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EPIGENETIC VARIATION: A NEW ANALYSIS ON NEURODEGENERATIVE DISORDERS

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Abstract:

Neurodegenerative diseases are incurable and debilitating conditions that result in progressive damage and death of neuronal cells, which leads to increasing loss of cognitive and physical functions. Although treatments may help alleviate some of the physical or mental symptoms associated with neurodegenerative diseases, there is currently no cure or way to slow disease progression. In general, the transdifferentiation process contains two stages, the conversion stage and the following maturation stage. The accumulation of somatic and genetic mutations which altered the structure and coding information of the DNA are the major cause of neurological disorders. However, our recent understanding of molecular mechanisms of 'epigenetic' phenomenon reveals that the modifications of chromatin play a significant role in the development and severity of neurological disorders. The basic aim of the study is to explore the epigenetic variation by small molecule compounds for different neurodegenerative disorders. Over the last decade, there has been a great expansion of the number of research papers and reviews published concerning epigenetic mechanisms in the nervous system, especially as related to adult CNS function. Regardless of that specific set of semantic conventions, it also seems clear that the term neuro epigenetic is emerging due to the discoveries of a wide variety of roles for epigenetic molecular mechanisms in the CNS regarding acquired behaviors, CNS disorders, neural plasticity, neurotoxicity, and drug addiction.

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INTRODUCTION:

Neurodegenerative diseases are incurable and debilitating conditions that result in progressive damage and death of neuronal cells, which leads to increasing loss of cognitive and physical functions. Although treatments may help alleviate some of the physical or mental symptoms associated with neurodegenerative diseases, there is currently no cure or way to slow disease progression. Epigenetic mechanisms include DNA methylation, histone modifications, nucleosome repositioning, higher order chromatin remodeling, non-coding RNAs, and RNA and DNA editing. RNA is centrally involved in directing these processes, implying that the transcriptional state of the cell is the primary determinant of epigenetic memory [1]. This transcriptional state can be modified not only by internal and external cues affecting gene expression and post-transcriptional processing, but also by RNA and DNA editing through activity-dependent intracellular transport and modulation of RNAs and RNA regulatory super complexes, and through trans-neuronal and systemic trafficking of functional RNA subclasses [2]. These integrated processes promote dynamic reorganization of nuclear architecture and the genomic landscape to modulate functional gene and neural networks with complex temporal and spatial trajectories. Epigenetics represents the long sought after molecular interface mediating gene–environmental interactions during critical periods throughout the lifecycle. Histone acetyltransferases (HATs) are epigenetic drivers that catalyze the acetyl transfer from acetyl-CoA to lysines of both histone and non-histone substrates and thereby induce transcription either by chromatin remodeling or direct transcription factor activation. Histone deacetylases (HDACs) conduct the reverse reaction to counter HAT activity [3]. Physiological processes such as cell cycle progression or apoptosis require a thoroughly balanced equilibrium of the interplay between acetylation and deacetylation processes to maintain or, if required, alter the global acetylome status. Aberrant HAT activity has recently been demonstrated to play a crucial role in the progression of various diseases such as prostate, lung, and colon cancers as well as glioblastomas and neurodegenerative diseases [4].

Transdifferentiation towards neuro-degenerative diseases

In general, the transdifferentiation process contains two stages, the conversion stage and the following maturation stage. Human iNs show a slower maturation process appear less plastic and have a higher epigenetic “hurdle” for reprogramming as compared with that induced from mouse cells. Standardized protocols with high transdifferentiation efficiency are desirable for generating neurons with neurotransmitter and region-specific phenotypes for research use or potential clinical application. Many studies have shown that hypoxia which activates transcriptional factors including hypoxia-inducible factors promotes not only cell reprogramming but also the direct conversion of various cell types to neurons. For example, the conversion efficiency of human fibroblasts to Microtubule Associated Protein 2 (MAP2) positive neurons by BAM and NeuroD1 is increased by 2.4 folds under hypoxia condition. Many fundamental cellular processes are affected by epigenetic modulation, and in recent years it has become evident that chromatin-based epigenetic mechanisms underlie important aspects of the aging process. However, despite the fact that age is a prominent risk factor in neurodegenerative disease (ND), there is remarkably little information on the role of epigenetic alterations in mechanisms of ND such as Alzheimer's disease (AD), Parkinson's dementia (PD), frontotemporal degeneration (FTLD) or amyotrophic lateral sclerosis (ALS). We believe that a detailed biological, mechanistic and molecular understanding of the epigenetic factors that are altered in human ND holds promise for an improved understanding of disease pathogenesis and for the development of novel therapeutic interventions [5]. The goals of this Project are to: (1) investigate whether major epigenetic modifications (histone post-translational modifications) change in the context of different NDs using an extensive bank of human samples available from the Penn Center for Neurodegenerative Disease Research (CNDR), (2) use our model systems to discover new epigenetic modifications that underlie ND disease, and (3) test the relevance of novel changes seen in human ND using models of ND [6].

