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Abstract: With an estimated life-time prevalence of 15 to 17% and an incapacitating illness in 50% of cases, depressive spectrum disorders represent a heavy public health burden. Despite considerable efforts to underpin the molecular and cellular changes associated with depressive states, a global understanding of the pathophysiology of major depressive disorders (MDD) is still lacking. It is now acknowledged that deficits in synaptic plasticity, such as those resulting from chronic stress, can set the stage for the onset of depression. As a corollary, antidepressants balance neurostransmitter systems and help restore neuronal activity. In recent years, microRNAs have emerged as key protagonists in numerous physiopathological conditions including CNS function and disease. This review summarizes the current evidence for an involvement of microRNAs in the pathophysiology of depression and their contribution to the action of antidepressants.

# MicroRNAs and depression

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## Abstract

With an estimated life-time prevalence of 15 to 17% and an incapacitating illness in 50% of cases, depressive spectrum disorders represent a heavy public health burden. Despite considerable efforts to underpin the molecular and cellular changes associated with depressive states, a global understanding of the pathophysiology of major depressive disorders (MDD) is still lacking. It is now acknowledged that deficits in synaptic plasticity, such as those resulting from chronic stress, can set the stage for the onset of depression. As a corollary, antidepressants balance neurostransmitter systems and help restore neuronal activity. In recent years, microRNAs have emerged as key protagonists in numerous physiopathological conditions including CNS function and disease. This review summarizes the current evidence for an involvement of microRNAs in the pathophysiology of depression and their contribution to the action of antidepressants.

## Introduction

Depressive spectrum disorders are a major public health concern, affecting 121 million people worldwide. According to the World Health Organization, these diseases are predicted to become the second leading cause of disability by 2020. Despite considerable advances over the past decades, a clear understanding of the etiology of depression is still lacking. This notably relates to the complex interplay between genetic, immuno-inflammatory and environmental factors that dictate the relative susceptibility of individuals to affective disorders (Blume et al., 2011; Dudley et al., 2011; Lesch, 2011). A widespread view is that neuronal plasticity is challenged in key areas of the depressed brain and that antidepressants trigger a set of adaptive changes that help restore these defects. In this review, we focus on the involvement of microRNAs in the pathophysiology of depression and on their contribution to the action of antidepressants.

## Depressive disorders: pathophysiological and etiological aspects

### *Neurotransmitter systems involved in the biology of depression*

In view of the complexity of the brain circuitry, grasping the overall changes associated with depression is obviously very challenging (Benton and Wiltshire, 2011; Tanti and Belzung, 2010). Analyses carried out on post mortem brains of patients suffering from major depressive disorder (MDD) have allowed to characterize neuroanatomical alterations, including reduced neuronal densities in the prefrontal cortex, the raphe nuclei and the locus coeruleus, hypertrophy of the amygdala and reductions in hippocampal volume (Hercher et al., 2009). The pathophysiology of depressive states appears to also include glial cells, since depressed patients exhibit a profound loss of oligodendrocytes and myelin as well as reductions in densities of astrocytes (Allen and Barres, 2009; Hercher et al., 2009). Brain imaging studies such as functional magnetic resonance imaging (fMRI) are providing further

information on the functional disturbances associated with depressive states, leading to the identification of a brain-based endophenotype for MDD (Peterson and Weissman, 2011).

