

Psychoneuroimmunology and Epigenetics

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SUMMARY: Epigenetics has engendered a renewed enthusiasm and appreciation for the capacity of the environment to modulate gene expression. It is clear that epigenetic modifications serve as the molecular basis for environmental signals that influence behavioral outcomes and, as such, provide a bridge between the psychosocial world and the biological. This is congruent with psychoneuroimmunology, which seeks to understand the impact of environmental stimuli, especially psychosocial stimuli, on behavior, emotions, neuroendocrine stress responsivity, and immune function. Illustrative examples of recent scientific developments are highlighted to demonstrate the influence of epigenetics in areas of research relevant to those who investigate phenomena within the scientific discipline of psychoneuroimmunology. These examples are presented in order to provide a perspective on how epigenetic analysis will add insight into the molecular processes that connect the brain with behavior, neuroendocrine responsivity and immune outcome.

KEYWORDS: Epigenetics, Psychoneuroimmunology, Behavior, Suicide, Post Traumatic Stress Disorder, Breast cancer

A remarkable growth in the understanding of epigenetics and the impact of epigenetics on contemporary biology has occurred in recent years¹. As well, the study of epigenetics has fueled research in the behavioral sciences, as recent work demonstrates that epigenetic modifications shape behavior, modulate stress responsivity, and alter immune function. This facet of epigenetics seeks to understand the interactive linkages that connect the psychological and social environment with the epigenetic processes that modulate gene expression and influence behavior².

The psychosocial context of the environment can substantially change behavior and alter nervous, endocrine and immune function³. Recent findings within the realm of behavioral epigenetics demonstrate that stressors and/or adverse psychosocial environments can affect gene expression by altering the epigenetic pattern of DNA methylation and/or chromatin structure. The vast majority of existent evidence within the scope of behavioral epigenetics emanates from investigations of early life adversity that produce epigenetic modifications within relevant brain regions that influence behavior. Emerging evidence shows that, adults also respond epigenetically to environmental signals, which in turn influence behavior, physiological outcome, and disease risk⁴.

Epigenome

Epigenetics refers to a variety of processes that affect gene expression independent of actual DNA sequence. Epigenetic information provides instruction on how, where, and when, genetic information will be used. Most importantly, epigenetic information is susceptible to change, and as such, represents an excellent target to understand how the environment may impact physiological function. While epigenetics refers to effects on single and/or sets of genes, epigenomics refers to global epigenetic modifications that encompass the entire genome. Epigenetic information provides instruction for the use

of that blueprint, permitting an ordered and regulated gene expression pattern.

Epigenetically regulated gene expression is a consequence of small covalent chemical modifications, which mark the genome and play a role in turning genes on or off⁵. Such marks are DNA methylation, histone modification, etc.⁶ For example, histone deacetylation results in transcriptional repression. Conversely, histone acetylation, which involves the covalent addition of acetyl groups to the lysine moieties in the amino terminal histone tails, results in an increase in gene expression. These distinct types of modification include: acetylation, methylation, phosphorylation, ubiquitylation, sumoylation, deimination and proline isomerization⁵.

