Report Title

Introduction

Introduction:
Neurodegenerative diseases, such as Alzheimer's, pose a significant challenge to public health due to their complex etiology and limited treatment options. The influence of epigenetic modifications on the development and progression of these diseases has garnered increasing attention. Epigenetic mechanisms, including DNA methylation, chromatin remodeling, histone post-translational modifications, and non-coding RNAs, play crucial roles in neuronal function and development. Recent research has shed light on critical functions of chromatin in the aging brain, with an emerging realization that the maintenance of a healthy brain relies heavily on epigenetic mechanisms. Studies have demonstrated the involvement of epigenetic modifications in synaptic plasticity, memory formation, and cognitive function, which are essential for understanding the underlying molecular mechanisms of neurodegenerative processes.

The dysregulation of epigenetic mechanisms in neurodegenerative diseases, such as Alzheimer's, Huntington's disease, and amyotrophic lateral sclerosis, has been implicated in the pathophysiology of these conditions. The aberrant DNA methylation patterns, histone modifications, and changes in nucleosome positioning have been observed in these diseases, emphasizing the impact of epigenetic dysregulation on neuronal development, differentiation, and cognitive function. Additionally, neuroinflammatory diseases linked to neurodegeneration are characterized by dramatic changes in the epigenetic profile, providing insights into potential prognostic and therapeutic factors for neuroinflammatory treatment.

Furthermore, the potential therapeutic implications of targeting epigenetic machinery to ameliorate the symptoms associated with neurodegenerative diseases highlight the translational relevance of understanding the intricate interplay between epigenetic modifications and disease pathogenesis. The investigation of epigenetic mechanisms in the context of neurodegenerative diseases holds promise for identifying potential therapeutic targets and personalized treatment strategies. Therefore, investigating the impact of epigenetic dysregulation on neurodegenerative diseases is crucial for advancing our understanding of these conditions and developing potential therapeutic strategies.

References:

1. [https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6174532/pdf/]
2. [https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6380351/pdf/]
3. [https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8618067/pdf/]
4. [https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9740629/pdf/]

Literature

Literature Review:

Epigenetic modifications play a crucial role in the development and progression of neurodegenerative diseases, particularly Alzheimer's, by influencing neuronal function, memory formation, and synaptic plasticity. The emerging field of neuroepigenetics focuses on understanding the impact of epigenetic mechanisms, including DNA methylation, histone post-translational modifications, histone variants, miRNAs, and lncRNAs, on neuronal transcriptional output for information storage and circuit regulation.

Experimental evidence supports the significant role of DNA methylation in memory acquisition and storage. Studies involving the targeted deletion of specific methyltransferases in mice have demonstrated deficits in hippocampus-based learning and memory, emphasizing the importance of DNMTs in synaptic plasticity and cognitive function. Moreover, the upregulation of DNMTs in the adult rat hippocampus in response to contextual fear conditioning underscores the dynamic role of DNA methylation in brain function in adulthood.

In addition to DNA methylation, non-coding RNAs, particularly miRNAs and lncRNAs, have been implicated in the epigenetic regulation of gene expression and synaptic plasticity. Their involvement in RNA silencing and post-transcriptional gene expression regulation suggests their contribution to early brain development and cognitive function.

Furthermore, the reciprocal relationship between regulatory factors such as REST and CoREST and miRNAs in the context of neurodegenerative diseases like Huntington's disease highlights the potential implications for cognitive disorders. Moreover, studies have shown that epigenetic modifications, including histone post-translational modifications and changes in nucleosome positioning, are robust regulators of activity-dependent changes in gene transcription, thereby implicating their role in synaptic plasticity and memory formation.

The research literature also emphasizes the potential therapeutic implications of targeting epigenetic mechanisms in neurodegenerative diseases. The reversibility and dynamic nature of epigenetic modifications in neurons make them viable targets for therapeutic intervention, shedding light on emerging therapeutic approaches.

In conclusion, the literature review provides a comprehensive overview of the mechanisms through which epigenetic modifications influence the development and progression of neurodegenerative diseases, particularly Alzheimer's. The evidence presented underscores the intricate relationship between epigenetic mechanisms, memory formation, and cognitive function in the context of neuronal health and disease progression.

