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ABSTRACT

In this Introduction to the Named Series “Epigenetics, Brain, Behavior, and Immunity” an overview of epigenetics is provided with a consideration of the nature of epigenetic regulation including DNA methylation, histone modification and chromatin re-modeling. 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.

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1. Introduction

A remarkable growth in the understanding of epigenetics and the impact of epigenetics on contemporary biology has occurred in recent years. This growth in the field of epigenetics has transformed our conceptualization of the impact of the environment upon our genes and upon our health (Feinberg, 2008). 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 behavior (Zhang and Meaney, 2010). In a similar manner, the integrative field of psychoneuroimmunology continues to advance the understanding of the complex networks that connect brain, behavior and immunity. In that field, attention is now focused on the analysis and understanding of the molecular processes, which underlie these complex networks. This understanding, viewed through the lens of epigenetics, provides for a new opportunity to address longstanding as well as emerging issues in psychoneuroimmunology.

The psychosocial context of the environment can substantially change behavior and alter nervous, endocrine and immune function (Eskandari and Sternberg, 2002). 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. As well, emerging evidence shows that, adults also respond epigenetically to environmental signals, which in turn influence behavior, physiological outcome, and disease risk (Feinberg, 2008; Foley et al., 2009; Handel et al., 2010). At this time, however, few studies have evaluated whether

the epigenome of cells and tissues of the immune system is sensitive to the environmental context, and this area provides ample opportunity for further exploration. What is clear, however, is that the advances in this field add to the “seductive allure of behavioral epigenetics,” which has generated intense interest within many scientific disciplines (Miller, 2010). Given the central influence of the environment on the integrative network that links brain, behavior, and immunity; this allure promises to invigorate many facets of investigation in psychoneuroimmunology that seek to unravel how environmental signals are transduced to the genome.

The overarching mission of this Journal is to understand the behavioral, neural, endocrine, and immune system interactions relevant to health and disease. With this in mind, the purpose of this Introduction to the Named Series “Epigenetics, Brain, Behavior, and Immunity” is to; provide an overview of epigenetic processes, present available examples of scientific inquiry demonstrating the influence of epigenetics relevant to psychoneuroimmunology, and finally to provide a perspective on future possibilities wherein epigenetics may significantly enrich the understanding of the associations that exist among brain, neuroendocrine, immune and behavioral processes.

2. Overview of epigenetic processes

2.1. The 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. Hence, the importance of epigenetic information is that it regulates gene expression. Epigenetics can refer to heritable effects on gene expression, or to the stable long-term alteration of the transcriptional potential of a cell, which may not necessarily be heritable. Most importantly, epigenetic information is susceptible to change, and as such, represents an

excellent target to understand how the environment may impact physiological function. The impact could be manifest as long as the environmental factor is present or could persist, in its absence. The effect could be transient (during the duration) or extended (subsequent) to the environmental impact and although not necessarily transmittable (mitotically and/or meiotically) could exert significant influence. While epigenetics refers to effects on single and/or sets of genes, epigenomics refers to global epigenetic modifications that encompass the entire genome as described in: <http://nihroadmap.nih.gov/epigenomics/index.asp>. As such, genetic information provides the blueprint for the manufacture of the proteins necessary to cellular function; whereas, epigenetic information provides instruction for the use of that blueprint, permitting an ordered and regulated gene expression pattern.

2.2. Epigenetic regulation and chromatin re-modeling

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 off (Kouzarides, 2007). Such a mark is DNA methylation. In this process, methyl groups attach to the backbone of the DNA molecule at cytosine rings found at CpG dinucleotides (Razin, 1998). These methyl groups typically turn genes off by affecting the accessibility of DNA. Another type of mark, known as histone modification, indirectly affects the accessibility of DNA (see Fig. 1). There are a variety of such chemical marks that modify the amino terminal tails of histones (e.g. acetylation, methylation, phosphorylation), changing how tightly or loosely DNA is packaged. If the wrapping is tight, a gene may be hidden from the cell's transcription machinery, consequently

less accessible and hence switched off. In contrast, if the wrapping is loosened, a gene that was formerly inaccessible can become accessible. 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.

In vertebrates, approximately 2 m of DNA are contained within each cell and this DNA is packaged into chromatin in a manner that permits transcription of some loci and suppression of other loci. The basic unit of chromatin is the nucleosome, which is comprised of four core histones (H2A, H2B, H3, H4, two of each) around which 146 base pairs of DNA are wrapped (see Fig. 2). The core histones are predominantly globular except for their amino terminal "tails," which are unstructured. A striking feature of histones, and particularly of their tails, is the large number and types of amino acid residues that can be modified. These distinct types of modification include; acetylation, methylation, phosphorylation, ubiquitylation, sumoylation, deimination and proline isomerization (Kouzarides, 2007). Histone modification has been detected at over 60 different amino acid residues, but with extra complexity resulting from methylation at lysine or arginine residues that may be of three forms: mono-, di-, or trimethyl for lysines and mono- or di-(asymmetric or symmetric) for arginine. This vast array of modifications provide for enormous modification of functional responsiveness. The best understood histone modifications or marks are acetylation, methylation and phosphorylation.

The term "histone code" has been used to describe these modifications and the histone code hypothesis (Strahl and Allis, 2000; Jenuwein and Allis, 2001) proposes an epigenetic marking system

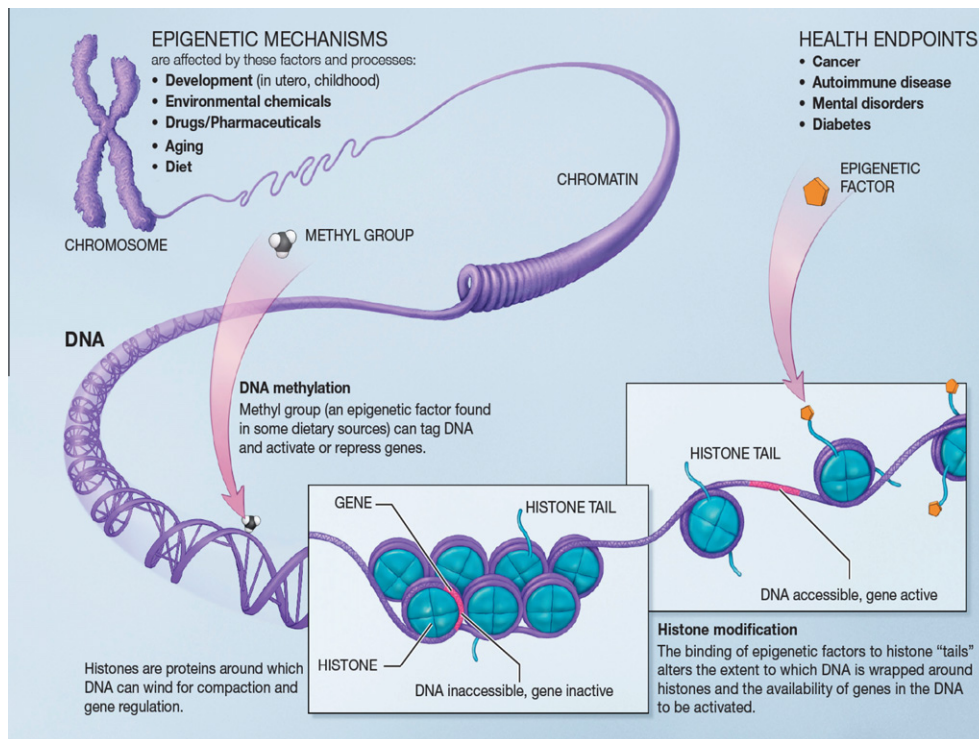


Fig. 1. Epigenetic processes, DNA methylation and histone modification. DNA methylation is an epigenetic mark which often represses gene transcription. Histones are proteins around which DNA is packaged and histone modifications can either repress or enhance gene transcription. Histone modifications occur when epigenetic factors are bound to histone "tails" and alter the extent to which DNA is wrapped around the histones, thus, altering the availability of DNA for transcription. DNA methylation and histone modification can impact health and may contribute to disease states such as cancer, autoimmune manifestations, mental disorders, or diabetes (Selvi and Kundu, 2009). Epigenetic mechanisms are affected by several factors and processes including; development *in utero* and in childhood, environmental stress, drugs and pharmaceuticals, aging, and diet, <http://nihroadmap.nih.gov/epigenomics/index.asp>. Permission is granted to copy, distribute and/or modify this document under the terms of the GNU Free Documentation License, Version 1.2 or any later version published by the Free Software Foundation. This work is in the public domain in the United States because it is a work of the United States Federal Government under the terms of Title 17, Chapter 1, Section 105 of the US Code. The website for this figure is as follows: http://commons.wikimedia.org/wiki/File:Epigenetic_mechanisms.jpg. (For interpretation to colours in this figure, the reader is referred to the web version of this paper.)

