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Review

Epigenetics and depression: return of the repressed

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ABSTRACT

Introduction: Epigenetics has recently emerged as a potential mechanism by which adverse environmental stimuli can result in persistent changes in gene expression. Epigenetic mechanisms function alongside the DNA sequence to modulate gene expression and ultimately influence protein production. The current review provides an introduction and overview of epigenetics with a particular focus on preclinical and clinical studies relevant to major depressive disorder (MDD).
Methods: PubMed and Web of Science databases were interrogated from January 1995 up to December 2012 using combinations of search terms, including "epigenetic", "microRNA" and "DNA methylation" cross referenced with "depression", "early life stress" and "antidepressant".
Results: There is an association between adverse environmental stimuli, such as early life stress, and epigenetic modification of gene expression. Epigenetic changes have been reported in humans with MDD and may serve as biomarkers to improve diagnosis. Antidepressant treatments appear to reverse or initiate compensatory epigenetic alterations that may be relevant to their mechanism of action.
Limitations: As a narrative review, the current report was interpretive and qualitative in nature.
Conclusion: Epigenetic modification of gene expression provides a mechanism for understanding the link between long-term effects of adverse life events and the changes in gene expression that are associated with depression. Although still a developing field, in the future, epigenetic modifications of gene expression may provide novel biomarkers to predict future susceptibility and/or onset of MDD, improve diagnosis, and aid in the development of epigenetics-based therapies for depression.

Contents

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1. Introduction

The causes of major depressive disorder (MDD) remain unclear, posing a major gap in our knowledge and an obstacle to improving therapies. Although the heritability of MDD is between 31–42% (Edvardsen et al., 2009; Middeldorp et al., 2005), human genome-wide association studies (GWAS) have failed to demonstrate reproducible gene loci that contribute to the disease (Wray et al., 2012). Furthermore, the high discordance rate of 50% between monozygotic twins suggests factors other than genetics contribute to disease genesis (Haque et al., 2009). Environmental stressors have been identified as risk factors for depression, although individual variability in the susceptibility to adverse environmental stimuli has been reported. Since MDD cannot be attributed to a single genetic mutation or exposure to one specific environmental cue, it has been proposed that MDD arises from genetic variation which is moderated by external influences (Kendler et al., 2002, 2006).

Epigenetics has recently emerged as a potential mechanism by which adverse environmental stimuli, such as stress encountered in early life, can result in stable, persistent alterations in gene expression (Onishchenko et al., 2008; Roth et al., 2009). The prefix "epi" means above or alongside and the term epigenetics refers to modulatory mechanisms that operate above or alongside the nucleotide bases that comprise a gene's deoxyribonucleic acid (DNA) sequence. Epigenetic mechanisms are thus responsible for alterations in the expression and function of a gene that are not encoded by the gene's DNA sequence itself. Epigenetic modifications in gene expression exert lasting changes without altering the genetic code (Schroeder et al., 2012). They are modifiable by environmental factors and are also potentially heritable (Franklin et al., 2010; Roth et al., 2009). This review aims to summarise current evidence of the role that epigenetic mechanisms, such as DNA methylation, histone acetylation and microRNA dysregulation, may play in depression, as well as what future directions this field may take.

2. Methods

Although the field of epigenetics is well developed in cancer and developmental biology, evidence for epigenetic modification of gene expression in mental disorders is only now emerging (Schroeder et al., 2012). Epigenetics offers an exciting new avenue for improving diagnosis and developing novel therapies and biomarkers for MDD. Given the novelty of the field and therefore the reasonably small number of relevant studies, we have conducted a narrative review of preclinical and clinical investigations. PubMed and Web of Science databases were interrogated from January 1995 up to December 2012 using combinations of search terms, including "epigenetic", "microRNA" and "DNA methylation" cross referenced with "depression", "early life stress" and "antidepressant". A total of 1576 potentially relevant articles were identified and 72 records removed when they did not meet the criteria of publication in a peer-reviewed journal and in the English language. Duplicate records were removed ($n=371$). A total of 1133 titles were screened followed by 251 abstracts. After abstract screening, and also review of references from identified articles, a total of 77 full text papers were then reviewed for the current article. Our aims are to provide a scientific background to epigenetics and inform academic and clinical psychiatrists, and those in related disciplines, about epigenetics research in depression.

3. Epigenetic mechanisms modulating gene expression

3.1. Introduction to gene expression and protein synthesis

Genomic DNA constitutes the total genetic information of an organism and is made up of four different nucleotide bases – guanine (G), cytosine (C), arginine (A) and thymine (T) – arranged to form a DNA double helix. The double helix consists of two chains of nucleotide bases organised in a specific order or "sequence" around a sugar–phosphate backbone. Bases that comprise the sequences are arranged in a complementary manner and attached to the backbone sugars to form base pairs such that C is found opposite to G and T is found opposite to A (Fig. 1). Genomic DNA comprises regions of gene sequences, which ultimately give rise to proteins, along with other non-protein coding regions that are important in the control of gene expression or have an unknown function. Indeed, this non-coding DNA, previously considered to be "junk" DNA, is now attracting great interest. The Encyclopedia of DNA Elements (ENCODE) project, for example, has enabled researchers to assign biochemical functions for 80% of the human genome, particularly in non-protein coding regions that contain regulatory elements important in the control of gene expression (Encode Project Consortium, 2012).

Gene expression is the synthesis of a gene product (e.g. a protein) from the DNA sequence of a particular gene. Epigenetic factors can regulate gene expression at a number of levels (Fig. 1). During protein synthesis, first a gene is expressed within the cell nucleus as a ribonucleic acid (RNA) copy of its genomic DNA sequence, known as messenger RNA (mRNA) (Clancy and Brown, 2008). mRNA synthesis is activated by the binding of specific enzymes, known as mRNA transcription initiating factors, to a regulatory region of the DNA sequence called the promoter region (Fig. 1). It is at this transcriptional level that two modes of epigenetic regulation of gene expression may exert an effect in the form of chromatin remodelling and DNA methylation.

Genomic DNA is packaged as chromatin within the cell nucleus (Fig. 1). Chromatin can be remodelled and exists in open or closed functional states, which regulate enzymatic accessibility (Fig. 2B). When chromatin is in its open state, genomic DNA is accessible to the mRNA transcription initiating factors and facilitates gene expression. Chromatin in its closed state limits DNA accessibility for mRNA transcription initiating factors, thus suppressing gene expression. The mechanisms underlying chromatin remodelling are discussed in more detail below (Section 3.3).

DNA methylation is the second epigenetic factor that may have an effect on gene expression at the transcriptional level. It can suppress gene expression directly and indirectly by preventing the binding of enzymes important in RNA synthesis at the promoter region (Figs. 1 and 2D) (Hervouet et al., 2009; Szyf, 2006; Weber and Schubeler, 2007) and is discussed in more detail below (Section 3.2).