The involvement of various brain regions and neurotransmitter systems in the pathophysiology of depression is now well-established. Based on the observation over 50 years ago that the first classes of antidepressants, i.e. monoamine oxidases inhibitors (MAOIs) and tricyclic antidepressants (TCAs), target the monoaminergic systems, it was initially proposed that depression results from imbalances in the brain levels of monoamines (Coppen, 1967; Lapin and Oxenkrug, 1969; Schildkraut, 1965). The "monoamine theory of affective disorders" was reinforced by the development of antidepressants targeting the serotonin transporter (SERT) (Serotonin Reuptake Inhibitors, SRIs), the norepinephrine transporter (NET) (Norepinephrine Reuptake Inhibitors, NRIs), or both (Serotonin Norepinephrine Reuptake Inhibitors, SNRIs). Incidentally, most antidepressants available to date increase serotonergic and/or noradrenergic neurotransmission (Baudry et al., 2011). However, these drugs suffer several limitations: (i) relatively modest remission rates (symptom improvement in about 50% of depressed patients and remission in 30 to 40%) (Rush et al., 2006), (ii) relatively slow onset of efficacy and delayed time to remission so that, of ultimate remitters, as many as half will not remit until 6 to 12 weeks of ongoing antidepressant therapy (Trivedi et al., 2006), and (iii) lower effectiveness for certain depressive symptoms such as sleep disturbances and fatigue than for others (Nierenberg et al., 1999). These clinical observations have motivated the quest for a better knowledge of the molecular and cellular events sustaining depressive states. There is now clear evidence that depression is associated with deficits in neurotransmitter systems other than serotonergic or noradrenergic.

For instance, extensive analysis of the mesolimbic dopamine reward circuit in mouse models of depression has uncovered a detrimental overactivation of dopamine neurons of the ventral

tegmental area (VTA), which is reversed upon long-term antidepressant treatment (Cao et al., 2010; Krishnan and Nestler, 2010). Dopaminergic neurons from the VTA project to the nucleus accumbens (NAc), a brain region located within the striatum, whose hypoactivity is associated with anhedonia, a prevalent manifestation of depression (Krishnan and Nestler, 2010; Shirayama and Chaki, 2006).

Most neurons within the NAc are medium spiny GABAergic projection neurons, whose activity is inhibited by dopamine (Shirayama and Chaki, 2006). Dysfunction of the GABAergic system in depression extends beyond the NAc and deficits in GABAergic transmission may notably contribute to stress-induced impairment of hippocampal neurogenesis (see below) (Luscher et al., 2010).

There is growing interest for the glutamatergic system, which is influenced by traditional antidepressants targeting the monoaminergic systems (Mitchell and Baker, 2010). Increased glutamate levels have been reported in the plasma and the brains of patients suffering for MDD (Hashimoto, 2010). The most compelling evidence for a role of glutamate in depression relates to the antidepressant effect of antagonists targeting the NMDA receptor (Li et al., 2011). Among these drugs, the non-selective NMDA channel blocker ketamine was shown to operate by enhancing synaptic plasticity via the mTOR pathway (Li et al., 2010). Ketamine is now under trial and is expected to provide an alternative treatment for patients resistant to traditional therapies (Cryan and O'Leary, 2010).

*Genetic susceptibility to depression*

In view of the significant heritability of MDD, estimated to range from 34% to 42% (Ebmeier et al., 2006), the identification of susceptibility genes has raised much interest. Candidate gene studies favour an association of several genes with the disease, including those encoding the brain-derived neurotrophic factor (BDNF), TPH2, and the SERT (SLC6A4 gene) (Levinson, 2006). More than 20 variants of the latter gene have been described (Murphy and

Moya, 2011). Among these, variations in the SERT-linked polymorphic region (5-HTTPLR) have been associated with reduced SERT expression and function, comparable to those recorded in Slc6a4+/- mice (Murphy and Lesch, 2008). This polymorphism may notably drive the vulnerability to depression in response to stressful life events (Caspi et al., 2003). In the near future, genome-wide association studies, despite present poor replication (Bosker et al., 2011), might shed further light on the genetic susceptibility to MDD, as recently documented for polymorphisms in the sodium-dependent neutral amino acid transporter gene SLC6A15 (Kohli et al., 2011) and the synaptic scaffolding protein HOMER1 (Rietschel et al., 2010).