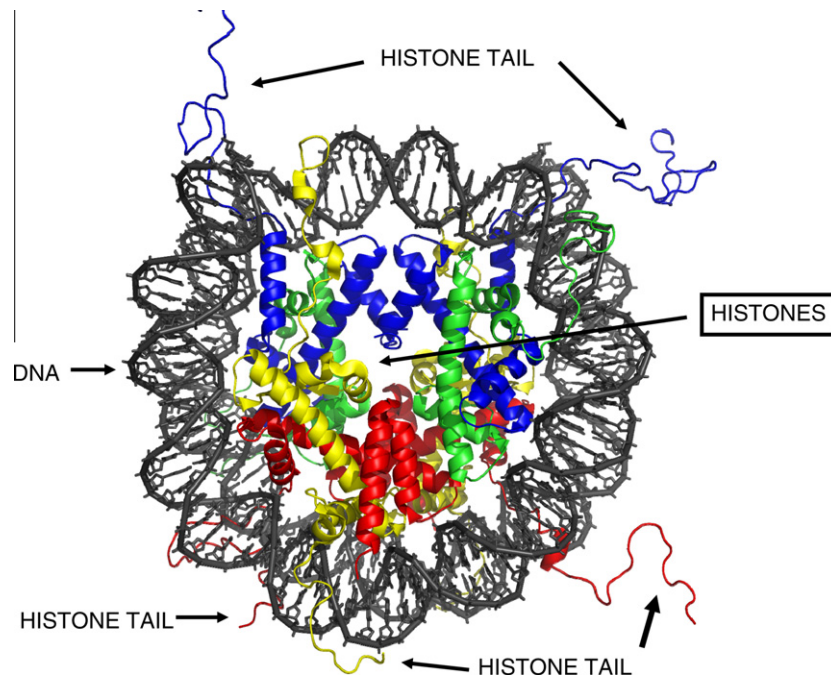


Fig. 2. Cross-sectional ribbon diagram of a nucleosome with central histones, their amino terminal tails, with DNA wrapped about the exterior surface. Permission is granted to copy, distribute and/or modify this document under the terms of the GNU Free Documentation License, Version 1.2 or any later version published by the Free Software Foundation. The figure is by Richard Wheeler (Zephyris), Sir William Dunn School of Pathology, University of Oxford, UK. Permission for its use has been obtained from Richard Wheeler, Zephyris, at the English language Wikipedia, the copyright holder of this work. The website for this figure is as follows: http://en.wikipedia.org/wiki/File:Nucleosome_1KX5_colour_coded.png. (For interpretation to colours in this figure, the reader is referred to the web version of this paper.)

of histone modification patterns, which regulate functional expression of the genome. This hypothesis proposes a combinatorial pattern of histone modifications in a given cellular and developmental context, brought about by a series of “writing” and “erasing” events by histone-modifying enzymes. The “writer” of histone modification refers to enzymes (e.g. acetyltransferases, methylases, phosphorylases) that catalyze a chemical modification of histones in a residue specific manner. The “eraser” of histone modification refers to enzymes (e.g. deacetylase, demethylase, phosphatases) that remove a chemical modification from histones (Strahl and Allis, 2000; Jenuwein and Allis, 2001; Klose and Zhang, 2007). The specific interpretation or the “reading” of the histone code is accomplished by “reader” or effector proteins (containing for example bromo domains, chromo domains, plant homeo domains) that bind to a specific or combinatorial histone modification, permitting the transcription of the histone code into a meaningful biological outcome. These may be either transcriptional activation or silencing (Strahl and Allis, 2000; Jenuwein and Allis, 2001; Klose and Zhang, 2007). In addition, histone modification can be achieved by direct physical modulation of chromatin structure or alteration of intra-nucleosomal and inter-nucleosomal contacts (Strahl and Allis, 2000; Jenuwein and Allis, 2001; Jones and Baylin, 2007). Each of these regulatory mechanisms functions broadly to create an epigenetic landscape that determines cell fate during both embryogenesis and development (Mikkelsen et al., 2007) as well as gene transcription throughout the life span (Shi et al., 2006).

The dynamic modifications that mediate epigenetic regulation are carried out in part by enzymes that remove such modifications. Such enzymes have been identified for; acetylation (Sternier and Berger, 2000), methylation (Zhang and Reinberg, 2001), phosphorylation (Nowak and Corces, 2004), ubiquitylation (Shilatifard, 2006), sumoylation (Nathan et al., 2006), deimination (Cuthbert et al., 2004), and proline isomerization (Nelson et al., 2006). The best characterized are the histone deacetylases (HDACs). For a review of HDACs (see De Ruijter et al., 2003). In addition to these “erasers” there are “writers” that covalently attach the same epigenetic marks

removed by the erasers. The best characterized are the histone acetyltransferases (HATs), histone methyltransferases (HMTs) as well as histone phosphorylases (mitogen and stress-activated protein kinases). For a review of HATs (see Selvi and Kundu, 2009). For a review of histone methyltransferases (see Cedar and Bergman, 2009). For a review of phosphorylases (see Ito, 2007). In addition to these, chromatin re-modeling complexes that are ATP dependent, alter the position of nucleosomes around the transcription initiation site and define accessibility of regulatory regions for the transcription machinery. There are direct relationships among histone residue modification, methylation and chromatin re-modeling (Bultman et al., 2005). For example, changes in the acetylation status of specific lysine residues form a molecular mark for the recruitment of chromatin re-modeling enzymes that function as transcriptional coactivators (e.g. Brahma-related gene 1, BRG-1; SWItch/Sucrose NonFermentable, SWI/SNF) (Hebbard and Archer, 2007). These coactivators allow for local chromatin unwinding and the recruitment of the basal transcriptional complex and RNA polymerase II (Trotter and Archer, 2007; Rosenfeld et al., 2006). Methylated residues are recognized by chromo domains (protein segments that bind to methylated lysines of H3) and also by unrelated plant homeo domains (protein segments which can bind to various methylated forms of H3-K4). Acetylated residues are recognized by bromo domains (protein segments that specifically bind acetyl-lysine), and phosphorylated residues are recognized by 14-3-3 proteins (proteins which recognize phosphorylated serine or threonine residues of histones). Further, higher-order chromatin structure may be modified by altering the contact between different histones in adjacent nucleosomes or by modification of histone/DNA interaction (Kouzarides, 2007).

2.3. Epigenetic effect of histone modification

Functional histone modifications are of two types: global and local. Global chromatin environments partition the genome into distinct domains: such as euchromatin, where DNA is kept “accessible”

for transcription; and heterochromatin, where chromatin is kept “inaccessible.” Within euchromatin, local histone modifications orchestrate chromatin opening to permit accessibility and/or transcription of particular genes. These tasks require the ordered recruitment of the machinery to unravel DNA, manipulate it and then put it back to the correct chromatin state (Li et al., 2007; Groth et al., 2007). Transcription requires disruption of the nucleosomal histone/DNA contact as RNA polymerase moves along the DNA, and is followed by the reformation of nucleosomes in the wake of the enzyme. A series of interlocking epigenetic histone marks occur during mRNA initiation and elongation and each is required for full transcriptional activity (Henikoff and Ahmad, 2005; Lieb and Clarke, 2005; Reinke and Horz, 2003). These histone epigenetic marks typically involve acetylation and/or phosphorylation of histones through activator-mediated recruitment of acetylase and kinase complexes, followed by phosphorylation of RNA polymerase II. The transit of RNA polymerase across the transcription unit is preceded by a leading wave of initial positive histone modifications that open the chromatin by transient displacement of nucleosomes (Govind et al., 2007). Deacetylases are required to remove these residues for re-closure after transcription is complete.