Provided that transcription factor binding is unhindered by the epigenetic modifications described above, the genomic DNA is then unwound and an enzyme known as RNA polymerase makes a

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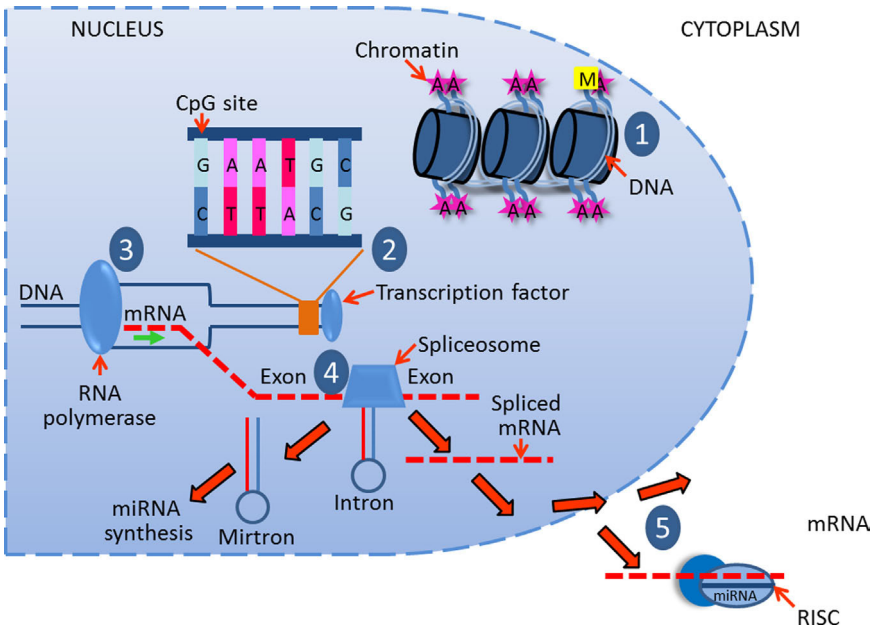

Fig. 1. Overview of gene expression and protein synthesis. (1) Within the cell nucleus, genomic DNA (shown as thin, pale blue/gray strands) is packaged as chromatin wrapped around a histone core. Epigenetic regulation of gene expression arises through the control of chromatin activation status. Active, open chromatin promotes gene expression by allowing access of mRNA transcription initiating factors to the genomic DNA. However, chromatin in its closed state suppresses gene expression by hindering transcription factor binding. The chromatin is shown in an open state. (2) Messenger RNA (mRNA) synthesis is initiated at the promoter region of a gene (represented by orange/black box) by the binding of enzymes known as mRNA transcription initiating factors (small blue/gray oval). The DNA sequence contained within the box is expanded above to show an example of the complementary arrangement of the four nucleotide bases – guanine (G), cytosine (C), arginine (A) and thymine (T) – that comprise the DNA double helix. Promoters usually contain multiple cytosine–guanine nucleotide pairings known as cytosine–phosphate–guanine dinucleotide (CpG) sites (example indicated by arrow). A second epigenetic mechanism known as DNA methylation can have an effect at the transcriptional level. DNA methylation involves the addition of methyl groups at CpG sites within the promoter. It can suppress gene expression directly and indirectly by preventing the binding of enzymes important in RNA synthesis at the promoter region. The DNA sequence shown is unmethylated therefore mRNA transcription can proceed. (3) After transcription is initiated, an enyzme called RNA polymerase makes a mRNA copy (broken red/gray line) of the DNA sequence. The direction of mRNA synthesis is shown by the white/green arrow. (4) Non-protein coding regions known as introns are removed from the mRNA sequence by a collection of enyzmes known as the spliceosome. Some introns may serve as templates for the synthesis of microRNAs (miRNAs) and are known as mirtrons. The protein coding exons are then spliced together and the mRNA is transported from the nucleus to the cytoplasm. (5) The mRNA is translated to protein by protein/enzyme complexes called ribosomes. Epigenetic modulation of gene expression may take place at the translational level due to the activity of miRNAs loaded into the RNA-induced silencing complex (RISC), which can suppress mRNA translation to protein. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

mRNA copy of the DNA by creating a chain of nucleotides specified by the DNA gene sequence. Non-protein coding regions called introns are first removed from the synthesised mRNA by a process known as splicing. The processed mRNA is then transported outside the nucleus. It is at this point that microRNAs (miRNAs), another group of epigenetic modulators, may have an effect on gene expression. At this stage post-transcription, the mRNA sequence is usually translated into protein by complexes known as ribosomes. However, this process may be hindered by the presence of miRNAs thus leading to a decline in protein synthesis (discussed in more detail below in Section 3.3.2, see Figs. 1 and 3). Translation of mRNA to protein by ribosomes involves the linking of amino acids, the basic building blocks of proteins found within the cytoplasm, to form an amino acid chain. The amino acids that comprise the protein are determined by the mRNA sequence. Post-translation, the amino acid chain then undergoes structural changes and folds in a specific manner to give rise to a protein.

3.2. DNA methylation

The most studied epigenetic modification to date is DNA methylation. Gene promoter regions usually contain multiple cytosine–guanine nucleotide pairings distributed repeatedly throughout, known as cytosine–phosphate-guanine dinucleotide (CpG) sites (Fig. 2D). DNA methylation generally entails the addition of a methyl group at CpG sites within the promoter region of a target gene by enzymes known as DNA methyltransferases (Fig. 2D) (Szyf, 2006; Weber and Schubeler, 2007). Methylation of CpG sites can suppress gene expression directly by preventing the binding of enzymes important in RNA synthesis at the promoter region (Hervouet et al., 2009; Szyf, 2006; Weber and Schubeler, 2007). CpG methylation can also hinder gene expression indirectly by recruiting enzymes and other proteins that promote gene-suppressive chromatin remodelling (discussed in detail below), ultimately leading to a decrease in protein production. Originally it was thought that the pattern of DNA methylation was laid down before birth and was irreversible in later life. Evidence has now emerged though that DNA methylation is responsive to, and alterable by, environmental signals (Weber and Schubeler, 2007).

3.3. Histone acetylation and methylation

To allow the storage of highly condensed genomic information within the cell nucleus, genomic DNA is organised in the form of chromatin. The basic unit of chromatin is called the nucleosome and it consists of approximately 147 nucleotide base pairs (bp) of negatively charged DNA sequence wrapped around a core of histone proteins (Fig. 2A) (Hayes and Hansen, 2001; Khorasanizadeh, 2004). Histones make up the major protein constituents of the nucleus. The nucleosome histone core contains two copies of four histone proteins: H2A, H2B, H3 and H4. Each core histone protein possesses an outward facing tail consisting of amino acids such as lysine (Fig. 2A). A fifth histone protein, H1, acts as a linker between nucleosome units.

Modifications, such as the addition of acetyl or methyl groups at lysine residues on the histone tails (Fig. 2B and C), can change