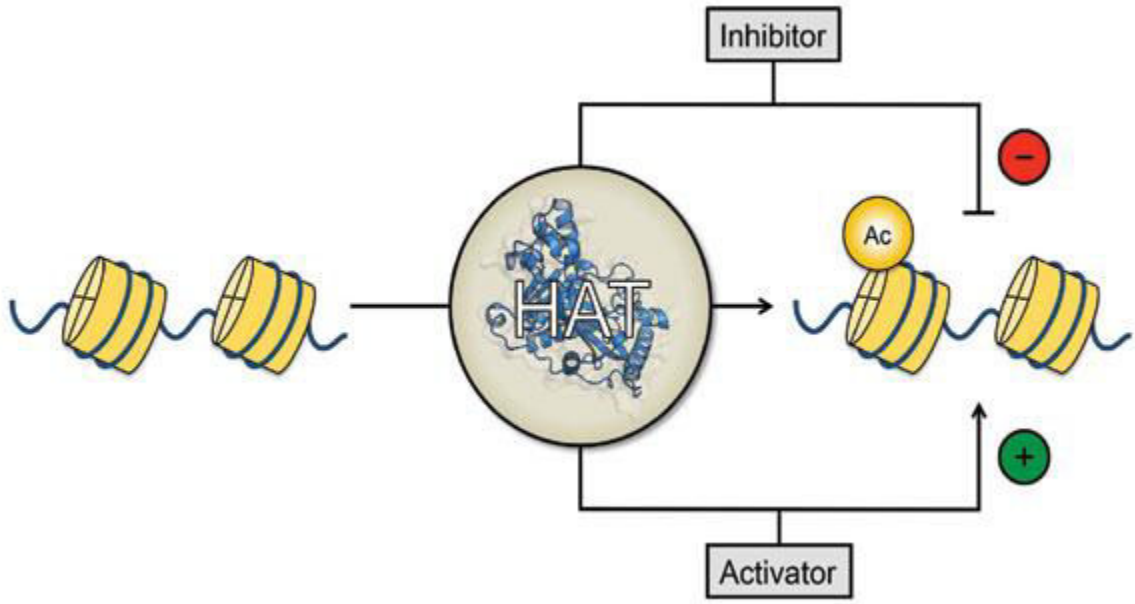

Figure 01: Graphical explanation of epigenetic modulation

Objectives of the study

The basic aim of the study is to explore the epigenetic variation by small molecule compounds for different neurodegenerative disorders.

Epigenetic modulation by small molecules

The accumulation of somatic and genetic mutations which altered the structure and coding information of the DNA are the major cause of neurological disorders. However, our recent understanding of molecular mechanisms of 'epigenetic' phenomenon reveals that the modifications of chromatin play a significant role in the development and severity of neurological disorders. These epigenetic processes are dynamic and reversible as compared to genetic ablations which are stable and irreversible. Therefore, targeting these epigenetic processes through small molecule modulators are of great therapeutic potential. To date, large number of small molecule modulators have been discovered which are capable of altering the brain pathology by targeting epigenetic enzymes. The field of epigenetics has undergone an exponential expansion as of late. A quick check of the PubMed publication database reveals that about 98% of all the research published in the broad area of epigenetics was published within the last 15 years [6].