References:

1. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6174532/pdf/
2. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6380351/pdf/
3. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8618067/pdf/
4. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9740629/pdf/

Discussion

difications, miRNAs, and lncRNAs in regulating gene expression and neuronal function, shedding light on their potential contribution to the pathophysiology of neurodegenerative diseases.

Strengths of the approach:

1. Comprehensive coverage of various epigenetic mechanisms involved in neurodegeneration, providing a holistic understanding of the topic.
2. Integration of both in vitro and in vivo evidence to support the role of epigenetic modifications in neurodegenerative diseases.
3. Clear explanation of the molecular pathways and interactions involved in epigenetic regulation of gene expression in the context of neurodegeneration.

Weaknesses of the approach:

1. Limited discussion on the specific impact of epigenetic modifications on Alzheimer's disease compared to other neurodegenerative diseases.
2. The article could benefit from more direct comparisons with the results of other studies in the field to strengthen the discussion and provide a broader perspective.
3. The discussion could be enhanced by addressing potential conflicting findings or unanswered questions in the current research on neuroepigenetics and neurodegenerative diseases.

Future research directions could include:

1. Investigating the specific epigenetic modifications associated with Alzheimer's disease to identify potential therapeutic targets.
2. Exploring the interplay between different epigenetic mechanisms and their collective impact on neurodegeneration.
3. Conducting longitudinal studies to elucidate the temporal dynamics of epigenetic changes in the progression of neurodegenerative diseases.

In summary, the article contributes to the understanding of the role of epigenetic modifications in neurodegenerative diseases, particularly Alzheimer's, by providing a comprehensive overview of the involved mechanisms. However, further research is needed to address the limitations and expand our knowledge of the specific epigenetic influences on Alzheimer's disease.

In conclusion, the discussion sections of the provided articles offer valuable insights into the role of epigenetic modifications in neurodegenerative diseases, particularly Alzheimer's. Each article provides a comprehensive analysis of the current understanding of epigenetic mechanisms and their impact on

disease pathophysiology. While the articles have strengths in their thorough exploration of various epigenetic pathways, they also acknowledge the need for further research to address specific mechanistic gaps and potential therapeutic targets. Overall, the articles make valuable contributions to the field of neuroepigenetics and set the stage for future investigations into targeted epigenetic therapies for neurodegenerative conditions.

Idea

Problem:
What are the specific epigenetic mechanisms contributing to neurodegenerative disorders, and how can these mechanisms be targeted for therapeutic intervention?

Rationale:

Given the emerging evidence implicating the dysregulation of epigenetic mechanisms in neurodegenerative disorders and diseases, there is a critical need to understand the specific epigenetic profiles involved in neurodegeneration. By identifying the key epigenetic modifications associated with different neurodegenerative diseases and exploring their potential as therapeutic targets, we can pave the way for the development of novel interventions aimed at modulating these epigenetic mechanisms to mitigate the progression of neurodegenerative disorders. This research problem is significant as it addresses a pressing issue in neuroscience and has the potential to uncover new avenues for therapeutic strategies in the treatment of neurodegenerative conditions.

Method

Method: Integrative Epigenomic Analysis of Neurodegenerative Disorders

Rationale:

The proposed method aims to comprehensively analyze the epigenetic landscape of neurodegenerative disorders through an integrative approach, leveraging existing studies and entities to identify specific epigenetic mechanisms contributing to these disorders and explore their potential as therapeutic targets. By integrating data from various epigenomic profiling techniques and applying cutting-edge computational analyses, this method seeks to elucidate the key epigenetic modifications associated with different neurodegenerative diseases and facilitate the identification of druggable epigenetic targets for therapeutic intervention.

1. Data Acquisition and Integration:

- Compile publicly available epigenomic datasets, including but not limited to DNA methylation profiles, histone modification patterns, chromatin accessibility assays, and non-coding RNA expression data, from relevant studies and databases focusing on neurodegenerative disorders.
- Integrate multi-omics data across different neurodegenerative disorders to capture the diverse and overlapping epigenetic signatures associated with these conditions.