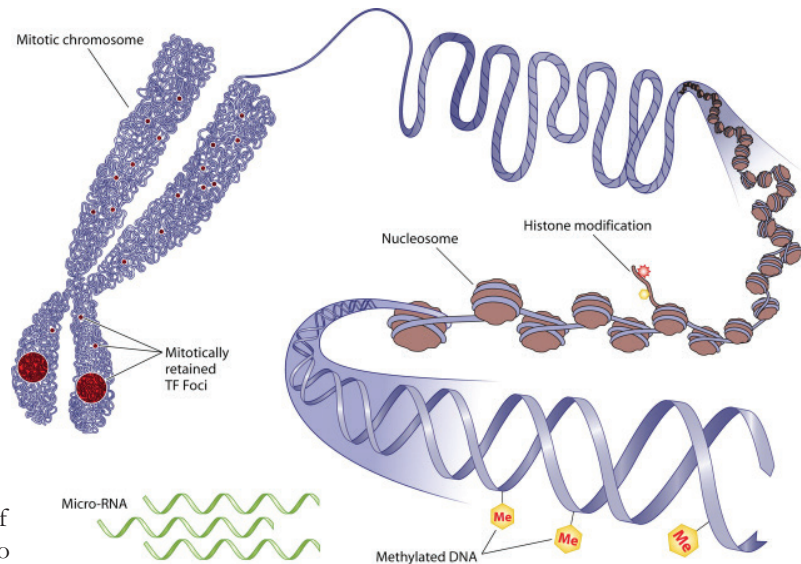
Illustrative Epigenetics

The majority of research concerning epigenetic modification, which impact the interactions among brain, behavior, and immunity, rests predominately within neuro-epigenetics. Early life experiences influence brain function and alter neuroendocrine set-points. These alterations can result in detrimental effects that impact behavior and health throughout life⁷. It is now apparent that epigenetic processes can mediate the effect of early life experiences on the brain and can influence neuroendocrine stress responsivity. Evidence that the epigenome is responsive to the psychosocial environment originates from seminal studies of maternal care behavior. The fetal and early postnatal periods are times of dynamic physiologic change and developing organs and tissues are extraordinarily vulnerable to environmental influences. During sensitive periods of development adverse events such as stress or maltreatment can more readily trigger epigenetic alterations which can adversely affect physiological function and behavior through adulthood^{8,9}.

Behavior Throughout Generations

In rodents, variations in maternal care behavior are transmit-

Fig 1. Epigenetic processes, DNA methylation and histone modification



ted across generations, such that lactating adult offspring of high levels of licking and grooming (HLG) mothers will also exhibit HLG behavior toward their young; whereas, offspring of low level of licking and grooming (LLG) mothers provide low levels of pup-directed LG^{10,11}. The apparent enduring effect of maternal care originates from modifications of the neuroendocrine processes that oversee oxytocin mediation of maternal behavior. Oxytocin strongly influences maternal LG behavior by interacting with dopamine and serotonin systems within the brain that mediate this behavior¹².

Suicide and Epigenetic Modification

The foregoing studies demonstrate the effect of rodent maternal behavior on epigenetic modification of the glucocorticoid receptor (GR) and raise the question as to whether, in humans, the postnatal and/or childhood environment might instill similar epigenetic modifications that alter adult stress responsivity and behavior. Indeed, childhood adversity in humans is associated with altered hypothalamic-pituitary-adrenal (HPA) axis responsivity, which is linked to greater risk for psychopathology, including suicide^{13,14,15}. To understand whether epigenetic modification of brain GR expression contributes to suicide risk, a recent study evaluated the epigenetic profile of postmortem brain hippocampal samples. The brain specimens were obtained from the Quebec Suicide Brain Bank, a brain repository that also contains the victim's psychological and developmental history, including history of childhood abuse or neglect. Findings revealed that suicide victims with a history of childhood abuse had significantly reduced total GR mRNA transcript from GR1F exon (the homolog of exon 17 of the rat) and increased GR gene (NR3C1) promoter DNA methylation. Given that this methylation state was restricted to suicide cases with a history of childhood abuse, implies that it emerged from childhood adversity rather than suicide per se. It is of interest that the observed changes in DNA methylation mirror the changes reported in methylation of genes encoding for the GR in the hippocampus of rats subjected to LLG¹⁶.

Prenatal Depression, Epigenetics and Infant Stress Response

Infants of mothers with prenatal depression exhibit an increased cortisol response to stress and are at risk for future behavioral disorders¹⁷. Mechanisms underlying these observations remain unknown. However, new findings link maternal prenatal depressed mood to altered methylation status of the newborn's GR gene (NR3C1) in umbilical cord blood mononuclear cells. That study showed that infants of mothers with depression had increased methylation of DNA at the predicted NGF1-A

binding site on NR3C1. These preliminary results suggest that at an epigenetic level maternal mood shapes the infant's future stress responsivity.