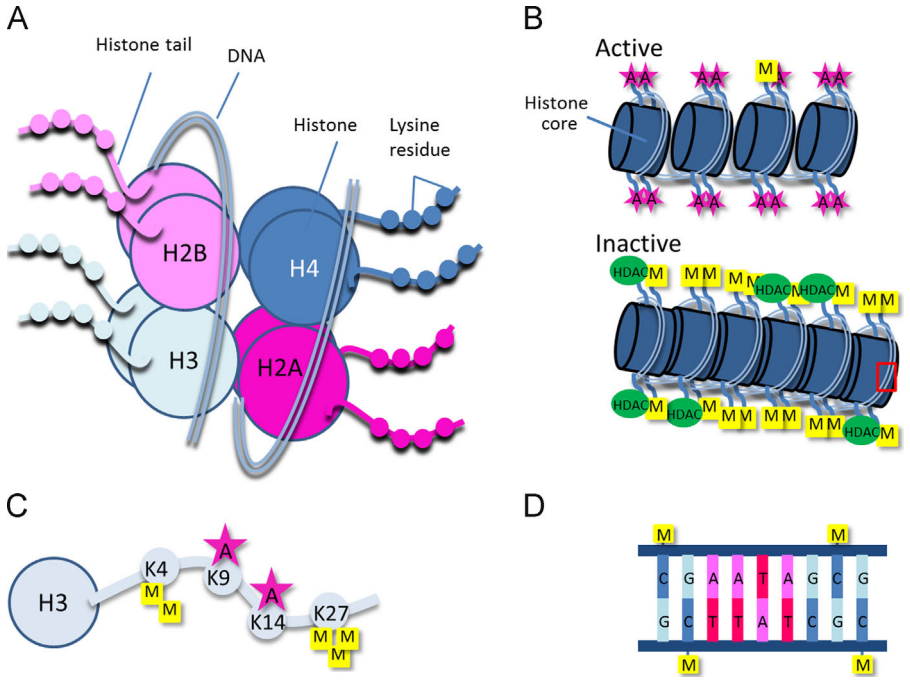

Fig. 2. Histone modifications. (A) A representation of the nucleosome showing double stranded DNA wrapped around the core comprising two copies of histones H2A, H2B, H3 and H4. Outward facing histone tails with lysine residues are shown. (B) Chromatin in its active open state and closed inactive state is shown. Acetylation of histone tails is associated with active chromatin. Acetyl (A) groups are represented by light grey/pink stars. Histone deacetylase (HDAC) enzymes, represented by the dark grey/green circles, remove acetyl groups and are associated with inactive chromatin. Methyl groups are represented by boxed Ms. The boxed region is expanded in D. (C) Histone 3 (H3) showing acetylated lysine (K) residues K9 and K14. Lysine acetylation generally promotes gene expression. Lysine methylation can promote or suppress gene expression depending on the lysine residue and the number of methyl groups added. The presence of two methyl groups at K4 and three methyl groups at K27 has been shown to promote and suppress gene expression, respectively. (D) Expansion of boxed region in B showing methylated genomic DNA which is often associated with inactive chromatin. The addition of methyl groups, shown by the boxed Ms, to cytosine–phosphate–guanine dinucleotide (CpG) sites within a gene promoter region can prevent the binding of transcription factors and hinder protein synthesis. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

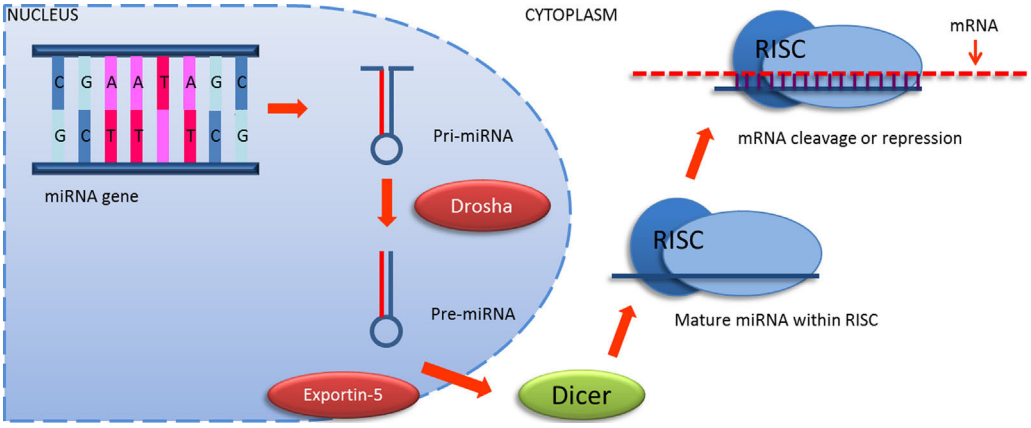

Fig. 3. miRNA biogenesis. Mature microRNAs (miRNAs) are formed following a series of steps involving RNA transcription to generate a primary miRNA (pri-miRNA). This is followed by RNase modification by Drosha to form a precursor miRNA (pre-miRNA) which is exported from the nucleus to the cytoplasm by Exportin-5. Pre-miRNA is cleaved by Dicer to form a 22 base pair duplex. From the duplex, one miRNA is then preferentially loaded into a *RNA-induced silencing complex* (*RISC*) where it binds to a target messenger RNA (mRNA) transcript, preventing translation.

the interaction between the genomic DNA and histone core, and are involved in control of gene expression (Berger, 2007; Hayes and Hansen, 2001). Chromatin enters its active state after addition of acetyl groups (hyperacetylation) to the histone tail by enzymes called histone acetyltransferases (HATs). This in turn promotes unfolding of the histone unit and decondensation of chromatin (Fig. 2B), allowing access of mRNA transcription initiating factors to the genomic DNA and promotes gene expression (Crosio et al., 2003; Eberharter and Becker, 2002; Grunstein, 1997; Hebbes et al., 1988; Korzus et al., 2004). On the other hand, removal of acetyl groups by enzymes known as histone deacetylases (HDACs) causes chromatin condensation (Fig. 2B) and decreases protein production (Grunstein, 1997; Pile et al., 2003). Alterations in the acetylation pattern of lysine residues comprising amino acid tails of histones 3 (Fig. 2C) and 4 have been implicated in depression (Iga et al., 2007; Levine et al., 2012; Onishchenko et al., 2008; Tsankova et al., 2006) and antidepressant treatment (Belzeaux et al., 2012; Dyrvig et al., 2012; Tsankova et al., 2006, 2004).

Alternatively to acetyl groups, methyl groups can be added to lysine residues on the histone tail (Fig. 2C). Chromatin activation status then depends on the particular lysine residue methylated as well as the number of methyl groups added to the residue (Fig. 2C)

(Dillon et al., 2005; Morgunkova and Barlev, 2006). The addition of three methyl groups at lysine 27 to the amino acid tail of histone 3 is associated, for example, with silencing of gene transcription in depressed patients (Lopez et al., 2013) and in an animal model of depression (Onishchenko et al., 2008). On the other hand, the addition of two methyl groups to lysine 4 of histone 3 has been shown to promote gene expression in a depression model following antidepressant treatment (Tsankova et al., 2006).

Chromatin activation status and DNA methylation often work in concert to control gene expression. Chromatin status can usually be correlated with the DNA methylation pattern of a gene. Active chromatin is partnered with unmethylated DNA whereas inactive chromatin is associated with methylated DNA (Szyf, 2006; Tachibana et al., 2008).

3.3.1. *microRNAs*

In the past 10 years, miRNAs have emerged as another important group of epigenetic modulators of gene expression. They are endogenous non-protein coding RNA molecules of approximately 21–23 nucleotide bases that bind to complementary regions at target mRNAs and regulate mRNA translation to protein (Kolshus et al., 2013). Over 1500 mature miRNA sequences have been reported in the human to date (Kozomara and Griffiths-Jones, 2011) and it appears that over 50% of mammalian mRNA species are potential targets for miRNAs (Friedman et al., 2009). A single mRNA may be regulated by multiple miRNAs and, conversely, some miRNAs have the potential to target hundreds of mRNAs. Typically, miRNAs suppress target gene expression; however, reciprocal relationships, whereby mRNA targets can control the level and function of miRNAs, are emerging (Pasquinelli, 2012). miRNAs are expressed during development and in adulthood, with the expression of some subsets being organ-specific (Sempere et al., 2004) and region-specific within organs such as the brain (Olsen et al., 2009). Functional studies indicate that miRNAs are involved in the control of many cellular processes including neurogenesis, synaptic plasticity, cell fate decision, and apoptosis (Bredy et al., 2011; Kloosterman and Plasterk, 2006; Luikart et al., 2012; Magill et al., 2010; Saba and Schratt, 2010). It follows therefore that dysregulation in their expression has been linked with human pathologies such as major depressive disorder, schizophrenia and cancer (Esteller, 2011; Im and Kenny, 2012).