In general, histone acetylation is associated with regions of actively transcribed chromatin. For example, selected lysines such as H4-K8, H4-K9, H4-K12 and H4-K14 are acetylated by HATs, which catalyze the attachment of acetyl groups. The addition of an acetyl group to lysine residues within the histone tail neutralizes their positive charge, thereby disrupting interaction with the negatively charged DNA, which loosens the chromatin structure. In addition, transcriptional activators are recruited by these acetylated-lysines via bromo domains which enhance gene activity (Haberland et al., 2009). Coactivators such as cyclic AMP binding protein (CBP/p300), steroid receptor coactivator-1 (SRC-1), and p300/CBP-associated factor (PCAF) (Roth et al., 2001; Santos-Rosa and Caldas, 2005) have associated HAT activity and mediate transcriptional activation (Roth et al., 2001; Smith and Denu, 2009). In contrast to acetylation, methylation of histone residues can either activate or repress gene transcription. Methylation modifications of H3-K4, H3-K36, and H3-K79 are found at active genes, while methylation of H3-K9 and H3-K27 and H4-K20 are found at transcriptionally repressed genes (Kouzarides, 2007). Histone lysine methyltransferases catalyze the addition of up to three methyl groups in a site-specific manner. Hence, histone hyper-acetylation of H4, along with di- or tri-methylation of H3-K4 is associated with chromatin de-condensation, accessibility of DNA to binding proteins and increased transcriptional activity. Whereas, histone hypo-acetylation and di- or tri-methylation of H3-K9 and tri-methylation of H3-K27 constitute repressive marks and contribute to chromatin condensation and transcriptional repression (Li, 2002; Peterson and Laniel, 2004; Cosgrove and Wolberger, 2005). H4-K12 acetylation and H3-S10 phosphorylation are typically associated with sites of chromatin opening (Strahl and Allis, 2000). Finally, it is worth noting that many histone-modifying enzymes have been found to have non-histone substrates as well (Sadoul et al., 2008; Huang and Berger, 2008).

2.4. Epigenetic effect of DNA methylation

DNA methylation is catalyzed by DNA methyl transferases. Forty percent of genes contain CpG-rich islands upstream of their transcriptional initiation sites, and up to 80% of these are methylated (Bird, 2002; Klose and Bird, 2006). DNA methylation during embryogenesis is involved in X-chromosome inactivation in females and DNA imprinting events, which result in monoallelic gene expression (Illingworth et al., 2008; Miranda and Jones, 2007; Delcuve et al., 2009). DNA methylation silences genes by

blocking access to DNA (Li, 2002) or by recruiting methyl binding proteins (e.g. MeCP2) that complex with histone deacetylases (HDACs) and co-repressor proteins, repressing transcription in a methylation dependent manner (Nan et al., 1998; Zhang et al., 1999; Bird and Wolffe, 1999). DNA methylation patterns in most cell types result from the balance of methylating (DNA methyltransferases, DNMTs) and demethylating (demethylase) activities (Delcuve et al., 2009; Turek-Plewa and Jagodzinski, 2005). In contrast to the variety of histone modifications, methylation represents the only known physiologic alteration of the chemical composition of DNA. A distinguishing characteristic of DNA methylation in vertebrate genomes is that not all CpGs are methylated in any given cell type (Razin, 1998) resulting in cell type specific patterns of methylation. Thus, the DNA methylation pattern confers upon the genome its' cell type identity. Since DNA methylation is part of the chemical structure of the DNA itself, it is more stable than other epigenetic marks and as such a potentially important marker relevant to the effect of the environment upon the genome (Beck et al., 1999). Significant progress has been made in understanding the influence of the environment on epigenetic modulation of stress responsivity. This work has been summarized below in Section 3.

2.5. Non-coding RNAs

Other relevant regulators of chromatin structure and gene expression are non-coding RNAs (ncRNAs, i.e., transcripts that are not translated into protein), which can range in size from a few nucleotides to several kilobases (Costa, 2008). A prominent member of the large ncRNAs is the *Xist* RNA, which mediates X-chromosome epigenetic inactivation in females (Ng et al., 2007). *Xist* is transcribed from the future inactivated X-chromosome and initiates silencing by direct interaction with the chromosome (Wutz, 2007). Stable silencing is finalized by enzymatic addition of repressive histone marks and DNA methylation. Small ncRNAs can mediate both transcriptional and post-transcriptional gene silencing (Bernstein and Allis, 2005). For example, microRNAs (miRNAs) are a group of small, ncRNA molecules (18–22 nt) that function as post-transcriptional regulators of gene expression (Moazed, 2009). These miRNAs are transcribed in the nucleus by the action of RNA polymerase II or III forming long precursor transcripts (Faller and Guo, 2008). These precursor RNA molecules are cleaved sequentially, in the nucleus, by the endonuclease activity of Drosha and then after export to the cytoplasm, by the endonuclease activity of Dicer. The resulting mature miRNAs bind to their target mRNAs by base pairing at distinct regions and, thus, alter mRNA stability or affect protein translation (Mendell, 2005). Typically, miRNAs preferentially bind to complementary sites located in the 3'UTR of target mRNAs and the degree of complementarity determines how the target will be repressed. Perfect complementarity results in mRNA cleavage, whereas partial complementarity represses translation (Zeng et al., 2003). Whichever way, repression is mediated by the RNA-induced silencing complex (RISC). It has been suggested, without formal proof, that the histone code is affected by these small RNAs. The potential impact of miRNA-mediated biological regulation is estimated to be considerable. For the over 1000 cloned or predicted human miRNAs, thousands of potential miRNA targets, affecting essentially all cellular processes, have been estimated. Since the transcriptional regulation of miRNAs is incompletely understood, it is unknown how these non-coding RNAs may exert an epigenetic effect. However, computational methods predict that up to one third of human transcripts are regulated by miRNAs (Lewis et al., 2005) and as such the potential biological effect is significant.

3. Illustrative epigenetic models relevant to psychoneuroimmunology

The following section provides a review of select studies that illustrate the effect of environmental perturbations in several model systems that result in epigenetic modification. Those chosen have relevance to investigation in psychoneuroimmunology (summarized in Table 1). It should be noted that at the current time, the majority of research concerning epigenetic modification, which impact the interactions among brain, behavior, and immunity, rests predominately within neuro-epigenetics. Further, most of these studies employ animal models that demonstrate epigenetic modification that occur in response to early life experiences or stressors, which alter the developing epigenome in the brain, particularly the hippocampus. As well, Section 3 describes emerging work that evaluates epigenetic modification using adult models of stress and depression, aging and aging-associated memory impairment, as well as a consideration of the role of epigenetics in resilient versus susceptible phenotypes. At this writing, however, there are few studies which have addressed environmental-induced epigenetic modification of the immune response and there are only a handful of studies that have addressed the effect of environmental stimuli or behavior on epigenetic modifications using human paradigms; those studies are included in this review. Given this background, the findings reviewed herein are intriguing and should stimulate interest and further investigation. Moreover, the

current state of science in this area emphasize that there is ample opportunity and good scientific rationale to incorporate an epigenetic perspective in future investigations within psychoneuroimmunology.

3.1. Maternal care models and epigenetic modulation of stress responsivity and behavior

Early life experiences influence brain function and alter neuroendocrine set-points. These alterations can result in detrimental effects that impact behavior and health throughout life (Schlotz and Phillips, 2009). 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 (Fenoglio et al., 2006; Fumagalli et al., 2007).

Maternal care models in rodents have provided tremendous insight as to how epigenetic processes translate the psychosocial environment to the epigenome. In particular, these models have

Table 1
Summary of representative epigenetic studies relevant to psychoneuroimmunology.