2. Computational Analysis:

- Apply advanced bioinformatics and statistical methods to process and analyze the integrated epigenomic datasets, including differential methylation and histone modification analyses, identification of regulatory chromatin regions, and exploration of epigenetic regulatory networks specific to neurodegenerative disorders.
- Utilize machine learning algorithms, network analysis, and pathway enrichment tools to unravel the complex interplay of epigenetic mechanisms and their functional implications in neurodegeneration.

3. Identification of Epigenetic Signatures:

- Identify specific epigenetic modifications (e.g., hypermethylation of regulatory regions, altered histone acetylation patterns) that are consistently associated with different neurodegenerative diseases, thereby delineating disease-specific epigenetic signatures.
- Characterize the regulatory elements and non-coding RNA transcripts that modulate the expression of disease-associated genes through epigenetic mechanisms, providing insights into potential therapeutic targets.

4. Validation and Functional Analysis:

- Validate the identified epigenetic signatures and regulatory elements using independent experimental approaches, including targeted epigenomic assays and functional studies in relevant cellular and animal models of neurodegenerative disorders.
- Investigate the functional impact of candidate epigenetic targets on disease-relevant pathways, neuronal function, and phenotypic outcomes, to validate their potential as actionable targets for therapeutic intervention.

5. Therapeutic Target Prioritization:

- Prioritize the identified epigenetic mechanisms and regulatory elements based on druggability, evidence of reversibility, and potential for modulating disease progression in neurodegenerative disorders.
- Utilize in silico screening and computational drug repurposing strategies to identify candidate compounds or interventions capable of targeting the prioritized epigenetic mechanisms for therapeutic intervention.

This method establishes a systematic and integrative framework for deciphering the specific epigenetic mechanisms contributing to neurodegenerative disorders and facilitates the translation of epigenomic insights into actionable targets for therapeutic intervention. The rigorous computational analyses and experimental validations incorporated in this method enhance its validity and generalizability across diverse neurodegenerative conditions, driving the discovery of innovative epigenetic-based therapeutic strategies in the field of neuroscience.

Experiment

as a key pathological hallmark and contributes to disease development, progression, and severity in numerous neurological diseases, such as Alzheimer's disease, Parkinson's disease, and multiple

sclerosis. By maintaining the roles performed in neural homeostasis and the regulation of immune responses, even in neurodegenerative diseases, epigenetic mechanisms have been found to govern the modulatory ability of pro- and anti-inflammatory factors, beyond its role in the activation, expansion, and function of immune cells, contributing to the stage of neuroinflammation, which directly influences the survival or death of neurons. This support points to potential approaches to the design of therapeutic options that prioritize strategies in which regulators may modify neuroinflammation in neurodegenerative diseases according to epigenetics.']

Entities: ['DNA methylation profiles', 'histone modification patterns', 'chromatin accessibility assays', 'non-coding RNA expression data', 'epigenomic datasets', 'neurodegenerative disorders', 'epigenetic mechanisms', 'REST', 'neuronal function', 'therapeutic', 'Alzheimer's disease', 'Huntington's diseases', 'amyotrophic lateral sclerosis', 'DNA methylation', 'post-translational modifications of histone proteins', 'chromatin remodeling enzymes', 'long non-coding RNAs', 'synaptic plasticity', 'neuroinflammation', 'Alzheimer's disease', 'Parkinson's disease', 'multiple sclerosis']

Given the research problem, scientific method, target paper, related papers, and entities provided, the proposed experiment will consist of the following design:

Title: Comprehensive Epigenomic Analysis of Neurodegenerative Disorders to Identify Therapeutic Targets

Experiment Design:

1. Data Acquisition and Integration:

- Compile publicly available epigenomic datasets, including DNA methylation profiles, histone modification patterns, chromatin accessibility assays, and non-coding RNA expression data, from relevant studies and databases focusing on neurodegenerative disorders.
- Access data from the related papers that highlight common and unique epigenetic mechanisms among different neurodegenerative diseases, Alzheimer's disease, Huntington's disease, and amyotrophic lateral sclerosis (ALS).
- Integrate multi-omics data across different neurodegenerative disorders to capture the diverse and overlapping epigenetic signatures associated with these conditions.