3.3.2. *microRNA biogenesis and regulation of protein synthesis*

Biogenesis of miRNAs can occur through various different pathways (see Figs. 1 and 3) (Havens et al., 2012). In the canonical miRNA biogenesis pathway, primary miRNAs (pri-miRNA) are enzymatically transcribed from independent miRNA genes located within the genomic DNA (Fig. 3). Within the nucleus, a processing complex made up of multiple proteins then removes regions of the pri-miRNA to generate the double-stranded precursor miRNA (pre-miRNA), which is generally between 70 and 110 nucleotides in length. Pre-miRNAs can also be derived via alternative means. They can be directly transcribed, for example, from introns and are known as mirtrons (Fig. 1) (Chong et al., 2010; Krol et al., 2010). Following synthesis, pre-miRNAs are then exported from the nucleus to the cytoplasm (Yi et al., 2003), where the pre-miRNA is processed to form a 22 bp molecule made up of two complementary RNA strands (Fig. 3) (Chendrimada et al., 2005). One strand from the duplex is then preferentially loaded into a protein complex called the RNA-induced silencing complex (RISC) (Kawamata and Tomari, 2010). Once loaded into the RISC, the miRNA guides the complex to the target mRNA transcripts (Figs. 1 and 3). Depending on the number of sequence mismatches between the miRNA and its mRNA target, miRNA induced regulation of the mRNA then occurs due to enzymatic degradation of the target or prevention of mRNA translational to protein due to steric hindrance of protein synthesis machinery (Carthew and Sontheimer, 2009; Krol et al., 2010; Wu et al., 2006).

4. Epigenetics and environmental risk factors for depression

Epigenetics provides a potential mechanism by which adverse stimuli can result in lasting changes in gene expression. Preclinical and clinical studies have recently focused on the epigenetic effects of various environmental stressors that have been identified as risk factors for poor mental health outcome. Epigenetic modifications of gene expression have been reported in rodent models after acute stress (Fuchikami et al., 2009), chronic stress (Sterrenburg et al., 2011; Tsankova et al., 2006; Uchida et al., 2011; Wilkinson et al., 2009), fear conditioning (Bredy et al., 2007; Mizuno et al., 2012) and in a rat model of post-traumatic stress disorder (Roth et al., 2011). In addition to these studies, the epigenetic changes elicited by exposure to early life stress (ELS) have been a major focus of research into the epigenetic mechanisms involved in the pathogenesis of MDD in rodent models (Table 1) and humans. Evidence suggests that adverse external stimuli encountered in early life can affect adult behaviour and predispose individuals to lifelong health problems, including increased risk of mental illnesses such as depression (Heim and Binder, 2012; Markham and Koenig, 2011; Talge et al., 2007). Epigenetic mechanisms such as DNA methylation, histone modifications and dysregulation of microRNA expression represent plausible means by which ELS may cause lifelong changes in gene expression.

4.1. *Epigenetics and early life stress (ELS)*

In animal models of depression, evidence exists for an association between ELS and epigenetic modulation of a range of genes previously implicated in depression. Alterations in DNA methylation and histone modifications at promoters of genes, such as brain derived neurotrophic factor (*Bdnf*), as well as changes in miRNA expression patterns, have been reported in the rodent brain after exposure to prenatal and/or perinatal stress (see Table 1 for a summary). Exposure to methylmercury from gestational day 7 to postnatal day 7, for example, has been shown to result in depressive-like behaviour in mice (Onishchenko et al., 2008). Methylmercury-exposed pups show a decrease in hippocampal *Bdnf* mRNA that is accompanied by increases in gene-suppressing methylation of DNA and histone 3 at lysine 27, and a decrease in expression-promoting acetylation of histone 3 at a *Bdnf* promoter region. Postnatal stressors such as maternal separation and/or exposure to low levels of maternal care or attention have also been linked with changes in DNA methylation and chromatin activation status of various genes expressed in the rodent brain (Table 1). Maltreatment of rat pups by stressed caretakers in early development (between postnatal days 1 and 7) resulted in decreased *Bdnf* mRNA expression in the prefrontal cortex that was accompanied by an increase in expression-suppressing DNA methylation at *Bdnf* promoter regions in adulthood, an effect that could be reversed by the application of the DNA methyltransferase inhibitor, zebularine (Roth et al., 2009).

Altered DNA methylation patterns of genes implicated in depression such as *BDNF* (Toledo-Rodriguez et al., 2010), the glucocorticoid receptor (Mulligan et al., 2012; Oberlander et al., 2008; Radtke et al., 2011) and serotonin transporter (Devlin et al., 2010), have been reported in children following exposure of mothers to prenatal stressors such as smoking, maternal depression, partner violence and war. Adversities experienced in early childhood have also been

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Table 1
Studies of epigenetic modification of gene expression following exposure to early life stress in rodent models.

Reference	Species/ strain	Stressor	Region/ age assessed	Epigenetic modification	Molecular and behavioural changes
Bai et al. (2012)	SD rats	MS from PD 1-13	HC/ > PD 91	↑miR16	↓Total BDNF mRNA inversely correlated with miR16 expression Depression-like behaviour
Chen et al. (2012)	SD rats	MS from PD 2-13	PVN and AMY/PD 60	↓DNA methylation of CRH in PVN	↑Heteronuclear RNA (mRNA precursor) for CRH following acute stress ↑Plasma CORT in response to stress
Jiao et al. (in press)	BALB/cJ &C57BL/ 6J mice	Strain-specific effects of gestational environment and maternal care	HC/PD 84-112	↑DNA methylation for CRP in BALB/cJ -gestated mice, no effect of maternal care on CRP DNA methylation	↑CRP mRNA in C57BL/6J gestated mice No effect of maternal care on CRP expression C57BL/6J gestated mice showed increased depression-like behaviour
Levine et al. (2012)	BALB/cJ &C57BL/ 6J mice	Strain-specific effects of MS from PD 2-15	Cortex/ PD 21, 28 and 60	↑H4K12 acetylation in Balb/cJ mice after MS	↓HDAC mRNA in Balb/cJ mice after MS Depression-like behaviour in Balb/cJ mice after MS
Matrisciano et al. (2013)	ND4 mice	Prenatal restraint stress	FC/PD 60	↑DNA methylation of GAD67 and reelin	↑GAD67 and reelin protein, ↑mRNA expression and protein levels of DNA methyltransferase enzymes Hyperactivity and deficits in social interaction, PPI and fear conditioning
Mueller and Bale (2008)	C57BL/ 6:129 mice	Chronic variable PS from GD 1-7	HYP, AMY, HC/PD 120	DNA methylation of CRH↓in HYP and AMY, and of GR↑in HYP	↑CRH mRNA in HYP and AMY, ↓GR in HC Depression-like behaviour
Murgatroyd et al. (2009)	C57BL/ 6N mice	MS from PD 1-10	PVN /PD 42, 84 and 1 year	↓DNA methylation of arginine vasopressin	↑Arginine vasopressin mRNA ↑Serum CORT response to stress and memory deficits
Mychasiuk et al. (2011)	LE rats	Mild or high PS from GD12-16	FC, HC/ PD 21	Global DNA methylation↑with mild PS and↓with high PS	Mild PS=↓locomotion High PS=↑locomotion
Novikova et al. (2008)	CD1 mice	Maternal cocaine (20 mg/kg) from GD8-19	HC/PD 3 and 30	Global DNA methylation—↓PD3 and ↑PD 30	Expression of selected genes was linked to DNA methylation
Onishchenko et al. (2008)	C57BL/ 6/Bk1 mice	Dams exposed to methylmercury from GD7-PD7	HC/PD 84 and 14 months	↑H3K27 tri-methylation, ↓H3K9K14 acetylation and↑DNA methylation at BDNF promoter	↓Total BDNF mRNA Depression-like behaviour
Roth et al. (2009)	LE rats	Abusive caretaker exposure from PD 1-7	FC/PD 8, 30 and 90	↑DNA methylation at BDNF promoters	↓Total BDNF mRNA
Uchida et al. (2010)	SD rats	MS from PD 2-14	FC/PD 14 and 58-60	PD14:↑in precursor miR-132, -124-1, -9-1, -9-3, -212, and -29a and ↑in mature miR132, -124, miR9 and -29a; PD 58-60:↑precursor miR-124, -212 and -132	↑mRNA for GluR2, NMDA receptor 1 subunit, CRH, CAM kinase II, cell adhesion molecule L1, adenylate cyclase 5, 5HT1aR and voltage-gated potassium channel subunit Kv3.1, ↓mRNA for neuron navigator 1 MS rats showed a greater HPA axis response to stress than controls.
Weaver et al. (2004)	LE rats	Effects of high and low levels of maternal care PD 1-7	HC/PD 90	↑DNA methylation and↓H3K9 acetylation of GR after low level maternal care	↓GR protein ↑Plasma CORT in response to stress