Aging-Associated Memory Impairment

Aging is associated with cognitive impairment and a decline in memory¹⁸. An epigenetic theory of aging-related cognitive dysfunction has been proposed, in which disruption of epigenetic regulatory mechanisms leads to the accumulation of aberrant epigenetic marks that disrupt neural plasticity and memory formation¹⁹. The hippocampus is central to memory formation and is affected during early stages of dementia²⁰. Recently, aged-associated memory impairment was shown to result from altered chromatin remodeling in the hippocampus when aged mice were tested in a contextual fear conditioning paradigm²¹. Aged mice exhibited memory impairment that was not a result of major changes in brain structure. However, the aged mice were unable to up regulate H4K12 acetylation within the hippocampus after fear conditioning, as compared to young mice. This was functionally linked to a decrease in the expression of learning induced genes.

Post-Traumatic Stress Disorder and Epigenetics

Psychosocial context influences brain stress response pathways and modifies stress-related behavior. Evidence from an evaluation of individuals with post traumatic stress disorder (PTSD) suggests this to be a possibility. Individuals with PTSD have altered stress reactivity, as well as distinct expression for genes involved in immune activation^{22,23}. Findings from a recent study support a biologic model of PTSD etiology in which a traumatic environmental event generates downstream alterations in immune function by reducing methylation levels of immune-related genes²⁴. That study evaluated whole blood derived DNA samples from individuals with PTSD compared to those without this condition. Analysis of CpG sites from more than 14,000 genes revealed a set of uniquely unmethylated genes that encode for immune function, particularly inflammatory and innate immune response genes, in individuals with PTSD compared to control subjects. Interestingly, affected genes were significantly and negatively correlated with traumatic burden (i.e., number of traumatic event exposure). Moreover, the observed epigenetic variability in immune function in those with PTSD was also associated with differences in immune response (greater antibody response) to cytomegalovirus, a latent

