the nucleus and HDAC inhibitor 4b preferentially inhibits HDAC3 followed by HDAC1, demonstrating the efficacy of HDAC inhibitor 4b in HD models [65]. These results are indirectly supported by knock-down of *Hdac6* and *Hdac7* in the R6/2 HD mouse, which demonstrated no effect on HD phenotype [66–69]. What is perplexing is that knockdown of *Hdac3* also did not effect the HD phenotype [69]. It should be noted that the *Hdac3* knockdown mouse does retain approximately 60 % of the nuclear HDAC3 levels and 100 % of cytoplasmic; perhaps reduced *Hdac3* levels are not sufficient to improve disease pathogenesis. Given that both HDAC1 and HDAC3

Fig. 1 The accumulation of numerous factors, including genetic, environmental, and oxidative stress, contribute to epigenetic changes within a cell. In the presence of global hypomethylation, increased histone acetylation of genes associated with cell proliferation induces re-entry into the cell cycle. The consequence depends on the context of the cell. Cells outside of the nervous system can clonally expand over time, leading to tumor formation. Neurons undergo cell death, leading to loss of cells in a population

are targets of HDAC inhibitor 4b, perhaps a double knock-out of HDAC3 and HDAC1 would clarify the discrepancy.

Conclusions

This review focuses on two key components of epigenetics, DNA methylation and histone acetylation. Both are fields of study where there is a great depth of knowledge, but in the context of developmental disorders and cancer biology, not neurodegeneration. As such, dynamic activity of DNA methylation and demethylation in the brain is an emerging story, suggesting that the methyl-DNA derivatives confer a biological significance related to neuronal activity. How does this activity and dynamic nature contribute to neurodegenerative disease? Perhaps cell types with greater functional dependence on dynamic methylation for cellular function are a greater risk of cell death or loss of function.

The study of histone modifications in neurodegeneration is better developed than DNA methylation. Here, mounting evidence suggests dysregulated HDAC activity, particularly class I and class II HDACs, contributes to neurodegenerative disease pathology. Several groups have demonstrated moderate success ameliorating disease phenotype using specific and non-specific HDAC inhibitors. These are certainly promising therapeutics. Furthermore, an interesting body of work suggests that class II HDACs, namely Sirt1, harbors neuroprotective activity. In this context, the therapeutic potential is activation of Sirt1 activity. Together, these studies reflect the beginning of what should lead to effective treatment of neurodegenerative disease.

Two key experimental hurdles thwart the elucidation of the neurodegenerative epigenome: heterogeneity of cell types within a tissue and cell loss. Heterogeneity of a tissue poses a problem to determining the accurate changes in the affected cells, especially as the sub-cell types, such as neurons and glia, have distinctive DNA methylation profiles [70]. Furthermore, in contrast to cancer research, where cancerous cells can be profiled relative to non-cancerous cells, the study of neurodegenerative disease is limited by neuron loss. Consider that by the time PD is diagnosed, there is a loss of dopamine neurons. Examination of post-mortem tissue reveals the molecular and epigenetic context of the cells that survived. This approach, while important, is as likely to reveal the molecular mechanisms that confer neuroprotection, as it is to represent neurodegeneration. Murine models provide the opportunity to perform a time course of disease pathogenesis, in the context of genetic causes. We must continue to foster new experimental paradigms, including single cell epigenetic profiling and single cell transcriptome sequencing.

In cancer, there is an initiating event that allows for cell proliferation (Fig. 1, left arrow). Consequently, the dividing

cell population expands, accumulating additional mutations overtime. Of course, this does not happen in neurodegeneration, instead, re-entry into the cell cycle induces cell death (Fig. 1, right arrow). However, not all cells die at the onset of degenerative disease, and rather than a clonal expansion of dysregulated cells, there is a discriminate reduction in cells, where only certain cells face cell death. The remaining cells continue to accrue mutations, reaching a point of loss of cell function and systematic cell death. Understanding neurodegeneration could be as simple as defining what set of genes enables a non-neuronal cell to live and a neuronal cell to die.

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