*Stress, impaired neurogenesis and disturbances in circadian rhythms: risk factors for depression*

A major contributing factor in the etiology of MDD is stress. Indeed, major depression is associated with impairments in learning and memory, hippocampal atrophy as well as hyperactivity of the HPA axis, all of which are known to be direct consequences of acute and chronic stress (Berton and Nestler, 2006; Lee et al., 2010; Pittenger and Duman, 2008). Chronic stress triggers excess glucocorticoid levels, in turn leading to impaired neurogenesis, excitotoxic damage and reduced levels of neurotrophins in the hippocampus (Anacker et al., 2011). Impaired hippocampal neurogenesis seems to represent a core pathological feature of major depression (Duman, 2004; Macqueen and Frodl, 2010; Pittenger and Duman, 2008), although the "neurogenesis hypothesis of depression" is currently under debate (Hanson et al., 2011). Excess glucocorticoid receptor activation, deficient neurotrophic signals, altered CREB signalling have all been monitored in depressed patients (Dwivedi, 2011). Basic and clinical studies provide some evidence for elevated secretion of the hypothalamic neuropeptides CRH and vasopressin in depression and anxiety (Holsboer and Ising, 2010). These findings suggest that CRH1 receptors may be potential drug targets.

Depression may further be influenced by disturbances in the circadian clock (Mendlewicz, 2009). The integration of circadian rhythms operates in the suprachiasmatic nucleus (SCN), within the hypothalamus. This brain region receives dense serotonergic innervation from the raphe as well as glutamatergic input from the retina. Its major output is the paraventricular nucleus of the hypothalamus, which supports the connection between the circadian clock and the HPA axis (Monteleone et al., 2010).

Hence, the onset of depression appears to be governed by multiple etiological factors, which may fuel each other within pathophysiological interplays. Further expansions of the current armamentarium of drug treatments of depression will depend on the discovery of new pathways and targets for antidepressant treatment, but fortunately several other lines of research hold promise for making these discoveries.

**Dysregulation of microRNAs in depression**

*Biogenesis and functions of microRNAs*

Over the past few years, microRNAs (miRNAs) have gained center stage as key post-transcriptional regulators of gene expression. By fine-tuning the translation of 50% of protein-coding genes, miRNAs appear as robust determinants of cellular states (Krol et al., 2010). MiRNAs are transcribed as pri-miRNA by RNA-polII, exported to the cell cytoplasm after processing into pre-miRNA by the Drosha complex, then further cleaved by Dicer to generate double stranded mature miRNAs. One strand of the mature miRNA is loaded within the RISC complex and binds its target mRNA to impair its translation or promote its degradation, while the other strand of the duplex is degraded (reviewed in (Krol et al., 2010)). The miRNA-dependent regulation of gene expression may in fact be more complex since, in some instances, miRNAs may on the contrary act as activators of translation (Krol et al., 2010). Finally, recent evidence suggests that they may also impair transcription by binding to gene promoters (Younger and Corey, 2011).

*microRNAs in the brain*

A large number of miRNAs was shown to be either specifically expressed in the brain or enriched in the central nervous system (Lagos-Quintana et al., 2002). A specificity of some neuronal miRNAs is their localization into the synaptodendritic compartment, associated with their ability to locally regulate the translation of target mRNAs (reviewed in (Schratt, 2009)). Interestingly, the turnover of miRNA in neurons appears to be faster than in other cell types, suggesting that the neuronal miRNA system may contribute to the rapid adaptation to neuronal activity (Krol et al., 2010). The production of miRNA at the synapse is indeed under the control of neuronal activity, and may involve calpain-dependent activation of Dicer (Schratt, 2009).

