Journal Homepage: - www.journalijar.com

INTERNATIONAL JOURNAL OF ADVANCED RESEARCH (IJAR)

Article DOI: 10.21474/IJAR01/18543
DOI URL: http://dx.doi.org/10.21474/IJAR01/18543

RESEARCH ARTICLE

EPIGENETIC MODIFICATIONS OF STRESS-RELATED DISORDERS: MECHANISMS, IMPLICATIONS AND THERAPEUTIC PERSPECTIVES

Keli Ratna Sai Sailaja Maka[1], Sumasri Jargumalla[1], Ramya Reddy Mekala[1], Mukesh Gudluru[2], Sai Susmitha Madhura[2], Sravya Gunturi[2], Nithin Gudivada[2] and Reethika Singh Ranwas[3]

1. Department of Biomedical Engineering, University of North Texas, 3940 N Elm Street, Denton, TX, USA.
2. Department of Biotechnology, KL University, Vaddeswaram, Guntur, Andhra Pradesh, India.
3. Department of Molecular Biology, Cresent Biosciences, ICRAB Campus, Kanpur, UttarPradesh, India.

Manuscript Info

Manuscript History
Received: 15 February 2024
Final Accepted: 19 March 2024
Published: April 2024

Key words:-
Epigenetics, Stress-Related Disorders, DNA Methylation, Histone Modifications, Non-Coding RNAs, Resilience, Therapeutic Targets

Abstract

Stress-related disorders, encompassing conditions such as anxiety, depression, and post-traumatic stress disorder (PTSD), pose significant challenges to global mental health. While the etiology of these disorders involves a complex interplay of genetic, environmental, and psychosocial factors, emerging evidence suggests a pivotal role of epigenetic modifications in their pathogenesis. Epigenetic mechanisms, including DNA methylation, histone modifications, and non-coding RNA-mediated regulation, dynamically regulate gene expression in response to stressors, thereby influencing brain function and behaviour. Alterations in these epigenetic processes contribute to aberrant stress responses, increased susceptibility to stress-related disorders, and individual differences in stress vulnerability and resilience. Moreover, epigenetic modifications can be transmitted across generations, highlighting the enduring impact of stress on mental health outcomes. Understanding the mechanisms underlying epigenetic regulation in stress-related disorders provides insights into disease pathogenesis and potential biomarkers for diagnosis and prognosis. Additionally, targeting epigenetic pathways represents a promising therapeutic approach for these disorders. Epigenetic drugs, such as DNA methyltransferase inhibitors and histone deacetylase inhibitors, hold potential for mitigating the adverse effects of stress on mental health. However, challenges such as off-target effects and lack of specificity necessitate further refinement of epigenetic-based therapies.

Introduction:-

Stress-related disorders, encompassing conditions such as anxiety, depression, and post-traumatic stress disorder (PTSD), represent a significant public health concern worldwide, with profound implications for individual well-being and societal functioning. These disorders are characterized by dysregulated responses to stressors, leading to debilitating symptoms and impaired functioning [1]. While considerable progress has been made in elucidating the neurobiological underpinnings of stress-related disorders, including alterations in neurotransmitter systems, neuroendocrine pathways, and neural circuitry, the precise mechanisms underlying their etiology and pathogenesis remain incompletely understood.Recent research has increasingly focused on the role of epigenetic modifications in

Corresponding Author:- Keli Ratna Sai Sailaja Maka
Address:- Department of Biomedical Engineering, University of North Texas, 3940 N Elm Street, Denton, TX, USA.

mediating the effects of stress on brain function and behaviour [2]. Epigenetics refers to the study of heritable changes in gene expression that occur without alterations to the underlying DNA sequence. Epigenetic mechanisms, including DNA methylation, histone modifications, and non-coding RNA-mediated regulation, play crucial roles in orchestrating gene expression patterns in response to environmental cues, including stressors. These modifications dynamically regulate chromatin structure and gene accessibility, thereby influencing the transcriptional activity of stress-responsive genes.