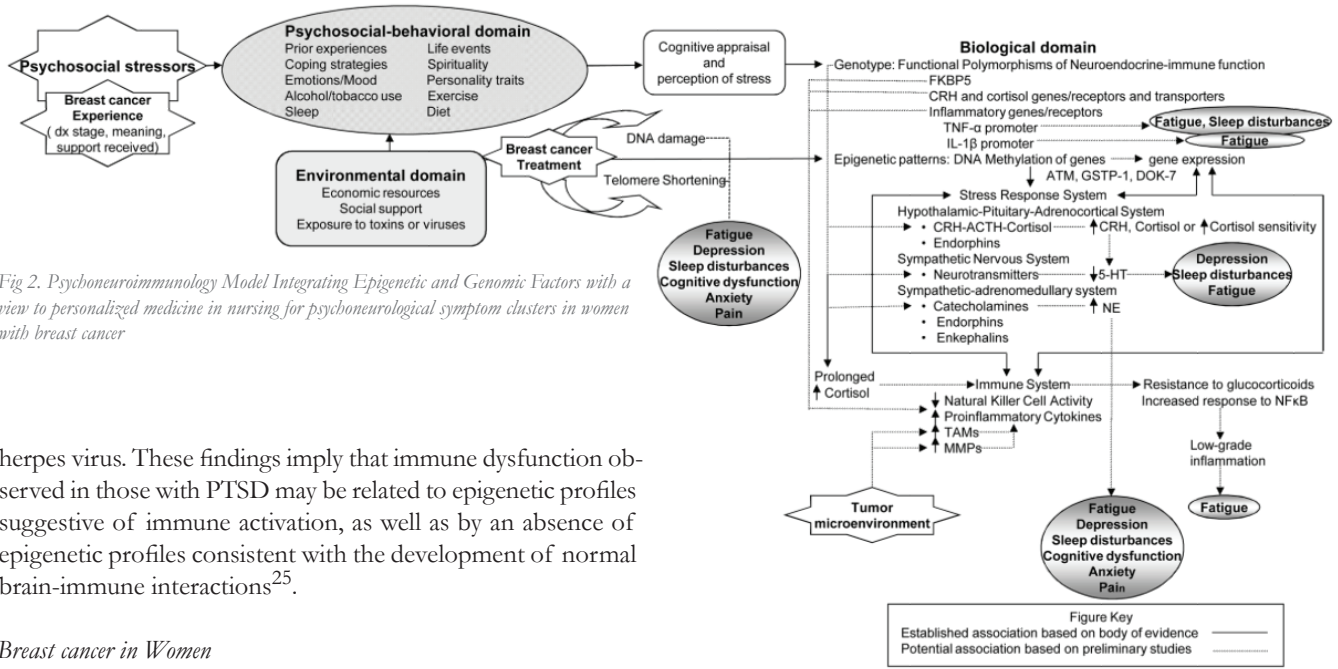


Fig 2. Psychoneuroimmunology Model Integrating Epigenetic and Genomic Factors with a view to personalized medicine in nursing for psychoneurological symptom clusters in women with breast cancer

herpes virus. These findings imply that immune dysfunction observed in those with PTSD may be related to epigenetic profiles suggestive of immune activation, as well as by an absence of epigenetic profiles consistent with the development of normal brain-immune interactions²⁵.

Breast cancer in Women

Although advances in treatment have substantially increased rates of survival for women with breast cancer (BCA), the women often report a number of distressing symptoms that worsen over the course of treatment, and may persist in survivorship^{26,27}. The most common, severe, and distressing symptoms that co-occur throughout the treatment trajectory and after treatment include depressive symptoms, anxiety, cognitive dysfunction, fatigue, sleep disturbance, and pain. This set of symptoms, which has been termed the psychoneurological (PN) symptom cluster²⁸, has been reliably associated with reduced quality of life^{29,30,31}.

Several studies have found an association between symptoms and dysregulation of the hypothalamic-pituitary-adrenocortical (HPA) axis^{32,33,34}. In addition, studies using a cytokine-induced “sickness behavior” framework have provided some evidence for the association of inflammation with physical and emotional symptoms commonly experienced by women with BCA^{35,36,37}. More recently, research focused on variability in symptom severity and persistence led to investigations focused on the contributions of genetic factors and epigenetic modifications that occur due to psychosocial stressors, the disease process and

treatment^{38,39}. Variability in the stress response system can occur due to genetic polymorphisms that alter neuroendocrine-immune signaling pathways, thereby leading to disruption in homeostatic regulation and increased vulnerability to persistent symptoms^{40,41,42}. Recent studies on gene-environment interactions demonstrate how genetic variants that regulate the stress response system can influence persistent symptoms. The FK506 binding protein 5 (FKBP5) gene codes for the protein that binds to glucocorticoid receptors and modulates glucocorticoid sensitivity⁴³. In adults with a history of childhood trauma, DNA methylation of one of the FKBP5 polymorphisms was found to increase the risk of developing psychiatric disorders, including symptoms of post-traumatic stress disorder⁴⁴. The proposed concepts will help bring nursing research and personalized medicine together, in hopes that this hitherto neglected and understudied area of biomedical research convergence may ultimately lead to the development of more targeted clinical nursing strategies in those illustrative examples with psychoneurological symptoms.

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Psihoneuroimunologija i epigenetika

SAŽETAK: Epigenetika je izazvala povratak entuzijazma i zahvalnosti za mogućnosti okoliša u moduliranju ekspresije gena. Jasno je da epigenetske promjene mogu poslužiti kao molekularna podloga za signale iz okoliša koji utječu na ishode u ponašanju i, kao takva, ona je most između psihosocijalnog i biološkog svijeta. To je u skladu i s konceptom psihoneuroimunologije, koji želi razumjeti utjecaj okolišnih podražaja, osobito psihostimulusa na ponašanje, emocije, neuroendokrini odgovor na stres i imunološki sustav. Ilustrativni primjeri nedavnih znanstvenih otkrića, u ovom su tekstu navedeni, kako bi se istaknuo utjecaj epigenetskih modifikacija u područjima istraživanja psihoneuroimunologije. U tekstu su odabrani primjeri koji daju uvid u epigenetsku analizu i molekularne procese koji povezuju mozak s ponašanjem, neuroendokrini odgovor i imunološki ishod.

KLJUČNE RIJEČI: Epigenetika, Psihoneuroimunologija, Ponašanje, Samoubojstvo, Post-Traumatski stresni poremećaj, Rak dojke