Model	Species	Tissue evaluated	Epigenetic mark	Functional effect	Reference
Maternal nurturing behavior	Rat	Brain – hippocampus	DNA methylation of GR promoter exon 17	GR expression. NGFI-A expression. HPA responsivity. Anxiety behavior. Reversible with: <ul style="list-style-type: none"> • TSA • Methionine • Cross-fostering 	Weaver et al. (2004, 2005, 2006, 2007)
Maternal nurturing behavior	Rat	Brain – hippocampus	DNA methylation of ER- α promoter	ER- α expression. Oxytocin receptor expression. Transgenerational transfer of behavior	Champagne et al. (2006, 2008)
Suicide victims with and without child abuse	Human	Brain – hippocampus	DNA methylation of NR3C exon	GR expression. Suicide risk	McGowan et al. (2009)
Prenatal depression	Human	Mononuclear cells: umbilical cord blood	DNA methylation of NR3C exon	Infant salivary cortisol response	Oberlander et al. (2008)
Maternal–infant separation stress	Mouse	Brain – paraventricular nucleus	DNA methylation of AVP enhancer region	AVP expression. HPA responsivity	Murgatroyd et al. (2009, 2010 – review)
Early life maltreatment/abuse	Rat	Brain – prefrontal cortex; hippocampus	DNA methylation of promoter regions	BDNF expression. Transgenerational transfer of behavior. Reversed by DNA methylation inhibitor	Roth et al. (2009)
Chronic social defeat model of depression	Mouse	Brain – hippocampus	H3-K27me2	BDNF expression. Depressive-like phenotype. Reversed by imipramine. (hyper-acetylation of BDNF promoter)	Tsankova et al. (2006)
Chronic social defeat versus social isolation models of depression	Mouse	Brain – nucleus accumbens	Genome wide H3-K9me2 H3-K27me2 Phospho-CREB H4-K12	Depressive phenotype. Resilient phenotype. Gene families: (that mediate inflammatory, cell death, redox state, gene regulation). Reversed by imipramine	Wilkinson et al. (2009)
Age-associated memory – Contextual fear conditioning model	Mouse	Brain – hippocampus	H4-K12	Learning induced genes. Reversed by HDAC inhibitor	Peleg et al., 2010
Forced swim model – Learned behavioral immobility	Rat	Brain – dentate gyrus	H3-S10P04	Require co-signaling through the GR and the glutamate signaling receptor (NMDA).	Bilang-Bleuel et al. (2005)
Acute versus chronic restraint stress	Rat	Brain – hippocampus; dentate gyrus	H3-K4me3 H3-K9me3 H3-K27me3	Differential histone methylation linked to stress duration	Hunter et al. (2009)
Novelty stress (escalating light intensity)	Rat	Brain – hippocampus	H3-S10P04 H3-K14Ac	Expression of the gene product c-fos; require co-signaling through the GR and the glutamate signaling receptor (NMDA)	Chandramohan et al. (2007)
Post-traumatic stress disorder	Human	Whole peripheral blood	DNA methylation	Immune regulation genes. Correlation with traumatic burden	Uddin et al. (2010)

GR = glucocorticoid receptor; NGFI-A = nerve growth factor-inducible protein-A; TSA = trichostatin A; ER- α = estrogen receptor alpha; AVP = arginine vasopressin; BDNF = brain derived neurotrophic factor; NMDA = N-methyl-D-aspartate.

been used to evaluate epigenetic modification of glucocorticoid receptor (GR) gene expression within the hippocampus. The hippocampus expresses the highest level of glucocorticoid receptors (GR) within the brain (Reul and De Kloet, 1985; Aronsson et al., 1988) and is particularly vulnerable to the effects of stressful experience (Conrad, 2008; Sapolsky, 2000; Lee et al., 2002; Mcewen et al., 1992). Hippocampal GR functions to regulate the HPA axis, by binding glucocorticoids and through negative feedback mechanisms turn-off the HPA response to a stressor (Jacobson and Sapolsky, 1991). As described below, evidence derived from maternal care models documents that adverse environmental stimuli alter GR expression through epigenetic modification.

Female rats exhibit a range of licking and grooming (LG) behavior toward their pups. LG provides nurturing and serves as a key source of tactile stimulation. Natural variations in maternal LG behavior during the early postnatal period give rise to persistent differences in stress responsiveness and behavior of adult offspring (as reviewed in Zhang and Meaney, 2010). Notably, offspring of mothers who provide high levels of LG (HLG) over the first postnatal week show increased hippocampal GR expression, enhanced glucocorticoid feedback sensitivity, and decreased hypothalamic CRF expression. As well these offspring exhibit a more moderate behavioral and hormonal response to stressors, compared to offspring of mothers who provided low levels of LG (LLG). Cross-fostering pups from a HLG mother to a LLG mother during the first postnatal week, or vice versa, reverses these effects and establishes that the resulting phenotype originates from maternal care behavior (Francis et al., 1999; Liu et al., 1997). More recently, variations in LG were shown to be associated with alterations in the methylation pattern of the GR promoter exon 1₇, such that offspring of LLG rat dams exhibit greater methylation of the GR promoter compared to offspring of HLG dams. This methylation pattern shapes the HPA and behavioral response to stress.

The exact mechanism whereby maternal LG behavior influences methylation of the GR promoter is currently unknown. Yet a series of studies implicate the involvement of the transcription factor, nerve growth factor-inducible protein A (NGFI-A), which functions to transcribe the gene that encodes for GR in the hippocampus. It is proposed that NGFI-A, couples with other transcription factors, cyclic-AMP response element binding protein (CREB) and specific protein 1 (SP-1), to bind to the GR 5' untranslated promoter exon 1₇. The binding of this complex of proteins has been theorized to contribute to the reconfiguring of the methylation pattern of GR promoter exon 1₇. The timing is critical in that this re-configuration of methylation is dependent upon levels of maternal LG during the first postnatal week (Weaver et al., 2004, 2007). Following birth there is rapid *de novo* methylation of GR exon 1₇, which is then demethylated over the course of the first postnatal week. It is this postnatal demethylation that is regulated by maternal LG behavior. The following describes a model of how this might occur. Tactile stimulation from HLG increases 5-HT in the hippocampus and initiates a cascade of intracellular signals that culminate in an increase in the expression of NGFI-A, CREB, and SP-1 (Weaver et al., 2007). Exon 1₇ includes a DNA binding sequence for SP-1, which overlaps with that for NGFI-A; the overlap site is the 5'CpG site that eventually is demethylated. SP-1 may contribute to the initiation of DNA demethylation at CpG sites (Brandeis et al., 1994), while CREB associated HAT activity acetylates histone tails and favors an open chromatin structure and this may increase access for the NGFI-A/CREB and SP-1 complex and facilitate demethylation. For offspring of HLG mothers, maternal tactile stimulation increases hippocampal expression of GR as a consequence of epigenetic modification. Whereas, offspring of LLG exhibit reduced expression of NGFI-A, reduced DNA accessibility, and reduced postnatal demethylation of GR promoter exon 1₇. This results reduced hippocampal GR expression, increased stress

reactivity, and more anxiety-like behaviors in offspring of LLG mothers (reviewed in (Zhang and Meaney, 2010)).

Even though the epigenetic effects produced by maternal care behavior are stable, they can be reversed by epigenetic manipulation during adulthood. For example, injecting a histone deacetylase inhibitor into the brain of adult offspring who received LLG during the first postnatal week of life, increases acetylation and reduces methylation of the hippocampal GR exon 1₇. Functionally, this increases GR expression levels to that of offspring who received HLG during the first postnatal week (Weaver et al., 2004). In contrast, increasing DNA methylation levels by central infusion of methionine reduces hippocampal GR expression in HLG offspring and these animals display greater stress responsiveness and more anxiety behaviors (Weaver et al., 2005, 2006). Together these studies provide evidence for a causal link between epigenetic modification and the effect of maternal care behaviors on GR expression.

Whether the observed effects of pharmacologic treatment represent short-lived or more permanent epigenetic modifications remains unclear. Equally important, it is also likely that modifications of DNA methylation may be limited to a small subset of genes that are more sensitive to epigenetic modification in the developing animal. It is recognized that the epigenome of adults may not be as responsive. Yet despite these limitations, this model system demonstrates that the DNA epigenetic pattern, although relatively stable, is capable of being modified by environmental and pharmacologic treatment.