Neurodegenerative disorders are among the real challenges and among the most therapeutic issues that ought to be with standed by the world, especially in light of extending populace age. They cause the degeneration and passing of nerve cells as they shape hopeless conditions for treatment. As indicated by a synergistic investigation of the WHO, the World Bank and the Harvard School of Public Health by 2020 neurodegenerative infections, dementia will be the eighth reason for sickness among created regions. It is additionally assessed that they will possess the world's second driving reason for death by 2050, surpassing growth. Amid embryogenesis and for separation of neural cells Epigenetic instruments are fundamental required. Accordingly, exact comprehension of epigenetic components, including DNA methylation and histone adjustment, is vital to explain the pathogenic pathways in neurodevelopmental issue [7].

Table 01: Areas Where Epigenetic Mechanisms in Human Nervous System Function

Function or Disorder	Mechanism(s) Implicated
learning and memory	histone modifications, DNA methylation, piRNAs, miRNAs
maternal nurturing	histone modifications, DNA methylation
adult neurogenesis	histone modifications, DNA methylation
stress responses	histone modifications, DNA methylation
Alzheimer's disease	histone modifications, DNA methylation
Rett syndrome	MeCP2 methylcytosine binding
fragile X mental retardation	DNA methylation, miRNAs
schizophrenia	DNA and histone methylation, miRNAs
Rubinstein-Taybi syndrome	histone acetyltransferase deficiency
Angelman syndrome	genomic imprinting (DNA methylation)
depression and/or suicide	DNA methylation
bipolar disorder	histone modifications, DNA methylation, miRNAs
addiction and reward behavior	histone modifications, DNA methylation, miRNAs
PTSD	histone modifications, DNA methylation
ATR-X syndrome (α-thalassemia mental retardation)	SNF2 chromatin remodeling, H3.3
cognitive aging	histone modifications, DNA methylation
Coffin-Lowry syndrome	histone phosphorylation
Kleefstra syndrome	histone methylation
epilepsy	histone modifications, DNA methylation, miRNAs

Applications

Current therapies for neurodegenerative diseases are restricted to controlling symptoms. At present, there is no effective treatment to prevent or retard the clinical progression of these diseases. In fact, the mechanisms underlying neurodegeneration are poorly understood, thus making the target-based drug screening strategies rather difficult[8]. The possibility to obtain patient-specific iNs would be an important source for proteomic and transcriptomic studies that may help identifying sets of molecular signatures for the neurodegenerative disease. In addition, these patient-specific cells represent a powerful tool for personalized drug tests. Finally, direct conversion to obtain patient-specific neurons can eventually allow personal medicine and the development of autologous cell types for cell therapy in neurodegenerative disease such as ALS, Alzheimer's Disease (AD), and Parkinson's Disease (PD) [9].

With the realization of inducing easily accessible cells, such as skin fibroblasts or peripheral blood mononuclear cells, to inaccessible cells that are lost in the degenerative diseases (e.g. midbrain DA neurons in PD), it becomes possible to generate cells in vitro that are increasingly similar to their in vivo counterparts and then apply these induced cells for transplantation. Several studies are exploiting transdifferentiation as a possible tool to fight neuronal loss in brain [10].

DISCUSSION:

Over the last decade, there has been a great expansion of the number of research papers and reviews published concerning epigenetic mechanisms in the nervous system, especially as related to adult CNS function. These burgeoning neuroscience discoveries have necessitated a redefinition of epigenetics, at least in regard to epigenetic mechanisms in adult neurons. As mentioned already, epigenetic mechanisms were originally defined as heritable either in a procreative organismal sense or at the cellular level across cell division[6]. An epigenetic molecular mark in an adult neuron can be long-lasting, permanent, and self-regenerating but cannot be inherited by a daughter cell since the neuron does not divide [10,11].

CONCLUSION:

Regardless of that specific set of semantic conventions, it also seems clear that the term neuro epigenetic is emerging due to the discoveries of a wide variety of roles for epigenetic molecular mechanisms in the CNS regarding acquired behaviors, CNS disorders, neural plasticity, neurotoxicity, and drug addiction

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