2. Computational Analysis:

- Apply advanced bioinformatics and statistical methods to process and analyze the integrated epigenomic datasets.
- Utilize machine learning algorithms, network analysis, and pathway enrichment tools to unravel the complex interplay of epigenetic mechanisms associated with neurodegenerative disorders.

3. Identification of Epigenetic Signatures:

- Identify specific epigenetic modifications that are consistently associated with different neurodegenerative diseases as indicated in the related papers.
- Characterize the regulatory elements and non-coding RNA transcripts that modulate the expression of disease-associated genes through epigenetic mechanisms.

4. Experimental Validation and Functional Analysis:

- Validate the identified epigenetic signatures and regulatory elements using independent experimental approaches, including targeted epigenomic assays in relevant cellular and animal models of neurodegenerative disorders.
- Investigate the functional impact of candidate epigenetic targets on disease-relevant pathways, neuronal function, and phenotypic outcomes to validate their potential as actionable therapeutic targets.

5. Therapeutic Target Prioritization:

- Prioritize the identified epigenetic mechanisms and regulatory elements based on druggability, evidence of reversibility, and potential for modulating disease progression in neurodegenerative disorders.
- Combine in silico screening and computational drug repurposing strategies with experimental validation data to identify and prioritize candidate compounds or interventions capable of targeting the prioritized epigenetic mechanisms for therapeutic intervention.

Conclusion:

This comprehensive epigenomic analysis of neurodegenerative disorders, integrating data from publicly available sources, related papers, and independent experimental validations, will provide crucial insights into specific epigenetic mechanisms contributing to these diseases and facilitate the identification of novel, druggable epigenetic targets for therapeutic intervention. The rigorous computational analyses, combined with experimental validation, will ensure the generalizability and validity of the results, driving the development of innovative epigenetic-based therapeutic strategies for neurodegenerative disorders.

More related paper

Paper 1
Title:Epigenetic Regulation in Neurodegenerative Diseases.

Abstract:Mechanisms of epigenetic regulation, including DNA methylation, chromatin remodeling, and histone post-translational modifications, are involved in multiple aspects of neuronal function and development. Recent discoveries have shed light on critical functions of chromatin in the aging brain, with an emerging realization that the maintenance of a healthy brain relies heavily on epigenetic mechanisms. Here, we present recent advances, with a focus on histone modifications and the implications for several neurodegenerative diseases including Alzheimer's disease (AD), Huntington's disease (HD), and amyotrophic lateral sclerosis (ALS). We highlight common and unique epigenetic mechanisms among these situations and point to emerging therapeutic approaches.

DOI:10.1016/j.tins.2018.05.005
The impact factor:16.978

Paper 2

Title:The emerging field of epigenetics in neurodegeneration and neuroprotection.

Abstract:Epigenetic mechanisms - including DNA methylation, histone post-translational modifications and changes in nucleosome positioning - regulate gene expression, cellular differentiation and development in almost all tissues, including the brain. In adulthood, changes in the epigenome are crucial for higher cognitive functions such as learning and memory. Striking new evidence implicates the dysregulation of epigenetic mechanisms in neurodegenerative disorders and diseases. Although these disorders differ in their underlying causes and pathophysiologies, many involve the dysregulation of restrictive element 1-silencing transcription factor (REST), which acts via epigenetic mechanisms to regulate gene expression. Although not somatically heritable, epigenetic modifications in neurons are dynamic and reversible, which makes them good targets for therapeutic intervention.

DOI:10.1038/nrn.2017.46
The impact factor:38.755

Paper 3

Title:Epigenetic Mechanisms in Memory and Cognitive Decline Associated with Aging and Alzheimer's Disease.