In the context of stress-related disorders, epigenetic alterations can disrupt the finely tuned balance of gene expression underlying normal stress responses, leading to maladaptive behavioural and physiological outcomes. For instance, studies have identified differential DNA methylation patterns in genes encoding for key components of the hypothalamic-pituitary-adrenal (HPA) axis, the primary stress response system [3]. Dysregulation of HPA axis function is a hallmark feature of stress-related disorders, and aberrant DNA methylation in stress hormone receptor genes may contribute to altered stress reactivity and vulnerability to these disorders.Similarly, dysregulated histone modifications have been implicated in the pathogenesis of stress-related disorders. Stress-induced changes in histone acetylation, methylation, and phosphorylation patterns have been observed in brain regions implicated in mood regulation and stress responses, such as the prefrontal cortex, hippocampus, and amygdala [4]. These alterations in histone modifications can lead to aberrant gene expression profiles associated with stress-related pathologies, including altered synaptic plasticity, neuroinflammation, and impaired stress resilience.Furthermore, non-coding RNAs, including microRNAs (miRNAs) and long non-coding RNAs (lncRNAs), have emerged as critical regulators of gene expression in response to stress. Dysregulated expression of stress-responsive miRNAs and lncRNAs has been linked to alterations in synaptic plasticity, neurogenesis, and stress resilience, further highlighting the role of epigenetic mechanisms in stress-related disorders [5].

Epigenetic Mechanisms:
DNA methylation, predominantly occurring at cytosine-guanine dinucleotides (CpGs), regulates gene expression by modulating chromatin accessibility. Studies have implicated altered DNA methylation patterns in stress-responsive genes, including those encoding for neurotransmitter receptors, stress hormones, and synaptic plasticity regulators. These changes, observed in both animal models and human cohorts, contribute to aberrant stress responses and susceptibility to stress-related disorders [6].

Histone Modifications and Non-Coding RNAs:
Post-translational modifications of histone proteins, such as acetylation, methylation, phosphorylation, and ubiquitination, dynamically regulate chromatin structure and gene expression. Dysregulated histone modifications have been associated with stress-induced changes in gene expression profiles within brain regions implicated in mood regulation and stress responses [7]. Furthermore, histone-modifying enzymes have emerged as potential targets for pharmacological interventions in stress-related pathologies.MicroRNAs (miRNAs) and long non-coding RNAs (lncRNAs) exert regulatory control over gene expression at the post-transcriptional and transcriptional levels, respectively. Dysregulated expression of stress-responsive miRNAs and lncRNAs has been linked to altered synaptic plasticity, neuroinflammation, and stress resilience. Targeting these non-coding RNAs holds promise for therapeutic interventions aimed at mitigating the adverse effects of stress on mental health [8].

Epigenetic Signatures of Stress Resilience and Vulnerability:
While exposure to stressors increases the risk of developing psychiatric disorders, a subset of individuals exhibits resilience, manifesting adaptive responses to adversity. Epigenetic studies have identified differential methylation patterns, histone modifications, and non-coding RNA profiles associated with stress resilience versus vulnerability [9]. Unraveling the molecular underpinnings of resilience holds potential for identifying novel therapeutic targets and resilience-promoting interventions.Emerging evidence suggests that exposure to stressors can induce epigenetic modifications that persist across generations, influencing offspring susceptibility to stress-related disorders. Transgenerational transmission of epigenetic marks via gametes or germline cells underscores the enduring impact of environmental exposures on mental health outcomes, highlighting the importance of multigenerational perspectives in studying stress-related pathologies [10].