*microRNA dysfunction: genetic and epigenetic mechanisms*

Disease-associated dysregulation of miRNAs may encompass a variety of aberrant pathways (Fig. 1). These include altered miRNA expression, which may itself relate to genomic deletion or amplification, epigenetic changes or single nucleotide polymorphisms (SNP) ((Sethupathy and Collins, 2008) and references therein). Alternatively, polymorphisms within target genes may abrogate the recognition site for relevant miRNAs and create seed sequence for inappropriate miRNAs (Sethupathy and Collins, 2008; Sun et al., 2009). While these overall pathogenic mechanisms have been largely documented in the cancer field (Garzon et al., 2010; Ryan et al., 2010), only few of them have turned out to be involved in depression at present. To date, such examples are in fact limited to two polymorphisms located in pre-miR-30e (Xu et al., 2010) and pre-miR-182 (Saus et al., 2010) that are associated with major depressive disorder risk, in particular with late insomnia for the latter. In the case of pre-miR-182, the SNP leads to an up-regulation of miR-182 and a decrease in its targets -notably CLOCK- providing a molecular explanation for the clinical signs of circadian disturbance in patients. As for SNPs in the 3'UTR region of mRNAs encoding proteins involved in

pathophysiology of depression, the only defect in miRNA recognition reported to date relates to the serotonergic 5-HT1B receptor (Jensen et al., 2009). By lowering the affinity for miR-96, the rs13212041 SNP located in the 3'UTR of the 5-HT1B receptor mRNA leads to increased receptor expression and reduced aggressive behaviour (Jensen et al., 2009). A very recent study further suggests that the rs27072 SNP in the 3'UTR of the dopamine transporter (DAT) may affect miRNA-mediated regulation (Pinsonneault et al., 2011). This SNP is associated with bipolar disorder, an affective disorder with partial overlap with MDD (Pinsonneault et al., 2011). In view of the multiplicity of SNPs in the genes encoding the SERT or the NET (Baffa et al., 2010; Murphy and Moya, 2011), one cannot exclude that some may impact miRNA recognition.

*microRNAs and susceptibility to depression: facts and hypotheses*

An appealing approach to probe for dysregulated miRNA in depression would be to carry out large-scale analyses on post-mortem brain material (Dwivedi, 2011). Beyond technical hurdles, one difficulty relates to possible variations according to brain regions, as observed with BDNF levels (Wang et al., 2008). An alternative approach would be to exploit so-called animal models of depression (Nestler and Hyman, 2010), with the possibility to further assess the impact of antidepressant treatment on global miRNA expression, as carried out for in transcriptome studies (Surget et al., 2009).

Theoretically, any dysregulation of miRNAs involved in the pathways associated with vulnerability to affective disorders may precipitate or aggravate depression (Fig. 1). As mentioned above, stress, impaired neurogenesis and defects in synaptic plasticity represent three interconnected factors that are associated with depression. The global miRNA response to acute and chronic stress is only beginning to be disclosed (Meerson et al., 2010; Rinaldi et al., 2010; Uchida et al., 2010). Along the glucocorticoid-stress axis, several candidate miRNAs promoting the downregulation of the glucocorticoid receptor (GR) have already

been identified, and may have relevance as to depression. These include miR-18, which was shown to be increased in the paraventricular nucleus of the hypothalamus of stress-hyperresponsive rats. Another GR-targeting miRNA is miR-124a, the most abundant miRNA in the brain (Lagos-Quintana et al., 2002). Because GR activation may interfere with hippocampal neurogenesis (Anacker et al., 2011), miR-124 may be critical for maintaining GR expression at levels permissive to neurogenesis (Cheng et al., 2009). Beyond miR-124, adult hippocampal neurogenesis appear to be associated with changes of a wide array of miRNAs (Luikart et al., 2011). miR-132 and miR-212 feature among the most highly upregulated miRNAs in response to neuronal activity in the dentate gyrus (Luikart et al., 2011). In line with this observation, cre-mediated deletion of miR-132/212 results in decreased dendritic arborization of newborn neurons in this brain region (Magill et al., 2010). Much effort is definitely being made to assess the contribution of miRNAs to the control of neuronal maturation, synapse formation and functional integration of new neurons in the brain circuitry (Shi et al., 2010).