Collectively, these studies of rodent maternal care behavior suggest potential implications for adult disease risk, as altered HPA stress reactivity is linked to disorders of mood and cognition (De Kloet et al., 2005; Lupien et al., 2009). As well, a stress-sensitive phenotype marked by greater stress-induced elevations in glucocorticoids may contribute to the development of adult-onset disease, such as cardiovascular disease or Type II diabetes (Cottrell and Seckl, 2009; Gluckman et al., 2005) and is consistent with the developmental origins of health (Gluckman et al., 2008, 2007; Cooney, 2006; Godfrey et al., 2007). The observation that the epigenetic imprint produced in response to maternal care behavior is reversible suggests that there is the possibility to lessen disease vulnerability through epigenetic modification. From another perspective, it is also significant that the stimulus for epigenetic modification of HPA stress responsivity was maternal tactile stimulation (i.e., LG behavior). In humans the psycho-biological benefits of maternal touch on human infant development are well-established (Ferber et al., 2008; Moszkowski et al., 2009; Liaw, 2000). Similar to the studies in rodents, human maternal touch attenuates infants' physiological reactivity to stress as exhibited by lower cortisol levels. And akin to the rodent cross-fostering paradigm, in the absence of maternal touch, provision of touch by others can also reduce an infants' cortisol stress response (Feldman et al., 2010). Further, in the neonatal intensive care unit (an environment with limited opportunities for maternal–infant touch) implementation of skin-to-skin care for premature infants reduces the infants' cortisol response to painful stimuli and confers positive effects on infant development (Morelius et al., 2005; Feldman et al., 2002). Premature infants are undergoing critical brain development *ex-utero*, and consequently the brain of these infants is likely more susceptible to epigenetic modification. As well, impaired cognitive development subsequent to *in utero* exposure of infants to high maternal cortisol levels can be attenuated by more secure maternal–infant attachment, which includes more engagement in touch behaviors between the maternal–infant dyad (Bergman et al., 2010). Whether, the moderation of HPA reactivity in response to human touch emanates from epigenetic modifications, as shown in the rodent, remains to be determined. The caveat, however, is that such assessment will require evaluations in specimens other than brain. However, there is evidence that prenatal

depressed mood can modify genes regulating expression of GR in cord blood mononuclear cells (described below) (Oberlander et al., 2008). Translating research from animals to humans may shed light on problems in cognition and behavior that are already attributed to impaired maternal–infant attachment and disturbed stress responsivity (Sroufe, 2005; Moriceau and Sullivan, 2005; Winberg, 2005).

3.2. Epigenetic perpetuation of behavior across generations

In rodents, variations in maternal care behavior are transmitted across generations, such that lactating adult offspring of HLG mothers will also exhibit HLG behavior toward their young; whereas, offspring of LLG mothers provide low levels of pup-directed LG (Francis et al., 1999; Champagne et al., 2001). 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 behavior (Leng et al., 2008). The extent of oxytocin receptor levels within the hypothalamic medial preoptic area (MPOA) determines LG behavior and lactating rats with HLG behavior exhibit greater oxytocin receptor levels in the MPOA (Champagne et al., 2001; Francis et al., 2000). Further, the promoter region of the oxytocin receptor gene contains an estrogen response element, which allows estrogen to modify oxytocin receptor expression levels. Estrogen produces this effect by enlisting estrogen receptor alpha (ER- α), a ligand activated transcription factor. When the estrogen-ER- α complex binds to the estrogen response element within the promoter region of the oxytocin receptor gene there is an increase in transcription of the oxytocin receptor within the neurons of the MPOA. Compared to female offspring of HLG mothers, female offspring of LLG mothers exhibit reduced expression of ER-alpha in the MPOA which emerges during the first post-partal week and persists into adulthood (Champagne et al., 2003). Low levels of ER- α would then reduce the capacity of female offspring of LLG dams to respond to the estrogen surge that occurs at parturition. Therefore, these females would exhibit low levels of oxytocin receptor binding and a corresponding reduction in LG behavior, reviewed in (Champagne, 2008). Compared to female offspring of HLG dams, female offspring of LLG dams showed increased methylation at several sites within the ER- α promoter in the MPOA, which reduced oxytocin receptor expression and maternal nurturing behaviors. Further, the area of differential methylation of the ER- α promoter contains a Stat 5 response element. The Stat 5 response element is unmethylated in offspring from HLG dams but is highly methylated in offspring of LLG dams. Chromatin immunoprecipitation (ChIP) revealed reductions in Stat 5 binding in offspring of LLG dams as well as reduced expression of ER- α . Therefore, LLG during the first postnatal week increases methylation of the ER- α promoter so that Stat 5 binding is reduced and this, in turn, down-regulates expression of ER- α in the MPOA of female offspring. This impairs the ability of estrogen to boost expression of the oxytocin receptor at parturition. As a result this confers a phenotype in female offspring characterized by diminished LG behavior toward their own young (Champagne et al., 2006; Champagne, 2008). This work demonstrates that early life epigenetic modification can be instilled across generations. Yet it must be made clear that these epigenetic marks are not transmitted through the germ line but instead are dependent on maternal behavior which reinstates the epigenetic modification to the next generation. It is notable that this observation is consistent with studies in humans that show individual differences in infant-directed behaviors are transmitted from mother to daughter (Miller et al., 1997).

3.3. Child abuse, suicide, and epigenetic modification

The foregoing studies demonstrate the effect of rodent maternal behavior on epigenetic modification of the 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 HPA stress responsivity, which is linked to greater risk for psycho-pathology, including suicide (De Bellis et al., 1994; Pruessner et al., 2004; Heim and Nemeroff, 2001). 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 GR1_F exon (the homolog of exon 1₇ of the rat) and increased GR gene (NR3C1) promoter DNA methylation. This pattern was not observed in brain samples from suicide victims who had not suffered childhood abuse, nor was it observed in individuals who died due to accidental causes. 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 LLG. This suggests that results obtained with rodents might translate to the human experience. Yet such interpretation must be tempered, as this study was retrospective and did not directly demonstrate that childhood abuse led to the observed differences in brain methylation state (McGowan et al., 2009).

3.4. 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 disorders (Field et al., 2004). 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. From a functional perspective this increase in methylation pattern was also related to an increased infant salivary cortisol response, indicating that these infants have altered central regulation of the HPA axis consequent to maternal depressed mood (Oberlander et al., 2008). Although these results are quite provocative, the relationship between changes in hippocampal epigenetic regulation of GR expression and umbilical cord blood mononuclear cell expression of GR is not apparent, nor do correlative findings indicate causation. Further, analysis of cord blood mononuclear cells does not allow any discernment of the specific mononuclear cell population affected. Nevertheless, these findings represent one of few studies in humans linking epigenetic change to GR expression and to the psychosocial context (i.e., maternal prenatal depressive mood) as well as to infant cortisol response. These preliminary results suggest that at an epigenetic level maternal mood shapes the infant's future stress responsivity and are consistent with the animal maternal care models in the foregoing section. Whether depression-induced dysregulation of maternal hormones mediates the alteration in fetal epigenetic programming remains to be elucidated.

3.5. Maternal separation stress, AVP, and epigenetics

Arginine vasopressin (AVP) is a neuropeptide synthesized in the paraventricular nucleus (PVN) of the hypothalamus. AVP contributes to the regulation of the HPA axis by acting synergistically with CRH to stimulate the secretion of pituitary ACTH. Recent work in a mouse model showed that early life stress produced by maternal–infant separation induces epigenetic modifications that lead to excess production of AVP and a stress-sensitive phenotype (Murgatroyd et al., 2009, 2010). Pups separated from their mothers for 3 h/day on postnatal days 1 through 10 exhibited hyper secretion of basal and stress-induced corticosterone and altered stress coping and memory when tested through 1 year of age. The stress-sensitive phenotype was accompanied by elevations in AVP mRNA in the parvocellular PVN neurons within the hypothalamus, along with persistent hypomethylation of the enhancer region of the AVP gene. The hypomethylation centered on CpG residues that serve as DNA-binding sites for the methyl CpG binding protein 2 (MeCP2). MeCP2 serves as an epigenetic platform for maintenance of methylation by recruitment of histone deacetylases and DNA methyltransferases. During early life stress, depolarization of paraventricular neurons results in increased activation of Ca²⁺/calmodulin-kinase II resulting in phosphorylation of MeCP2. Phosphorylation of MeCP2 prevents it from occupying the AVP enhancer site. Without MeCP2 and associated DNA methyltransferases, the AVP enhancer is insufficiently methylated and AVP transcription is uncontrolled. However, MeCP2 is only transiently phosphorylated and by early adulthood regains its ability for interaction with the AVP enhancer. Yet, early life stress dependent phosphorylation of MeCP2 triggered an erosion of the AVP DNA enhancer methylation that strengthened dissociation of MeCP2 and as a result primed further demethylation (Murgatroyd et al., 2009). Thus, AVP regulation is persistently up-regulated, resulting in increased responsivity of the HPA axis to stress, which in turn, alters behavioral adaptation to stressors. These investigations suggest that epigenetic marks progress from more labile marks to stable long-lasting marks (i.e., hypomethylation of DNA). As such, there may be restricted windows of opportunity to administer timely interventions, which can attenuate or reverse these unfavorable epigenetic marks that result from maternal separation (Murgatroyd et al., 2010).