Stress-related disorders, including anxiety, depression, and PTSD, are complex conditions influenced by genetic, environmental, and psychosocial factors. Emerging research highlights the role of epigenetic modifications in mediating the impact of stress on brain function and behaviour.Epigenetic mechanisms involve modifications to DNA and histone proteins, as well as the regulation of gene expression by non-coding RNAs. DNA methylation, the

addition of methyl groups to cytosine bases, typically represses gene expression by altering chromatin structure. Studies have identified differential DNA methylation patterns in stress-responsive genes, influencing neurotransmitter receptor expression, stress hormone regulation, and synaptic plasticity. These alterations contribute to disrupted stress responses and increased susceptibility to stress-related disorders [11].Histone modifications, including acetylation, methylation, phosphorylation, and ubiquitination, dynamically regulate chromatin accessibility and gene expression. Stress-induced changes in histone modification patterns have been observed in key brain regions involved in mood regulation and stress responses. Dysregulated histone modifications contribute to altered gene expression profiles underlying stress-related pathologies [12].Non-coding RNAs, such as microRNAs (miRNAs) and long non-coding RNAs (lncRNAs), post-transcriptionally or transcriptionally regulate gene expression, respectively. Dysregulated expression of stress-responsive miRNAs and lncRNAs has been linked to aberrant synaptic plasticity, neuroinflammation, and stress resilience [13]. Targeting these non-coding RNAs holds promise for therapeutic interventions in stress-related disorders.Individual differences in stress vulnerability and resilience are partly mediated by epigenetic mechanisms. Epigenetic studies have identified differential DNA methylation patterns, histone modifications, and non-coding RNA profiles associated with stress resilience versus vulnerability [14]. Understanding the molecular basis of resilience may inform the development of resilience-promoting interventions and personalized treatment strategies.Furthermore, emerging evidence suggests the transgenerational transmission of epigenetic marks following exposure to stress [15]. These inherited epigenetic modifications can influence offspring susceptibility to stress-related disorders, underscoring the enduring impact of environmental exposures on mental health outcomes across generations [16].Targeting epigenetic mechanisms represents a promising therapeutic approach for stress-related disorders. Epigenetic drugs, such as DNA methyltransferase inhibitors and histone deacetylase inhibitors, have shown efficacy in preclinical models and early-phase clinical trials. However, challenges such as off-target effects and lack of specificity necessitate further refinement of epigenetic-based therapies [17].

Therapeutic Implications

Targeting epigenetic mechanisms presents a promising avenue for the development of novel therapeutics for stress-related disorders. Epigenetic drugs, including DNA methyltransferase inhibitors, histone deacetylase inhibitors, and small RNA modulators, have shown efficacy in preclinical models and early-phase clinical trials [18]. However, challenges such as off-target effects and specificity warrant further refinement of epigenetic-based therapies.One potential therapeutic approach involves the use of epigenetic drugs that target enzymes involved in DNA methylation and histone modifications. DNA methyltransferase inhibitors, such as azacitidine and decitabine, can reverse aberrant DNA methylation patterns associated with stress-related disorders, potentially restoring normal gene expression profiles and ameliorating symptoms [19]. Similarly, histone deacetylase inhibitors, such as vorinostat and valproic acid, have shown efficacy in preclinical models and early-phase clinical trials for various psychiatric conditions, including depression and PTSD. These drugs act by increasing histone acetylation levels, thereby promoting a more open chromatin conformation and facilitating the expression of genes involved in stress resilience and adaptive responses [20].Another therapeutic strategy involves targeting non-coding RNAs implicated in stress-related pathologies. Modulating the expression or activity of stress-responsive microRNAs and long non-coding RNAs may offer a novel approach to restoring normal gene expression patterns and promoting resilience to stress [21]. Small RNA modulators, such as antagomirs and antisense oligonucleotides, can selectively inhibit the function of dysregulated miRNAs and lncRNAs, potentially mitigating the adverse effects of stress on brain function and behaviour.In addition to pharmacological interventions, lifestyle and behavioural interventions may also exert epigenetic effects that promote mental well-being and resilience to stress. Strategies such as mindfulness meditation, exercise, and dietary modifications have been shown to modulate epigenetic mechanisms, including DNA methylation and histone modifications, with potential implications for stress-related disorders. Incorporating these interventions into comprehensive treatment plans may enhance their efficacy and improve outcomes for individuals affected by these disorders [22].