Abbreviations: 5HT1a-serotonin 5HT1a receptor, AMY-amygdala, BDNF-brain derived neurotrophic factor, CAM-calcium/calmodulin-dependent protein, CORT-corticosterone, CRH-corticotropin releasing hormone, CRP-calcitonin gene-related peptide, FC-frontal cortex, GAD67-Glutamate decarboxylase 67, GD-gestational day, GluR2-AMPA glutamate receptor 2 subunit, GR-glucocorticoid receptor, H-histone, HC-hippocampus, HDAC-histone deacetylase enzyme, HPA-hypothalamic-pituitary-adrenal, HYP-hypothalamus, K-lysine, mRNA-messenger RNA, LE-Long Evans, MS-maternal separation, NC-no change, NE-not examined, PD-postnatal day, PPI-prepulse inhibition, PS-prenatal stress, PVN-paraventricular nucleus of hypothalamus, SD-Sprague Dawley.

linked to epigenetic modulation of gene expression. Variations in DNA methylation status of the glucocorticoid receptor and ribosomal RNA promoter have been reported in the postmortem brains of suicide victims with a history of childhood abuse (McGowan et al., 2009, 2008). Additionally, early life poverty was associated with DNA methylation in an analysis of >14,000 genes in peripheral blood mononuclear cells in a community-based cohort stratified for early-life socioeconomic status (Lam et al., 2012).

Taken together, these studies indicate that exposure to a range of pre- and post-natal stressors are associated with epigenetic modifications in depression-related genes in both rodent models of ELS (Table 1) and in humans. Epigenetics may thus be one of the underlying mechanisms by which ELS exerts long-term effects on gene expression in individuals and their offspring. Epidemiological studies have shown that the offspring of individuals exposed to ELS may display behavioural/developmental disturbances similar to their parent even if they themselves have not experienced the trauma. Furthermore, these disturbances can be passed on to the subsequent generations (Brand et al., 2010; Harper, 2005; Kim et al., 2009). Persistent epigenetic modification of gene expression induced by an environmental stimulus, e.g. ELS, has been suggested as one of the mechanisms underlying transgenerational phenotypic transmission (Harper, 2005). Preclinical research in rodent models supports this hypothesis (Franklin et al., 2010; Morgan and Bale, 2011; Roth et al., 2009). However, a considerable amount of further study is required to fully understand the range of genes epigenetically regulated by exposure to early life stress and the implications for future generations.

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5. Epigenetics and major depressive disorder

Altered DNA methylation and chromatin activation status have been reported in humans with depression (see Table 2). Researchers have examined genome-wide DNA methylation patterns as well as epigenetic modification of individual depression-related genes such as the γ-aminobutyric acid (GABA) receptor subunits, synapsins and serotonin transporter as well as mRNA expression of enzymes involved in epigenetic modifications in patients with MDD (Table 2). Given the alterations in BDNF and its receptor Trk B observed in individuals with MDD (Dwivedi et al., 2003; Kim et al., 2007; Lee and Kim, 2010; Thompson Ray et al., 2011), particular attention has focused on epigenetic modification of the BDNF pathway in depression (Boulle et al., 2012). Alterations in DNA methylation of promoter regions of *BDNF* have been reported in the blood of patients with MDD (Fuchikami et al., 2011). Keller et al. (2010) observed an increase in DNA methylation at a *BDNF* promoter that was associated with decreased *BDNF* mRNA levels in Wernicke's area in brains of suicide victims, some of whom had a diagnosis of MDD (Keller et al., 2010). In the same cohort however, mRNA expression and DNA methylation of the BDNF receptor, *Trk B*, and its truncated form, *Trk B-T1*, in Wernicke's area did not correlate with suicidal behavior (Keller et al., 2011). On the other hand, decreased *Trk B-T1* mRNA in the frontal cortex was associated with increased methylation of CpG sites (Ernst et al., 2009b) and histone 3 at lysine 27 (Ernst et al., 2009a) in the promoter region of *Trk B-T1* in suicide completers, some of whom had MDD.

The few studies conducted to date in human subjects also provide evidence for alterations in miRNA directed translational regulation of coded proteins in major depression (Table 2). Recently, for example, Smalheiser et al. (2012) found that global miRNA expression was decreased and reorganised in a depressed suicide cohort compared to controls. The expression levels of 365 miRNAs were compared in the prefrontal cortex (Brodmann area 9) in 18 antidepressant-free depressed suicide subjects with 17 controls. The authors observed a global decrease in miRNA expression in the suicide group and identified 21 miRNAs that showed a statistically significant decrease of 30% or more. Approximately half of the downregulated miRNAs shared putative mRNA targets, including some that have been implicated in depression such as vascular endothelial growth factor and B-cell-CLL/lymphoma 2, and in the epigenetic control of gene expression including DNA methyltransferase 3b (Smalheiser et al., 2012). miRNAs exert their influence by binding to target mRNAs and ultimately suppressing protein synthesis according to sequence complementarity. Polymorphisms, which are naturally occurring variations in nucleotide sequences, have the potential to affect miRNA binding potential, and ultimately, miRNA-directed regulation of protein synthesis. In addition to changes in miRNA levels, polymorphisms in miRNAs and their precursors, their target mRNAs and in genes that regulate miRNA biogenesis have also been reported in MDD (Table 2).

Collectively, these studies suggest that alterations in DNA methylation, histone modifications and miRNA expression play an important role in dysregulation of gene expression in MDD. Clearly more research in epigenetic alteration of gene expression in individuals with depression is required, particularly into the role of chromatin activation status and miRNA changes in MDD given the paucity of literature on these topics. With further understanding, epigenetic modifications may serve as potential biomarkers to improve diagnosis and better understand the pathophysiology of MDD.

6. Epigenetics and antidepressant treatments

As well as its role in the pathogenesis of depression, research in animal models and humans suggests that epigenetic modulation of gene expression is also involved in the mechanisms of action of antidepressants (see Tables 3 and 4). Alterations in DNA

Table 2
Clinical studies of epigenetic modifications in mood disorders.