3.6. Early life adversity and epigenetic modification of BDNF expression

Brain derived neurotrophic factor (BDNF) is a growth factor that mediates neural plasticity through promotion of new synaptic connections between neurons (Greenberg et al., 2009; Cohen-Cory et al., 2010; Cowansage et al., 2010). Altered expression of BDNF is linked to early life adversity and may explain the association of mental illness with negative early life experiences (Liu, 2010; Cicchetti and Toth, 2005; De Bellis, 2005; Lee and Hoaken, 2007). Epigenetic modifications have been evaluated as potential mechanisms whereby stress affects expression of genes that encode for BDNF (Roth et al., 2009; Roth and Sweatt, 2010). Brain DNA methylation patterns were evaluated in adult rats that as pups were removed from their home nest and subjected to an abusive dam (30 min daily over the first postnatal week). In contrast, littermate control pups were also removed from their home nests but were placed with a non-abusive dam. [Note: maternal stress was induced by housing the foster dams in an unfamiliar environment with limited nesting resources and this instilled abusive behavior in the lactating dams.] Exposure to maternal abuse resulted in decreased BDNF total mRNA in the prefrontal cortex and hippocampus of male and female rats during adulthood. This was accompanied by a persistent increase in DNA methylation in

promoter regions for BDNF exons IX and IV. Central infusion of a DNA methylation inhibitor into adult rats previously subjected to maternal abuse reversed these effects, which demonstrates a causal relationship between early life abuse and methylation for gene regions that regulate transcription of BDNF. Further, the effects of maternal abuse were perpetuated across generations, as females who were abused as pups also displayed abusive behaviors toward their own offspring and their offspring exhibited greater brain DNA methylation of genes that influence BDNF expression. However, cross-fostering pups to non-abusive dams was unable to completely reverse the transgenerational carry over of abusive behavior, suggesting that factors in addition to a nurturing environment may be contributory (Roth et al., 2009). Overall, these results demonstrate the dynamic responsivity of DNA methylation across the life-course and are consistent with the known perpetuation of human child abuse across generations (Ney, 1989; Noll et al., 2009; Bifulco et al., 2002).

As a whole, the above studies demonstrate that the prenatal and early postnatal environment can ‘program’ stable changes in gene expression through epigenetic processes. This may serve as the foundation for individual differences in behavioral and neuroendocrine responses to stress in adult life, which could also shape the immune response to stress. As well, maternal abuse may modulate expression of BDNF and disrupt brain development. Overall, this evidence sets forth a potential epigenetic mechanism whereby cues from the early life environment influence an individual’s vulnerability or resistance to stressors and possible stress-induced illnesses over the lifespan. Further, the underlying epigenetic modifications that occur as a result of early life experiences can be reversed (i.e., cross-fostering, diet, and pharmacologic). These findings support the concept of a dynamic epigenome that transduces psychosocial stimuli to the genome. Moreover, the findings provide a foundation for exploration of novel epigenetic-based approaches to predict, prevent and treat disease rooted in early life adverse experiences.

3.7. Stress-induced depression models and epigenetic modification of BDNF

Depression often accompanies chronic stress and individuals with depression can have reduced hippocampal volumes (Sheline et al., 2003). Chromatin re-modeling of the BDNF gene in the hippocampus may play a role in stress-induced depression and depression-mediated changes in neural plasticity. Chronic social defeat stress is a model system in mice that induces depressive-like behaviors. The paradigm consists of physically exposing mice to a highly aggressive resident mouse and then housing the aggressor and the defeated mice in cages separated by a plastic divider with holes that allow visual, olfactory, and auditory contact. The resulting depressive-like phenotype is manifested by subordination and greater avoidance behaviors and less social interaction compared to control mice. Furthermore, the depressive-like phenotype is accompanied by reductions in hippocampal BDNF gene expression. This can be reversed with chronic administration of an anti-depressant (imipramine), suggesting that chronic defeat affects neural circuits that participate in depression. Further, the depression induced by chronic social defeat results in long-lasting histone modifications of the BDNF gene, including a marked increase in H3-K27me2, a repressive histone mark, at the BDNF P3 and P4 promoters. Chronic imipramine treatment did not reverse this methylation mark; however, this treatment did induce long-lasting hyper-acetylation of histone H3 at BDNF promoter regions P3 and P4. Hence, acetylation of these promoters was sufficient to de-repress BDNF mRNA transcription. Further, over expression of a histone deacetylase (HDAC5) in mice exposed to chronic social defeat prevented imipramine from reversing avoidance and increasing social interaction (Tsankova et al., 2006).

The above observations indicate that chronic defeat stress induces methylation of H3-K27 at the BDNF gene, which persists long after the end of stress. This chromatin modification induces a more closed chromatin state and thereby mediates the stable repression of the BDNF gene. The regulation of histone acetylation, DNA methylation and HDAC5 expression are not affected after chronic stress alone, which suggests that repression of the BDNF gene is mediated mainly via histone methylation. Chronic imipramine induces hyper-acetylation of H3 at the BDNF promoter after chronic defeat stress, an effect that is likely mediated, at least in part, by means of the down regulation of HDAC expression. Hyper-acetylation of the promoter overcomes its methylation induced repression and leads to a more open chromatin state at the BDNF promoter. This is theorized to cause de-repression of the BDNF gene and contributes to imipramine's anti-depressant activity (Tsankova et al., 2006). The epigenetic insight gained from these findings may advance the development of epigenetic-based approaches to not only treat, but also possibly to prevent stress-induced depression.

Another study of epigenetic modification and stress-induced depression focused on the nucleus accumbens, a chief brain reward center linked to depression in animals (Nestler and Carlezon, 2006) and humans (Tremblay et al., 2005). That study compared chronic social defeat to prolonged social isolation, both of which result in depressive behavior in mice, to determine whether epigenetic modifications in the nucleus accumbens are linked to a depressive phenotype. Histone dimethylation marks at lysine positions 9 and 27, which associate with reduced gene expression (Kouzarides, 2007), and phospho-CREB (the transcriptionally active form of CREB) binding to gene promoters were evaluated. Compared to mice not subjected to either depressive paradigms, both chronic social defeat and social isolation exposed mice exhibited significant differences in the relative levels of H3-K9me2 and H3-K27me2 in regions of gene promoters immediately upstream of their initiation sites. A positive correlation between enrichment and attenuation of H3-K9me2 and H3-K27me2 binding between the depression models indicated that social defeat and social isolation affect many similar gene regulatory events. In contrast social defeat stress was associated with increased levels of genome wide levels of phospho-CREB in the nucleus accumbens, while social isolation was associated with decreased phospho-CREB levels in the nucleus accumbens. These changes were observed throughout the promoter regions, as opposed to being near transcription initiation sites as seen with H3 methylation. The global view of these epigenetic changes in phospho-CREB binding showed a negative correlation between social defeat and social isolation stress, as opposed to the positive correlation observed for H3 methylation. Chronic administration of the anti-depressant, imipramine, reversed the histone methylation and phospho-CREB changes induced by social defeat, demonstrating the role of these epigenetic marks in the mediation of depressive behavior (Wilkinson et al., 2009).