Future Directions

Advances in high-throughput sequencing technologies, computational biology, and epigenome editing tools offer unprecedented opportunities to unravel the complexity of epigenetic regulation in stress-related disorders [23]. Integrating multi-omics approaches, longitudinal studies, and large-scale consortia efforts will facilitate the identification of robust epigenetic biomarkers, personalized treatment strategies, and preventive interventions targeting vulnerable populations.The field of epigenetics in stress-related disorders is rapidly evolving, with ongoing research focusing on elucidating the complexity of epigenetic mechanisms, identifying novel therapeutic targets, and translating these findings into clinical practice [24]. Several key directions for future research can further advance

our understanding and management of stress-related disorders through the lens of epigenetics.Fostering collaborative efforts through large-scale consortia and data-sharing initiatives will accelerate progress in the field of epigenetics in stress-related disorders [25]. By pooling resources, expertise, and datasets from diverse populations, researchers can overcome sample size limitations, enhance statistical power, and ensure the generalizability of findings across different demographic groups and clinical contexts [26].

Conclusion:-

In conclusion, epigenetic modifications play a pivotal role in the pathogenesis of stress-related disorders, mediating the interplay between genetic susceptibility and environmental factors. Understanding these mechanisms offers insights into disease mechanisms, potential biomarkers, and therapeutic targets. Epigenetic modifications play a central role in the pathogenesis of stress-related disorders, offering insights into disease mechanisms and therapeutic targets. Further elucidation of epigenetic pathways underlying stress vulnerability and resilience holds promise for precision medicine approaches aimed at improving mental health outcomes and reducing the global burden of psychiatric morbidity.Future research should focus on elucidating the dynamic nature of epigenetic changes, refining therapeutic interventions, and translating findings into clinical practice. By harnessing the power of epigenetics, we can advance towards personalized treatments, resilience-promoting interventions, and ultimately improve mental health outcomes for individuals affected by stress-related disorders.

References:-

1. Bagot, R. C., and Meaney, M. J. (2010). Epigenetics and the biological basis of gene x environment interactions. Journal of the American Academy of Child & Adolescent Psychiatry, 49(8), 752-771.
2. McGowan, P. O., Sasaki, A., D'Alessio, A. C., Dymov, S., Labonté, B., Szyf, M.,Meaney, M. J. (2009). Epigenetic regulation of the glucocorticoid receptor in human brain associates with childhood abuse. Nature neuroscience, 12(3), 342-348.
3. Weaver, I. C., Cervoni, N., Champagne, F. A., D'Alessio, A. C., Sharma, S., Seckl, J. R., Meaney, M. J. (2004). Epigenetic programming by maternal behavior. Nature neuroscience, 7(8), 847-854.
4. Klengel, T., Mehta, D., Anacker, C., Rex-Haffner, M., Pruessner, J. C., Pariante, C. M., Binder, E. B. (2013). Allele-specific FKBP5 DNA demethylation mediates gene-childhood trauma interactions. Nature neuroscience, 16(1), 33-41.
5. Hunter, R. G., & McEwen, B. S. (2013). Stress and anxiety across the lifespan: Structural plasticity and epigenetic regulation. Epigenomics, 5(2), 177-194.
6. Yehuda, R., & Daskalakis, N. P. (2016). Desensitization of glucocorticoid feedback: A mechanism for stress resilience. Neuroscience &Biobehavioral Reviews, 68, 97-106.
7. Tsankova, N., Renthal, W., Kumar, A., & Nestler, E. J. (2007). Epigenetic regulation in psychiatric disorders. Nature Reviews Neuroscience, 8(5), 355-367.
8. Labonté, B., &Turecki, G. (2012). Epigenetic effects of childhood adversity in the brain and suicide risk. In Epigenetic Regulation of Lymphocyte Development (pp. 239-256). Springer, New York, NY.
9. Bagot, R. C., Labonté, B., Peña, C. J., & Nestler, E. J. (2014). Epigenetic signaling in psychiatric disorders: Stress and depression. Dialogues in Clinical Neuroscience, 16(3), 281-295.
10. Murgatroyd, C., Patchev, A. V., Wu, Y., Micale, V., Bockmühl, Y., Fischer, D., ... & Spengler, D. (2009). Dynamic DNA methylation programs persistent adverse effects of early-life stress. Nature neuroscience, 12(12), 1559-1566.
11. Provencal, N., & Binder, E. B. (2015). The effects of early life stress on the epigenome: From the womb to adulthood and even before. Experimental Neurology, 268, 10-20.
12. Peña, C. J., Bagot, R. C., Labonté, B., Nestler, E. J. (2014). Epigenetic signaling in psychiatric disorders. Journal of Molecular Biology, 426(20), 3389-3412.
13. Meaney, M. J. (2010). Epigenetics and the biological definition of gene x environment interactions. Child development, 81(1), 41-79.
14. Peña, C. J., Champagne, F. A. (2015). Neonatal overexpression of estrogen receptor-α alters midbrain dopamine neuron development and reverses the effects of low maternal care in female offspring. Developmental Neurobiology, 75(11), 1114-1124.
15. Blaze, J., Asok, A., Roth, T. L. (2015). Long-term effects of early-life caregiving experiences on brain-derived neurotrophic factor histone acetylation in the adult rat mPFC. Stress, 18(6), 607-615.