Reference	Tissue	Diagnosis	Epigenetic modification, molecular changes and other outcomes
Cruceanu et al. (2013)	Prefrontal cortex (BA 10)	MDD or BP	↑H3K4 methylation at *SYN1* promoter in MDD ↑mRNA for *SYN1a* in BP and MDD ↑mRNA for *SYN1b* in MDD only ↑H3K4 methylation at *SYN2* promoter in BP ↑mRNA for *SYN2a* in BP and ↑mRNA for *SYN2b* in MDD
Ernst et al. (2009a), Ernst et al. (2009b)	Frontal cortex	Suicide completers, some of whom had MDD	↑DNA and H3K27 methylation of *Trk B-T1* ↓Trk B-T1 mRNA
Fuchikami et al. (2011)	Blood	MDD	Altered BDNF DNA methylation pattern in MDD
He et al. (2012)	Blood	MDD	SNPs in microRNA processing genes in DGCR8 and AGO1 DGCR8 SNP associated with ↑suicide risk and improved antidepressant response and AGO1 SNP associated with ↓suicide risk
Iga et al. (2007)	Blood	MDD	↑HDAC 5 mRNA
Keller et al. (2011), Keller et al. (2010)	Wernicke's area	Suicide completers, some of whom had MDD	↑DNA methylation and ↓mRNA for BDNF but no correlation between *Trk B* and *Trk B-T1* DNA methylation and suicide
Philibert et al. (2008)	Lymphoblast cell lines	MDD	Females showed higher levels of DNA methylation of SERT compared to males Trend for association between ↑SERT DNA methylation and MDD
Poulter et al. (2008)	Frontal cortex	Suicide completers with MDD	↑DNA methylation of $GABA_A$ receptor subunit α1
Rahman et al. (2010)	Buccal epithelial cells	MDD or BP	Association between a polymorphism in P2X7 purinergic receptor gene and target site for miR-625 and -1302
Saus et al. (2010)	Blood	MDD	Association between a polymorphism in the circadian clock modulator pre-miR-182 and late insomnia
Smalheiser et al. (2012)	Prefrontal cortex (BA 9)	Suicide completers with MDD	Global ↓and reorganisation in miRNA expression in MDD ↓21 miRNAs
Uddin et al. (2011)	Blood	MDD	Altered DNA methylation pattern in MDD
Xu et al. (2010)	Blood	MDD	Polymorphism in pre-miR30e associated with MDD and difficulties with the speed of perception and processing of auditory stimuli

Abbreviations: AGO1, Argonaute 1 regulatory protein; BA-Brodmann area; BDNF, brain derived neurotrophic factor; BP, bipolar disorder; DGCR8, DiGeorge syndrome critical region gene 8; H-Histone; HDAC, histone deacetylase; K, lysine; MDD, major depressive disorder; mRNA, messenger RNA; NE, not examined; SERT, serotonin transporter; SNPs, single nucleotide polymorphism; SYN, synapsin; Trk B-T1, truncated form of tyrosine kinase B receptor.

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methylation and chromatin activation status have been reported after antidepressant administration in preclinical and clinical investigations. In addition, antidepressants also appear to act by modifying miRNA expression, as evidenced by in vitro studies and research in animal models and humans.

Electroconvulsive therapy (ECT) is the most acutely effective treatment available for severe depression (Eranti et al., 2007; UK Ect Review Group, 2003). The precise mechanisms of action of ECT remain unknown but evidence in animal models suggests that treatment with ECS (electroconvulsive stimulation), the animal model equivalent of ECT, results in epigenetic modification of gene expression (Table 3). Tsankova et al. (2004), for example, examined histone modifications of *Bdnf* at 30 min, two hours and 24 h after acute and chronic ECS in the rat brain hippocampus. Their results indicated that histone modifications controlling the expression of *Bdnf* after ECS administration are dependent on treatment duration, post-treatment time and gene promoter region. ECS also results in histone modifications and accompanying alterations in mRNA for *CREB and c-Fos* (Dyrvig et al., 2012; Tsankova et al., 2004) as well as an increase in DNA methylation at the *Arc* promoter (Dyrvig et al., 2012). Taken together, these findings imply that epigenetic modulation of gene expression is important

Table 3
Antidepressant treatment associated epigenetic modifications in in vitro and preclinical studies.

Reference	Species	Tissue	Treatment	Treatment associated epigenetic modification, molecular changes and other outcomes
Angelucci et al. (2011)	Human	Cell line	Paroxetine	Rapid ↑in *BDNF* mRNA expression and protein synthesis followed by ↑in miR-30a-5p, a BDNF inhibitor, at six and 12 h after treatment
Baudry et al. (2010), Launay et al. (2011)	Mouse	RN LC HC	Fluoxetine applied at RN for 3 days	↓miR-16 and serotonin transporter in RN ↓miR-16 and↑serotonin transporter in LC and HC Anti-miR-16 applied at HC results in anti-depressant behaviour
Dyrvig et al. (2012)	SD rat	HC	ECS, 1 day	↑H4 acetylation at *C-fos* promoter 1 hr post-ECS, ↑DNA methylation of *Arc* 24 hr post-ECS
Melas et al. (2012)	FSL rat	PFC	Escitalopram, 3 weeks	Pre-treatment: ↑DNA methylation,↓mRNA and protein of P11 membrane trafficking protein Post-treatment: *P11* DNA methylation returned to control levels,↑ *P11* mRNA, ↓mRNA for DNA methyltransferase enzymes, *Dnmt1* and *Dnmt3a*
Onishchenko et al. (2008)	Mouse	HC	Fluoxetine, 21 days from PND 63	↑H3 acetylation at *Bdnf* promoter and ↑*Bdnf* mRNA compensating for epigenetic effects of perinatal methylmercury exposure (Table 1)
Oved et al. (2012)	Human	Cell line	Paroxetine, 3 days	Paroxetine sensitive cells had higher basal expression levels of miR-151-3p, associated with↓mRNA for miR-151-3p effector, *CHL1*, a neural cell adhesion molecule Basal levels of miR-212, mir-132, miR-30b*, let-7b and let-7c also differed significantly by more than 1.5 fold between the high and low sensitivity cell groups
Rodrigues et al. (2011)	Human	Cell lines	Fluoxetine, 24 h	↓miR124a in SH-SY5Y and BE(2)–M17 cell lines ↑miR-27b in BE(2)–M17 cell line
Tsankova et al. (2006)	Mouse	HC	Imipramine 4 weeks	Pre-treatment: ↑methylation of H3K27 at *Bdnf* promoters, ↓*Bdnf* mRNA after social defeat stress Post-treatment: ↑H3 acetylation at *Bdnf* promoters, ↑*Bdnf* mRNA, ↓HDAC5 mRNA
Tsankova et al. (2004)	SD rat	HC	ECS 1 or 7 days	↑ H3 and H4 acetylation at *Bdnf* promoter II 2 h after 1 and 7 days ECS, ↑*Bdnf* mRNA ↑H3 acetylation at *Bdnf* promoters III and IV 24 h after 7 days ECS, ↑*Bdnf* mRNA ↑ H3 and H4 acetylation at *C-fos* promoter 2 h after 1 and 7 days ECS,↑*C-fos* mRNA ↓H3 acetylation at *Creb* promoter 2 h after 1 and 7 days ECS, ↓H4 acetylation 24 h after 7 days ECS with ↓*Creb* mRNA
Zhou et al. (2009)	Wistar rat	HC	Lithium, VPA, 4 weeks	37 miRNAs altered by lithium, 31 miRNAs altered by VPA, nine miRNAs regulated by both drugs: ↓let-7b and let-7c, miR-105, miR-128a, miR-24, miR-30c, miR-34a, miR-221 and miR-136, and↑miR-144

Abbreviations: BDNF-brain derived neurotrophic factor, ECS-electroconvulsive stimulation, FSL-Flinders Sensitive Line, H-histone, HC-hippocampus, HDAC-histone deacetylase, h-hours, K-lysine, LC-locus coeruleus, mRNA-messenger RNA, PFC-prefrontal cortex, PND-postnatal day, RN-raphe nucleus, SD-Sprague Dawley, VPA-valproic acid.