Abstract:Epigenetic mechanisms, which include DNA methylation, a variety of post-translational modifications of histone proteins (acetylation, phosphorylation, methylation, ubiquitination, sumoylation, serotonylation, dopaminylation), chromatin remodeling enzymes, and long non-coding RNAs, are robust regulators of activity-dependent changes in gene transcription. In the brain, many of these epigenetic modifications have been widely implicated in synaptic plasticity and memory formation. Dysregulation of epigenetic mechanisms has been reported in the aged brain and is associated with or contributes to memory decline across the lifespan. Furthermore, alterations in the epigenome have been reported in neurodegenerative disorders, including Alzheimer's disease. Here, we review the diverse types of epigenetic modifications and their role in activity- and learning-dependent synaptic plasticity. We then discuss how these mechanisms become dysregulated across the lifespan and contribute to memory loss with age and in Alzheimer's disease. Collectively, the evidence reviewed here strongly supports a role for diverse epigenetic mechanisms in memory formation, aging, and neurodegeneration in the brain.

DOI:10.3390/ijms222212280
The impact factor:6.208

Paper 4

Title:The Role of Epigenetics in Neuroinflammatory-Driven Diseases.

Abstract:Neurodegenerative disorders are characterized by the progressive loss of central and/or peripheral nervous system neurons. Within this context, neuroinflammation comes up as one of the main factors linked to neurodegeneration progression. In fact, neuroinflammation has been recognized as an outstanding factor for Alzheimer's disease (AD), amyotrophic lateral sclerosis (ALS), Parkinson's disease (PD), and multiple sclerosis (MS). Interestingly, neuroinflammatory diseases are characterized by dramatic changes in the epigenetic profile, which might provide novel prognostic and therapeutic factors towards neuroinflammatory treatment. Deep changes in DNA and histone methylation, along with histone acetylation and altered non-coding RNA expression, have been reported at the onset of inflammatory diseases. The aim of this work is to review the current knowledge on this field.

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The impact factor:6.208

Paper 5

Title:Epigenetic Changes in Prion and Prion-like Neurodegenerative Diseases: Recent Advances, Potential as Biomarkers, and Future Perspectives.

Abstract:Prion diseases are transmissible spongiform encephalopathies (TSEs) caused by a conformational conversion of the native cellular prion protein (PrP(C)) to an abnormal, infectious isoform called PrP(Sc). Amyotrophic lateral sclerosis, Alzheimer's, Parkinson's, and Huntington's diseases are also known as prion-like diseases because they share common features with prion diseases, including protein misfolding and aggregation, as well as the spread of these misfolded proteins into different brain regions. Increasing evidence proposes the involvement of epigenetic mechanisms, namely DNA methylation, post-translational modifications of histones, and microRNA-mediated post-transcriptional gene regulation in the pathogenesis of prion-like diseases. Little is known about the role of epigenetic modifications in prion diseases, but recent findings also point to a potential regulatory role of epigenetic mechanisms in the pathology of these diseases. This review highlights recent findings on epigenetic modifications in TSEs and prion-like diseases and discusses the potential role of such mechanisms in disease pathology and their use as potential biomarkers.

DOI:10.3390/ijms232012609
The impact factor:6.208

Paper 6

Title:The Essential Role of Epigenetic Modifications in Neurodegenerative Diseases with Dyskinesia.

Abstract:Epigenetics play an essential role in the occurrence and improvement of many diseases. Evidence shows that epigenetic modifications are crucial to the regulation of gene expression. DNA methylation is closely linked to embryonic development in mammalian. In recent years, epigenetic drugs have shown unexpected therapeutic effects on neurological diseases, leading to the study of the epigenetic mechanism in neurodegenerative diseases. Unlike genetics, epigenetics modify the genome without changing the DNA sequence. Research shows that epigenetics is involved in all aspects of neurodegenerative diseases. The study of epigenetic will provide valuable insights into the molecular mechanism of neurodegenerative diseases, which may lead to new treatments and diagnoses. This article reviews the role of epigenetic modifications neurodegenerative diseases with dyskinesia, and discusses the therapeutic potential of epigenetic drugs in neurodegenerative diseases.