The gene families implicated in the depression-induced alterations in H3 methylation and phospho-CREB binding were those involved in inflammatory, cell death, redox state, and gene regulation. Functionally, this suggests that epigenetic modification in the nucleus accumbens subsequent to these forms of stress-induced depression might lead to increased inflammation and decreased ability to attenuate oxidative stress. Because proinflammatory cytokines are known to be associated with depressive behavior in animals (Dantzer et al., 2008), it is possible that the alterations of the regulation of genes involved in inflammatory pathways may be implicated in the behavioral manifestations (i.e., depression) of chronic defeat stress. Also, differences in phospho-CREB binding occurred in genes that regulate actin in the social defeat versus the social isolation model. Altered actin re-modeling in response to stress may relate to morphological

changes in the brain, such as the reduced hippocampal volume observed in humans in response to chronic stress and depression (Egger et al., 2008; Magarinos et al., 1996; Wilkinson et al., 2009). Another gene affected was Sep-15, which encodes a selenoprotein, an antioxidant. Sep-15 is known to be dysregulated in neurodegenerative disorders, like Alzheimer's disease (Chen and Berry, 2003) and these results raise the possibility of an epigenetic mechanism whereby chronic stress might contribute to neurodegenerative disease. This concept is consistent with evolving work which has implicated epigenetic mechanisms in memory formation, as well as the decline of memory, cognition, and learning that occurs with aging or dementia (Roth and Sweatt, 2009; Peleg et al., 2010).

3.8. Epigenetic mechanisms in aging-associated memory impairment

Aging is associated with cognitive impairment and a decline in memory (Crook and Ferris, 1992). 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 formation (Penner et al., 2010). The hippocampus is central to memory formation and is affected during early stages of dementia (Mesulam, 1999). Recently, aged-associated memory impairment was shown to result from altered chromatin re-modeling in the hippocampus when aged mice were tested in a contextual fear conditioning paradigm (Peleg et al., 2010). 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 H4-K12 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. In response to the learning paradigm, young mice showed differential regulation of 2,229 genes within the hippocampus. The majority of these genes were linked to associative learning and were involved in biological processes (transcription, protein modification, or intracellular signaling). In contrast, aged mice exhibited essentially no change in their hippocampal gene expression in response to learning, suggesting that the aged mice displayed marked impairment in regulatory gene expression upon exposure to situations that typically promote learning behavior. The delivery of an HDAC inhibitor directly into the hippocampus led to an increase in hippocampal H4-K12 acetylation in response to the fear conditioning paradigm and this occurred in coding regions of learning-regulated genes. Importantly, the HDAC inhibitor restored expression of the learning-regulated genes and recovery of cognitive abilities in the aged mice in response to fear conditioning. These provocative findings provide evidence that deregulated H4-K12 plays a causal role in age-associated memory impairment and suggests that H4-K12 is an "early biomarker for an impaired genome-environment interaction in the aging brain" (Peleg et al., 2010). These results are consistent with other findings that demonstrate that the administration of histone deacetylases completely reverses contextual memory deficits in a mouse model of Alzheimer's disease (Kilgore et al., 2010). Although it is conceivable that pharmaceuticals might be developed to restore H4-K12 acetylation and thus, prevent and/or re-establish memory in the elderly, issues of specificity and potential toxicity for such HDAC inhibitors must be addressed. Other models of stress-related memory formation have implicated chromatin modification. For example, the learned behavioral immobility response of rats in response to re-exposure to forced swimming was shown to be dependent upon chromatin re-modeling within the dentate gyrus (Bilang-Bleuel et al., 2005). Moreover, chromatin re-modeling observed in this model of stress-induced memory, appears to involve glucocorticoid co-signaling through the GR as well as signaling via glutamate receptors (Chandramohan et al., 2008).

3.9. Resilience to stress-induced depression and epigenetics

Resiliency refers to the capacity of a person who when challenged by adversity, continues to demonstrate adaptive psychological and physiological stress responses, as opposed to developing affective disorders like depression (Charney, 2004). Inbred mice exhibit two responses to chronic social defeat stress; a susceptible response in which the mice develop depressive symptoms and a resilient response in which the mice resist developing the depressive phenotype. This dichotomous response (susceptible vs. resilient) allows the determination as to whether these phenotypes result from a differential chromatin pattern within the nucleus accumbens. That was found to be the case, as the pattern of H3 methylation observed in resilient mice following completion of the defeat regimen was quite different than that of the susceptible mice, and in fact, was more similar to that of the control, untreated mice. A total of 546 genes showed differential levels of H3 methylation in the resilient versus the susceptible mice and these genes were involved in inflammation, redox state, and gene regulation. Nevertheless, despite the general similarity in H3 methylation between the resilient and the control mice, there were still significant differences in methylation status between these two groups. The latter finding suggests that resilience is an 'active process' reflected by unique chromatin modification that occur in response to a stressor. It may be that so-called "resilience genes" impart protection against the development of depression and may account for individual differences in the depressive response to chronic stress. Conversely, there may be other genes that mediate vulnerability to the depression that accompanies chronic stress (i.e., a susceptible phenotype). Moreover, treatment with the anti-depressant, imipramine, produced changes in H3 methylation status that also resembled that observed in the resilient mice, suggesting that this anti-depressant's mechanism of action involves a similar pattern of H3 chromatin modification. However, the fact that a number of genes were still differentially regulated in the resilient versus the imipramine treated mice further indicates that there might be other novel genes responsible for resilience, which can be targeted by anti-depressants (Wilkinson et al., 2009; Feder et al., 2009).

3.10. Stressor duration and epigenetic modification

Stressful life circumstances trigger an integrative adaptive response by the nervous, neuroendocrine, and immune systems. Adaptation in which stability is maintained through change has been termed allostasis. Prolonged and enduring stress, however, can exert a cost on adaptive systems. Allostatic load is the cost of adaptation to unrelenting environmental stress and is manifest by altered regulation of stress response systems. In some cases this may result in changes in brain structure, particularly the hippocampus (McEwen, 2001), as chronic stress decreases hippocampal neurogenesis (Gould et al., 1997) and the complexity of dendritic arborization (Magarinos and McEwen, 1995). It is possible that epigenetic processes contribute to the vulnerability of the hippocampus to prolonged stress (Conrad, 2008; Sapolsky, 2000; Lee et al., 2002; Mcewen et al., 1992). In order to understand whether epigenetic marks presage or signify the transition from allostasis to allostatic load, the hippocampal methylation status was evaluated in response to acute versus chronic restraint stress in the rat. That study showed that that global chromatin re-modeling (i.e., histone methylation) was differentially sensitive to the duration of stress of various durations (methylation marks listed in Table 1). Acute stress produced rapid and large chromatin modifications, demonstrating that these methylation marks are labile in adults; whereas, chromatin modification in response to chronic stress was less marked (Hunter et al., 2009). Rapid changes in hippocampal chromatin re-modeling have also been observed when rats are sub-

jected to novelty, a mild psychological stressor (Chandramohan et al., 2007). It is possible that the observed attenuation of the chromatin response to repeated stress observed by Hunter et al. could relate to the known habituation of the HPA axis, which occurs after repeated exposure to the same stressor (Uchida et al., 2008; Girotti et al., 2006; Kudielka et al., 2009). Conceivably stress-induced chromatin re-modeling in the brain might contribute to the plasticity of the hippocampus to stress, as well as the neuro-pathogenic effects of stress on this brain region. Evaluations, such as these provide mechanistic insight into the potential role of chromatin re-modeling in adaptive versus maladaptive responses of the brain to stressors (Hunter et al., 2009).

3.11. Post-traumatic stress disorder and epigenetics

As described above, ample evidence demonstrates that the psychosocial context influences brain stress response pathways and modifies stress-related behavior. Yet, the question remains as to whether psychosocial stress can lead to epigenetic modifications for genes that regulate immune function. 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 (Segman et al., 2005; Zieker et al., 2007). 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 genes (Uddin et al., 2010). 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 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 interactions (Wrona, 2006). However, given the cross-sectional design, it is not possible to discern whether the distinctive methylation patterns characteristic of PTSD pre-existed before the traumatic exposure and thus represent a biologic vulnerability. Also, the small sample size prevented any analysis of the epigenetic profiles with respect to PTSD subtype and/or phenotypic heterogeneity, while the whole blood epigenetic analyses did not allow determination of cell-specific differences in epigenetic profiles. Nonetheless, these preliminary results suggest that environmental exposure to a traumatic life event induces downstream alterations in immune function by reducing methylation levels of immune-related genes. This may influence the psycho-physiologic manifestations of PTSD.