Table 4
Antidepressant treatment associated effects on miRNA expression in in vitro, preclinical and clinical studies.

Reference	Species	Tissue	Treatment	Treatment associated epigenetic modification, molecular changes and other outcomes
Angelucci et al. (2011)	Human	Cell line	Paroxetine	Rapid ↑in *BDNF* mRNA expression and protein synthesis followed by ↑in miR-30a-5p, a BDNF inhibitor, at six and 12 hours after treatment
Baudry et al. (2010), Launay et al. (2011)	Mouse	RN LC HC	Fluoxetine applied at RN for 3 days	↓miR-16 and serotonin transporter in RN ↓miR-16 and↑serotonin transporter in LC and HC Anti-miR-16 applied at HC results in anti-depressant behaviour
Belzeaux et al. (2012)	Human, MDD	Blood	Various antidepressants 8 weeks	↑miR-20b-3p, miR-433, miR-409-3p, miR-410, miR-485-3p, miR-133a, miR-145 ↓miR-331-5p
Bocchio-Chiavetto et al. (2013)	Human, MDD	Blood	Escitalopram, 12 weeks	↑28 miRNAs including *BDNF*-related miR-132 ↓ miR-34c-5p and miR-770-5p
Oved et al. (2012)	Human	Cell line	Paroxetine, 3 days	Paroxetine sensitive cells had higher basal expression levels of miR-151-3p, associated with↓mRNA for miR-151-3p effector, *CHL1*, a neural cell adhesion molecule Basal levels of miR-212, mir-132, miR-30b*, let-7b and let-7c also differed significantly by more than 1.5 fold between the high and low sensitivity cell groups
Rodrigues et al. (2011)	Human	Cell lines	Fluoxetine, 24 h	↓miR124a in SH-SY5Y and BE(2)–M17 cell lines ↑miR-27b in BE(2)–M17 cell line
Zhou et al. (2009)	Wistar rat	HC	Lithium, VPA, 4 weeks	37 miRNAs altered by lithium, 31 miRNAs altered by VPA, nine miRNAs regulated by both drugs: ↓let-7b and let-7c, miR-105, miR-128a, miR-24, miR-30c, miR-34a, miR-221 and miR-136, and↑miR-144

Abbreviations: BDNF-brain derived neurotrophic factor, HC-hippocampus, LC-locus coeruleus, MDD-major depressive disorder, miRNA-microRNA, RN-raphe nucleus, VPA-valproic acid.

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in the mechanism of action of this powerful antidepressant treatment. However, the epigenetic effects of ECS in animal models of depression and ECT in humans are still to be reported.

Epigenetic modification of gene expression has been reported following administration of antidepressant drugs in various models of depression (Table 3). In adult mice, epigenetic modifications of *Bdnf* have been reported after social defeat stress, which results in phenotypic behaviours that mimic depressive symptoms in humans (Tsankova et al., 2006). In a study by Tsankova et al. (2006), social defeat stress was associated with decreased *Bdnf* mRNA in the hippocampus of mice and was accompanied by an increase in gene-suppressing methylation of histone 3 at lysine 27 at *Bdnf* gene promoter regions. Antidepressant treatment with imipramine in this model resulted in increased mRNA levels for *Bdnf*. Although methylation of histone 3 at lysine 27 was not reversed by imipramine, compensatory *Bdnf* gene expression enhancing epigenetic modifications were observed, including hyperacetylation of histone 3 at *Bdnf*-promoters, and a decrease in mRNA levels for histone deacetylase 5 (HDAC5), an enzyme that decreases gene expression by decreasing histone acetylation (Tsankova et al., 2006). In addition, HDAC5 overexpression prevented the ability of imipramine to reverse the depressive phenotype in stressed animals, highlighting the importance of histone acetylation in the antidepressant effect.

Studies examining the expression of miR-16, which targets the serotonin transporter, have provided insight into the mechanism of action of fluoxetine in the mouse brain (Baudry et al., 2010; Launay et al., 2011). Infusion of fluoxetine into the raphe nucleus, a major source of ascending serotonergic projections in the brain, resulted in a decrease in miR-16 and a two-fold reduction in binding of serotonin transporter (Baudry et al., 2010). Fluoxetine applied at the raphe, also appears to affect miRNA expression in the locus coeruleus (Baudry et al., 2010) and hippocampus (Launay et al., 2011) causing a reduction in miR-16 and a subsequent increase in serotonin transporter levels in both brain regions. Furthermore, neutralisation of miR-16 in the hippocampus by application of anti-miR16 results in antidepressant-like behavioural effects highlighting the importance of its role in the downstream effects of fluoxetine (Launay et al., 2011).

Few studies to date have reported on the epigenetic effects of antidepressant treatment in humans (Belzeaux et al., 2012; Bocchio-Chiavetto et al., 2013; Chen et al., 2011; Lopez et al., 2013; Sharma et al., 2006) (Table 4). Chen et al. (2011) reported an increase in *BDNF* expression in the prefrontal cortex postmortem that was associated with a decrease in gene-repressing methylation of histone 3 at lysine 27 in patients taking a variety of antidepressants (Chen et al., 2011). In a follow-up study, citalopram treatment for eight weeks induced an increase in BDNF protein levels in peripheral blood of treatment-naïve MDD patients (Lopez et al., 2013). This was accompanied by a decrease in methylation of histone 3 at lysine 27 primarily in blood plasma in patients that were drug responders. miRNA changes following antidepressant treatment have been reported in two studies (Belzeaux et al., 2012; Bocchio-Chiavetto et al., 2013). miRNA changes were examined in blood from 10 patients with MDD following 12 weeks of administration of the SSRI escitalopram. After treatment, 28 miRNAs were upregulated, including the *BDNF*-related miR-132, while two miRNAs, miR-34c-5p and miR-770-5p, were robustly downregulated (Bocchio-Chiavetto et al., 2013). Predicted target genes included growth factors such as *BDNF* and vascular endothelial growth factor, calcium channels and neurotransmitter receptors. Further analysis indicated that miRNA expression was enriched for pathways important in brain function such as axonal guidance and long-term potentiation.

Collectively, the results of studies in humans and animal models suggest that antidepressant treatment reverses or elicits compensatory epigenetic changes such as histone hyperacetylation and DNA hypomethylation that promote previously decreased gene expression. The research highlighted above also provides evidence of miRNA regulation following antidepressant treatment both in vitro and in vivo. The miRNAs altered by antidepressants are important in neuronal processes that are affected in MDD such as neurogenesis and long-term potentiation which is important in memory formation. Epigenetics-based treatments have shown promising results in clinical trials for cancer (O'Rourke et al., 2013; Qiu et al., 2013; Tan et al., 2010), hepatitis C (Janssen et al., 2013) and provide an exciting new field for the development of therapies for MDD. Gaining a greater understanding of the epigenetic mechanisms underlying antidepressant mechanisms may guide the development of novel treatments for MDD, e.g. targeted HDAC and DNA methyltransferase inhibitors, and inhibition of miRNAs with small molecules. Additionally, miRNA expression profiles may serve as useful biomarkers to predict treatment response in individuals.