The involvement of miRNAs in synaptic plasticity is also being actively scrutinized (reviewed in (Siegel et al., 2011)). The first report on the regulation of local protein synthesis in dendrites by microRNAs was by Schratt *et al.* (Schratt et al., 2006). In this work, the brain-specific miR-134 was shown to interfere with the growth of dendritic spines by targeting the Lim kinase 1 (LIMK-1) and to be downregulated when neurons are exposed to BDNF. Further, excessive levels of miR-134 impair memory and plasticity by repressing the expression of the cAMP response element binding protein (CREB) (Gao et al., 2010). The downregulation of this transcription factor in turn decreases the expression of BDNF (Gao et al., 2010), highlighting reciprocal antagonism between miR-134 and BDNF (Siegel et al., 2011). Another feedback loop contributing to neuronal plasticity involves the miR-124/CREB duo (reviewed in (Siegel et al., 2011)). In Aplysia, miR-124 controls serotonin-induced

synaptic facilitation through post-transcriptional repression of CREB (Rajasethupathy et al., 2009) and, conversely, CREB can regulate the expression of miR-124 (Rajasethupathy et al., 2009). The network of synaptic miRNAs also includes miR-132, which is increased in response to BDNF and regulates neuronal morphogenesis by targeting the GTPase activating protein p250GAP (Vo et al., 2005). Interestingly, excess glucocorticoids were recently shown to interfere with the BDNF/miR-132 cascade (Kawashima et al., 2010). Recent data actually posit miR-132 as a key player in the integration of neuronal functions. For instance, a well-characterized target of miR-132 is the transcriptional regulator MeCP2 (Klein et al., 2007), involved in neuronal activity (Chahrour et al., 2008; Diaz de Leon-Guerrero et al., 2011; Greer and Greenberg, 2008). Finally, miR-132 may play a role in circadian rhythms since it is induced by light in the suprachiasmatic nucleus and regulates the expression of Period genes (Alvarez-Saavedra et al., 2011).

**Involvement of microRNAs in the action of antidepressants**

*A role for miR-16 in the action of SRI antidepressants*

The involvement of microRNAs in the response to antidepressants is only beginning to be explored. Recently, we have unveiled a key role for miR-16 in the antidepressant action of the SRI fluoxetine (Baudry et al., 2010). miR-16 acts as a posttranscriptional repressor of the SERT, the pharmacological target of SRIs. miR-16 is expressed at higher levels in noradrenergic than serotonergic cells, both *in vitro* and *in vivo*. In noradrenergic neurons, neutralization of miR-16 unlocks SERT expression and renders the cells competent to bind SRI antidepressants. Based on the observation that SRIs reduce SERT protein while not altering its mRNA levels (Benmansour et al., 2002), we postulated that antidepressants may promote changes in miR-16. Indeed, in mice, chronic fluoxetine treatment increases the level of miR-16 in raphe, which decreases the protein level of SERT. From a mechanistic point of view, the raise in miR-16 results from an increased maturation from pri/pre-miR-16. This

process depends on the activation of GSK3β, an effector of the Wnt canonical pathway. Serotonergic neurons additionally respond to fluoxetine by releasing the neurotrophic factor S100β. S100β secreted by serotonergic neurons acts on noradrenergic neurons by promoting a decrease in miR-16, which turns on the expression of SERT. Other serotonergic functions are also implemented following the reduction of miR-16, notably serotonin synthesis. This observation is in keeping with the monoamine theory of affective disorders, according to which increasing brain serotonin levels is beneficial to depressive states. Building upon these observations, we explored whether miR-16 may relay the action of SRIs in other brain regions. This is indeed the case in the hippocampus: fluoxetine promotes a decrease in miR-16, which in turn triggers a raise in the protein levels of SERT as well as those of the anti-apoptotic factor bcl-2, a well-established target of miR-16 in cancer (Aqeilan et al., 2010), thereby sustaining hippocampal neurogenesis (Launay et al., 2011). These results allow to define miR-16 as a "missing link" between SRIs and adult hippocampal neurogenesis. Further, in view of its impact on multiple targets, miR-16 behaves as a micromanager of the hippocampal response to fluoxetine. Taken together, our observations support the view that miR-16 is widely involved in the brain response to fluoxetine. Importantly, the fluoxetine-induced changes in miR-16 actually sustain the antidepressant action of the drug. Indeed, using mouse models of depression, we observed that the upregulation of miR-16 in raphe or the downregulation of miR-16 in the locus coeruleus (Baudry et al., 2010) or in the hippocampus (Launay et al., 2011) induce behavioural responses that compare that induced by fluoxetine.