DOI:10.1007/s10571-021-01133-z
The impact factor:4.231

Paper 7

Title:Neuroepigenetic mechanisms in disease.

Abstract:Epigenetics allows for the inheritance of information in cellular lineages during differentiation, independent of changes to the underlying genetic sequence. This raises the question of whether epigenetic mechanisms also function in post-mitotic neurons. During the long life of the neuron, fluctuations in gene expression allow the cell to pass through stages of differentiation, modulate synaptic activity in response to environmental cues, and fortify the cell through age-related neuroprotective pathways. Emerging evidence suggests that epigenetic mechanisms such as DNA methylation and histone modification permit these dynamic changes in gene expression throughout the life of a neuron. Accordingly, recent studies have revealed the vital importance of epigenetic players in the central nervous system and during neurodegeneration. Here, we provide a review of several of these recent findings, highlighting novel functions for epigenetics in the fields of Rett syndrome, Fragile X syndrome, and Alzheimer's disease research. Together, these discoveries underscore the vital importance of epigenetics in human neurological disorders.

DOI:10.1186/s13072-017-0150-4
The impact factor:5.465

Paper 8

Title:Histone Modifications in Alzheimer's Disease.

Abstract:Since Late-onset Alzheimer's disease (LOAD) derives from a combination of genetic variants and environmental factors, epigenetic modifications have been predicted to play a role in the etiopathology of LOAD. Along with DNA methylation, histone modifications have been proposed as the main epigenetic modifications that contribute to the pathologic mechanisms of LOAD; however, little is known about how these mechanisms contribute to the disease's onset or progression. In this review, we highlighted the main histone modifications and their functional role, including histone acetylation, histone methylation, and histone phosphorylation, as well as changes in such histone modifications that occur in the aging process and mainly in Alzheimer's disease (AD). Furthermore, we pointed out the main epigenetic drugs tested for AD treatment, such as those based on histone deacetylase (HDAC) inhibitors. Finally, we remarked on the perspectives around the use of such epigenetics drugs for treating AD.

DOI:10.3390/genes14020347
The impact factor:4.141

Paper 9

Title:Biological aging processes underlying cognitive decline and neurodegenerative disease.

Abstract:Alzheimer's disease and related dementias (ADRD) are among the top contributors to disability and mortality in later life. As with many chronic conditions, aging is the single most influential factor in the development of ADRD. Even among older adults who remain free of dementia throughout their lives, cognitive decline and neurodegenerative changes are appreciable with advancing age, suggesting shared pathophysiological mechanisms. In this Review, we provide an overview of changes in cognition, brain morphology, and neuropathological protein accumulation across the lifespan in humans, with complementary and mechanistic evidence from animal models. Next, we highlight selected aging processes that are differentially regulated in neurodegenerative disease, including aberrant autophagy, mitochondrial dysfunction, cellular senescence, epigenetic changes, cerebrovascular dysfunction, inflammation, and lipid dysregulation. We summarize research across clinical and translational studies to link biological aging processes to underlying ADRD pathogenesis. Targeting fundamental processes underlying biological aging may represent a yet relatively unexplored avenue to attenuate both age-related cognitive decline and ADRD. Collaboration across the fields of geroscience and neuroscience, coupled with the development of new translational animal models that more closely align with human disease processes, is necessary to advance novel therapeutic discovery in this realm.

DOI:10.1172/JCI158453
The impact factor:19.456

Paper 10

Title:The m(6)A epitranscriptome: transcriptome plasticity in brain development and function.

Abstract:The field of epitranscriptomics examines the recently deciphered form of gene expression regulation that is mediated by type- and site-specific RNA modifications. Similarly to the role played by epigenetic mechanisms - which operate via DNA and histone modifications - epitranscriptomic modifications are involved in the control of the delicate gene expression patterns that are needed for the development and activity of the nervous system and are essential for basic and higher brain functions. Here we describe the mechanisms that are involved in the writing, erasing and reading of N(6)-methyladenosine, the most prevalent internal mRNA modification, and the emerging roles played by N(6)-methyladenosine in the nervous system.

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The impact factor:38.755