7. Limitations

Given the novelty of the field, a narrative approach was taken with regard to this review which has its limitations in terms of subjective bias. This review is meant to give an overview of an emerging field and does not lend itself to meta-analysis. Many of the included studies were carried out in small samples and have not been validated or replicated. Caution should also be used in extrapolating findings from pre-clinical settings to patient populations. The technical analyses of epigenetic alterations are still under development and in some instances there has been failure to replicate findings in the field of neuropsychiatric epigenetics (Houston et al., 2013). For example, inconsistent results have been reported regarding hypermethylation of the REELIN gene promoter in brains of patients with schizophrenia (Abdolmaleky et al., 2005; Tochigi et al., 2008). The current methods available to study epigenetic factors can be crude and imprecise, and researchers face a number of challenges when studying epigenetic changes, particularly in humans, some of which are detailed below.

Disease aetiology and varying exposure to environmental factors, including alcohol and psychostimulants, can alter epigenetic marks such as DNA methylation. Variations in glia to neuron ratio can introduce a high degree of heterogeneity and thus affect reproducibility of epigenetic studies examining cohort-based effects in relatively small samples (Houston et al., 2013).

In addition, the techniques for analysis of chromatin activation or DNA methylation status typically require relatively large amounts of input material and lack single-cell resolution (Akbarian and Huang, 2009). This can pose a problem when working with brain tissue, particularly in preclinical studies due to the relatively small brain size of rodents. One solution is to use whole-brain lysates. However, epigenetic changes can vary between brain areas (Roth et al., 2009) and researchers run the risk of neglecting subtle, region-specific changes. Although region-specific studies give a more precise view of epigenetic changes in the brain, tissue-homogenates comprise a heterogeneous set of neurons, glia and other cells, making identification of specific neuronal subtype (e.g. GABAergic interneuron) epigenetic alterations difficult (Houston et al., 2013). Purification techniques for separating neuronal and non-neuronal cells are now available and may improve the precision of post-mortem brain analyses.

Alternatively to post-mortem brain tissue, peripheral blood offers a relatively accessible biological fluid that can be sampled multiple times from the same individual. Using peripheral blood, changes in miRNA expression and epigenetic modulation of genes such as *BDNF* have been reported in patients with MDD before and

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after antidepressant treatment (Tables 2 and 4; (Lopez et al., 2013)). It remains to be seen to what degree changes in blood represent changes in the brain (Peedicayil, 2008). Furthermore, it is not clear if changes in blood reflect the pathological state or compensatory alterations in response to the pathological condition and/or treatment (Fass et al., 2013). Nonetheless, alterations in peripheral blood may serve as useful biomarkers in the diagnosis and treatment of psychiatric conditions including MDD (Cheng et al., 2013; Lopez et al., 2013).

Alterations in chromatin remodelling and/or DNA methylation can be measured globally or at a specific gene promoter. Promoter specific studies usually involve an isolation step to separate the epigenetically modified DNA (e.g. chromatin immunoprecipitation or bisulfite conversion), followed by analysis using PCR amplification (Fuchikami et al., 2011; Roth et al., 2009; Tsankova et al., 2004). Researchers examining changes in this manner must take into account multiple splice variants of genes of interest and design primers and PCR assays accordingly. For example, transcription of *BDNF* can arise from 11 different exons in humans and eight in rats, giving rise to multiple transcripts, known as splice variants, which can be individually epigenetically regulated (Boulle et al., 2012; Tsankova et al., 2004). As mentioned above, heterogeneity at the subject and tissue levels can also affect reproducibility in target-gene focused investigations. Furthermore, recent research indicates that in some conditions (e.g. autism), chromatin remodelling affects gene expression in subjects on an individual basis, a caveat which may limit findings in certain gene-specific studies (Houston et al., 2013).

Methodologies to assess epigenetic alterations on a global, genome-wide basis may help to overcome some of the limitations of target specific studies and provide the opportunity to identify previously unknown mechanisms involved in the pathology and treatment of MDD (Vialou et al., 2013). In terms of chromatin remodelling for example, genome-wide analysis was initially carried out using a technique known as ChIP-chip. Chromatin immunoprecipitation (ChIP) is a procedure whereby DNA bound to epigenetically modified lysine residues on histone tails (e.g. histone 3 at lysine 9, see Fig. 2) can be precipitated using targeted antibodies. Sequences of interest are then identified by hybridising bound DNA to a chip (microarray) containing a number of known DNA sequences. Wilkinson et al. (2009) used ChIP-chip with an antibody for histone 3 lysine 9 to identify genes that were upregulated or downregulated in the nucleus accumbens in mice one month after exposure to chronic stress, before and after imipramine treatment.

ChIP-chip is now being superseded by ChIP-seq (Houston et al., 2013). ChIP-seq analysis, which combines ChIP with next generation sequencing (NGS) technologies involving high-throughput sequencing of all enriched DNA sequences, provides the opportunity for increased sensitivity, higher resolution and more comprehensive screening of genomic profiles whilst requiring less input material than ChIP-chip (Park, 2009). NGS analysis is now also being combined with other techniques to identify epigenetic marks on a genomic scale. For instance, methods for characterising DNA methylation in human and rodent brain tissue have been combined with NGS analysis to create a database of genome-wide DNA methylation profiles (Xin et al., 2012). NGS also has the potential to examine miRNA alterations in psychiatric conditions and has already been used to study miRNA changes in the hippocampus of Alzheimer's patients (Lau et al., 2013). With the recent development of more widely available and affordable sequencing platforms, as well as databases containing epigenetic profiles of the human and rodent brain allowing cross-study and -species comparisons, NGS will enhance precision and resolution in pre-clinical and clinical epigenetic studies (Fass et al., 2013; Wang et al., 2013; Xin et al., 2012).

8. Summary and conclusions

Epigenetic mechanisms operate alongside the DNA sequence and promote or suppress gene expression, ultimately influencing protein production. Epigenetic modifications of gene expression include alterations in DNA methylation, chromatin remodelling and miRNA expression patterns. Epigenetics is an important new area in the field of MDD research and provides a mechanism for understanding the link between the long-term effects of adverse life events and the changes in gene expression that are associated with depression. Indeed, risk factors for depression, such as early life stress, are associated with epigenetic changes in gene expression in both preclinical and clinical studies. Persistent epigenetic modification of gene expression induced by environmental stimuli may also play a role in the transgenerational transmission of behavioural disturbances such as depression. In individuals with MDD, epigenetic modification of genes such as *BDNF* and its receptor *Trk B* as well as synapsins and GABA receptor subunits have been observed. Alterations in miRNA levels and polymorphisms in miRNAs, their precursors, their target mRNAs and in genes that regulate miRNA biogenesis have also been noted in MDD. Although still a developing field, in the future, epigenetic modifications of gene expression may provide novel biomarkers to predict future susceptibility and/or onset of MDD, to improve diagnosis and to better understand the pathophysiology of depression.

Epigenetics also appears to be important in the mode of action of antidepressant treatments. In preclinical studies, ECS, the animal model equivalent of the most acutely effective treatment for depression, causes alterations in chromatin activation status and DNA methylation of depression-related genes. Antidepressant drug treatments appear to reverse or bring about compensatory changes in gene expression in an animal model of depression and in clinical studies of MDD. Furthering our knowledge of the epigenetic modifications of gene expression elicited after antidepressant treatment may aid in the development of epigenetics-based therapies for depression and to predict treatment outcome.

Conflict of interest

All authors declare that they have no conflicts of interest.

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