As rightly suggested by Millan (Millan, 2011), whether fluoxetine influences the expression of miRNAs other miR-16, notably the closely related miR-15 and miR-107 will have to be assessed. Another related issue concerns the potential miRNA-mediated post-transcriptional regulation of other key monoaminergic functional molecules. For instance, can miRNAs

regulate the expression of the NET and take part to the response to antidepressants? In direct support of this hypothesis, long-term treatments with various antidepressants reduce the protein levels of NET while having no effect on NET mRNA (Zhao et al., 2009). The regulation of NET expression by miRNAs would notably provide some explanation for the perplexing lack of alteration in the expression of genes associated with monoaminergic systems in MDD (Fiori and Turecki, 2011).

*Antidepressant responses: established pathways, candidate microRNAs*

Our understanding of the pathways sustaining the response to antidepressant drugs has greatly progressed over the past few years (Baudry et al., 2011). The current knowledge of the effectors at play further allows considering the implication of miRNAs (Fig. 2). For instance, a large body of evidence supports a contribution of the Wnt-GSK3 pathway to the action of antidepressants ((Baudry et al., 2011; Wada, 2009) and references therein). The GSK3 kinase is the target of the mood stabilizer lithium (Beaulieu and Caron, 2008). Large scale analysis of the hippocampal miRNA changes induced by lithium and valproate, another mood stabilizer, has revealed decreases in let-7b, let-7c, miR-128a, miR-24a, miR-30c, miR-34a, miR-221 and a raise in miR-144 (Zhou et al., 2009). Except for an increase in the mGluR7 receptor as a result of reduced miR-34a levels, the mechanisms through which these changes in miRNA contribute to the therapeutic effect of lithium remain to be investigated (Zhou et al., 2009). Further, from a mechanistic point of view, how GSK3 may regulate the levels of specific miRNAs is elusive. It may notably relate to the blockade of pri/pre-miRNA maturation, as we observed for miR-16 in the locus coeruleus (Baudry et al., 2010). That GSK3 may regulate pri-miR maturation is notably supported by the recent observation that GSK3 controls the nuclear localization of the RNAase III enzyme Drosha through phosphorylation (Tang et al., 2011)

The therapeutic action of antidepressants further involves the restoration of neuronal plasticity (Duman, 2004; Macqueen and Frodl, 2010; Pittenger and Duman, 2008). This process may in part rely on neurotrophic signals, able to counteract stress-induced impairment of hippocampal neurogenesis (Duman, 2004). In direct support of this hypothesis is our recent demonstration that fluoxetine operates on the hippocampus by mobilizing BDNF, Wnt2, and 15-Deoxy-delta12,14-prostaglandin J2 (Launay et al., 2011). These signalling molecules emanating from the raphe synergize to downregulate miR-16, and increase SERT and bcl-2 protein levels in the hippocampus (Launay et al., 2011). Notably, the normalization of BDNF levels in response to antidepressants (Castren and Rantamaki, 2010; Launay et al., 2011) is likely to sustain a cascade of beneficial events leading to appropriate control of miRNA expression, beyond the regulation of miR-16. Of note, BDNF has the capacity to regulate gene expression by activating the mTOR pathway (Schratt et al., 2004). Whether the BDNF-dependent activation of mTOR also regulates miRNA expression deserves further consideration.