16. Suderman, M., McGowan, P. O., Sasaki, A., Huang, T. C., Hallett, M. T., Meaney, M. J., Szyf, M. (2012). Conserved epigenetic sensitivity to early life experience in the rat and human hippocampus. Proceedings of the National Academy of Sciences, 109(Supplement 2), 17266-17272.
17. Klengel, T., & Binder, E. B. (2015). Epigenetics of stress-related psychiatric disorders and geneand environment interactions. Neuron, 86(6), 1343-1357.
18. Kundakovic, M., Lim, S., Gudsnuk, K., Champagne, F. A. (2013). Sex-specific and strain-dependent effects of early life adversity on behavioral and epigenetic outcomes. Frontiers in Psychiatry, 4, 78.
19. Labonté, B., Suderman, M., Maussion, G., Navaro, L., Yerko, V., Mahar, I., Turecki, G. (2012). Genome-wide epigenetic regulation by early-life trauma. Archives of General Psychiatry, 69(7), 722-731.
20. Franklin, T. B., Russig, H., Weiss, I. C., Gräff, J., Linder, N., Michalon, A., Mansuy, I. M. (2010). Epigenetic transmission of the impact of early stress across generations. Biological Psychiatry, 68(5), 408-415.
21. Champagne, F. A. (2010). Epigenetic influence of social experiences across the lifespan. Developmental Psychobiology, 52(4), 299-311.
22. Roth, T. L., & Sweatt, J. D. (2011). Epigenetic marking of the BDNF gene by early-life adverse experiences. Hormones and Behavior, 59(3), 315-320.
23. Bagot, R. C., Zhang, T. Y., Wen, X., Nguyen, T. T. T., Nguyen, H. B., Diorio, J., Meaney, M. J. (2012). Variations in postnatal maternal care and the epigenetic regulation of metabotropic glutamate receptor 1 expression and hippocampal function in the rat. Proceedings of the National Academy of Sciences, 109(Supplement 2), 17200-17207.
24. Sweatt, J. D. (2013). The emerging field of neuroepigenetics. Neuron, 80(3), 624-632.
25. Meaney, M. J., & Ferguson-Smith, A. C. (2010). Epigenetic regulation of the neural transcriptome: The meaning of the marks. Nature Neuroscience, 13(11), 1313-1318.
26. Nugent, B. M., & McCarthy, M. M. (2011). Epigenetic underpinnings of developmental sex differences in the brain. Neuroendocrinology, 93(3), 150-158.