4. Perspective and conclusion

Epigenetics has engendered a renewed enthusiasm and appreciation for the capacity of the environment to modulate gene expression. It is clear that epigenetic modifications (e.g. those described above) 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. There is no doubt that the genome of an individual provides the blueprint for biological responsivity. However, the epigenome adds another layer ‘on top of the genome’ and serves to modulate gene expression in response to environmental cues. It is likely that the interconnectivity among brain, behavior, and immunity may in fact be directed epigenetically. How, when and where the genetic blueprint will be used in response to a particular stimulus will be a summation of biological networks within the individual. This will include not just DNA recognition events or transcriptional circuits but also the instruction for the use of the blueprint, by epigenetic responsivity that regulates ordered or disordered gene expression patterns. Given the focus of psychoneuroimmunology, epigenetic approaches are particularly appealing and, most importantly, consistent with the concept that brain, behavior and immunity are intimately linked and responsive to environmental context. Intriguing and emerging evidence implicates epigenetic modifications as mediators of psychosocial-biological effects and makes analysis of epigenetics/epigenomics essential to understanding the interconnections among those systems that represent the core of psychoneuroimmunology. Such analysis has been ongoing but now epigenetics offers a new approach, to gain insight into the molecular mechanisms that underlie adaptive, as well as maladaptive, responses to environmental stimuli.

Epigenetic processes operate at the interface between genetics and the environment and have the potential to violate the assumption of independence between genotype and the environment. It is the interplay between the epigenome and the genome that will drive future investigational studies that seek to understand gene-environment interactions. Epigenetic considerations need be kept in mind when interpreting published studies of genome-wide association. If epigenetic changes are sufficiently permanent, these epigenetic modifications will be in linkage disequilibrium with single nucleotide polymorphisms commonly used to interrogate various regions of the genome. Thus, genome-wide association studies need consider both genetic and epigenetic loci and such a requisite is evidenced by the current NIH Epigenomic Project: <http://nihroadmap.nih.gov/epigenomics/initiatives.asp>. The potential impact and possible promise of this project may be the development of interventions that may intersect and modify the influence of the environment upon the genome, since, unlike the DNA sequence, epigenetic modifications appear to be reversible. In particular, trans-generational effects observed with DNA methylation and/or histone modifications (as described above) may endure long after the original environmental stimulus has been removed. An intersecting intervention may circumvent those modifications and improve health. Such interventions may be pharmaceutical or lifestyle-based. With regard to the latter, it has been demonstrated that rats who engage in physical activity (i.e., access to a running wheel) prior to being subjected to stress exhibit resistance to stress-induced chromatin re-modeling within the dentate gyrus (Bilang-Bleuel et al., 2005). In addition to exercise, other unexplored life-style approaches to prevent or reverse epigenetic modification, such as behavior-based interventions, await exploration.

Epigenetics does hold substantial promise to resolve and explain many unsolved questions and issues in modern biology. The focus of this Introduction to the Named Series is upon psychoneuroimmunology and the animal models and human studies presented demonstrate and/or suggest a significant impact of epigenetics upon the brain and behavior. However, there is scant evidence that psychosocial distress, maladaptive behaviors or emotions result in epigenetic modifications that impact immune function; even though significant literature links each of these. However, evidence does exist demonstrating epigenetic influence upon the differentiation of T and B-lymphocytes and upon the fate

and function of individual immune cell populations (Cuddapah et al., 2010; Martino and Prescott, 2010). Further, there is evidence that immunological diseases are in part mediated by and/or modified by epigenetic modification in both animal models and in clinical studies. These epigenetic effects have been demonstrated to be related to forms of histone modification, DNA methylation and/or ncRNA expression for a variety of immune based diseases including; systemic lupus erythematosus and rheumatoid arthritis (Martino and Prescott, 2010; Trenkmann et al., 2010) type 1 diabetes, celiac disease and idiopathic thrombocytopenia (Brooks et al., 2010), multiple sclerosis (Lincoln and Cook, 2009), as well as asthma and allergy (Martino and Prescott, 2010; Handel et al., 2010). There have been suggestions that psychosocial distress may contribute to either the exacerbation or development of these diseases. It is therefore plausible that psychosocial distress may impact the immune system by epigenetic processes, as suggested in the study of individuals with PTSD discussed above (Uddin et al., 2010). Another example is the effect of glucocorticoid upon epigenetic processes that regulate natural killer cell function (Krukowski et al., 2010). That study showed that at least in part, glucocorticoids dysregulate immune function (natural killer cell activity and cytokine production), by modifying chromatin accessibility at promoter regions proximal to immune effector genes. On another front, evolving evidence suggests that epigenetic modification may contribute to major psychoses and depression (Feinberg, 2010; Janssen et al., 2010) or obesity (Handel et al., 2010). However, no data directly demonstrate a linkage among specific epigenetic modifications and these disorders.

The vast majority of research in behavioral epigenetics has evaluated epigenetic modifications in models of early life adversity and focused on such modifications within specific brain regions that regulate stress response pathways or brain plasticity (i.e., neuro-epigenetics). The developing brain is malleable and more readily affected by environmental insult, as significant neurobiological development takes place during early life. Consequently, the developing brain may be more susceptible to environmentally induced epigenetic modification. Yet, it is also likely that other vulnerable periods exist throughout the lifespan, such as during puberty or senescence. Using a lifespan approach to understand vulnerability to epigenetic modification will yield valuable insight regarding when epigenetic modification are more likely to be induced, attenuated or even reversed. Moreover, not all genes may be responsive or susceptible to epigenetic modification. Much of DNA is inaccessible within a cell and may not be responsive to environmentally induced chromatin re-modeling signals (Fraser and Bickmore, 2007). For example, Weaver et al. found that infusion of an HDAC inhibitor into the adult rat hippocampus altered expression of only about 2% of all genes normally expressed (Weaver et al., 2006). It is possible that a relatively restricted pool of adult genes may be dynamically responsive to environmental cues. Certainly, it is unlikely that all genes can be modified through environmentally induced epigenetic processes. Future investigations will be challenged to link epigenetic modifications to functional changes in the expression of specific genes and moreover, to relate these changes to physiological and/or psychological outcomes. It is such linkages that are essential to draw meaningful conclusions as to the biological and health-relevant significance of epigenetic modification.

Further, investigations linking epigenetics and psychoneuroimmunology will require mechanistic studies in animal models that parallel human paradigms. For human investigations, the initial focus will likely be on those human conditions for which psychosocial stress or behavioral factors are already thought to be important risk factors. However human epigenetic investigations will face the existent difficulty of obtaining appropriate tissue specimens for evaluation. It is unclear whether the evaluations of surrogate epigenetic marks in blood, saliva, and/or buccal swabs reflect such

marks in other disease associated tissues. Epigenetic marks are tissue and cell specific, as well as dependent on stage of life and gender. Evaluation of postmortem specimens provides useful data but is also fraught with issues related to tissue preservation and retrospective design limitations. Yet, significant insight regarding environmental-signaled epigenetic modifications in human tissues and cells may be gleaned from the evaluation of surgically removed tissues/organs. Despite these challenges, integrating epigenetics into human investigations in psychoneuroimmunology offers exciting possibilities for the future. Such studies can provide key insight regarding the impact of environment–gene interaction on behavior and vulnerability to disease over the lifespan. Likewise, understanding those epigenetic processes that contribute to a resilient phenotype in human paradigms can lead to new insight about individual differences in response to environmental challenge.

In conclusion, it is likely that epigenetic patterns translate or at least contribute to the relationship between the environment and human health. This possibility opens wide a vista of potential interventions, including behavioral or dietary interventions that can take advantage of the plasticity of the epigenome (Handel et al., 2010). Interventions aimed at manipulating the epigenome are currently underway for many hematological malignancies and many more will follow. Direct manipulation of the epigenome is a real and promising possibility (Feinberg, 2008). Although there is much work to do, epigenetics and the epigenome deserve consideration for any investigation analyzing the linkages among brain, behavior, and immunity. The scope of epigenetics offers ample opportunity to chart new directions in basic, translational, and clinical research within the broad framework of psychoneuroimmunology. Important questions await investigation that can integrate multiple levels of inquiry, from molecular to behavioral. More than 25 years ago, scientists were captivated by the allure of the emerging field of psychoneuroimmunology. At this juncture, it is now clear that psychoneuroimmunology and the emerging field of epigenetics share a common vision that guides discovery, and the fusion of these two fields can only lead to remarkable scientific advancements.

Conflicts of interest

Authors declare that there are no conflicts of interest.

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