Interestingly, the mTOR pathway is also involved in the antidepressant action of ketamine (Li et al., 2010). Whether the ketamine-mTOR cascade mobilizes miRNAs to enhance synaptic plasticity has yet to be investigated. mTOR further exerts a regulatory role in the entrainment of the mammalian circadian clock (Cao and Obrietan, 2010). Again, whether mTOR signalling regulates miRNA expression in the suprachiasmatic nucleus has not been addressed. Beyond mTOR-dependent mechanisms, the restoration of the BDNF/CREB/miR-132 cascade in this brain region following antidepressant treatment is certainly critical to the resetting of the circadian clock (Cheng and Obrietan, 2007).

Adding another layer of complexity to the picture, there is now clear-cut evidence that the action of antidepressants may involve chromatin remodeling (Baudry et al., 2011; Covington et al., 2010). Epigenetic mechanisms distinct from miRNA changes notably operate at the

level of BDNF gene transcription (Tsankova et al., 2006). Their contribution to adult hippocampal neurogenesis is also largely documented (Hsieh and Eisch, 2010; Ma et al., 2010). The regulation of miRNA expression is intimately connected with the epigenetic machinery (Iorio et al., 2010). A dramatic example is the association between aberrant methylation of defined miRNAs and cancer (Iorio et al., 2010). Cleary, more work is needed to assess the potential implication of epigenetic regulators in the miRNAs response to antidepressants.

*Lessons from resilience*

Our ability to adapt to adverse events is highly promiscuous and may notably depend on early life stress (Feder et al., 2009). The molecular mechanisms associated with resilience, i.e. the capacity to respond positively to stressfull events, are still very elusive (Feder et al., 2009). Recent works suggest that resilience is associated not only with an absence of changes in gene expression seen in vulnerable individuals but also with the induction of distinct beneficial changes, in response to stress (Feder et al., 2009; Uchida et al., 2011). The possibility that these changes include the regulation of specific miRNAs deserves consideration. Analysing the profile of miRNA expression in the brain of stress-resilient versus stress-sensitive mice may help shed some light on this issue. Another approach would be to exploit the few transgenic mouse models exhibiting a depression-resistant phenotype, such as animals rendered insensitive to regulators of GPCR signalling (RGS), one of the first example being a negative regulator of the serotonin 5-HT1A receptor function (Talbot et al., 2010). Profiling studies may alternatively benefit from mice deficient in NET, which behave like antidepressant-treated wild-type mice (Haenisch and Bonisch, 2011).

## Conclusion and future directions

To date, the actual experimental evidence for an involvement of miRNAs in the pathophysiology and treatment of depression remains scarce. Nevertheless, the involvement of miRNAs in the diverse pathways known to be associated with depression argues for a dysregulation of miRNA-related homeostatic loops in MDD. On another hand, the restoration of efficient neurogenesis, neurotransmission, structural and functional brain plasticity as well as circadian rhythms upon antidepressant treatment is likely to require a concerted miRNA response. The challenge now is to reach an integrated view of the network of miRNAs that are mobilized by antidepressants as a function of the brain regions at play. Further, the identification of functionally relevant targets of these miRNAs should help unravel the global molecular and cellular changes sustaining the therapeutic action of antidepressants. Another important issue to be addressed relates to the reversibility of these changes. Indeed, the rapid turnover of neuronal miRNAs allows for a dynamic adaptation to external inputs (Rajewsky, 2011). Deciphering the step-wise changes in the expression of appropriate miRNAs should eventually help identify the molecular events that trigger recovery from depression.

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**Legends to Figures**

Figure 1: Potential dysregulated pathways involving miRNAs that may contribute to depressive disorders. Genomic deletion or amplification, epigenetic changes or SNPs may all lead to aberrant miRNA expression, with further impact on their targets. Reciprocally, SNPs

within target genes may abrogate recognition sites for appropriate miRNAs and/or create seed sequence for irrelevant miRNAs.

Figure 2: Schematic representation of the pathways mobilized by antidepressants that may involve miRNAs. Antidepressant-mediated regulation of miRNAs may occur at the level of miRNA gene expression or at the various steps of maturation.

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**Figure 1**

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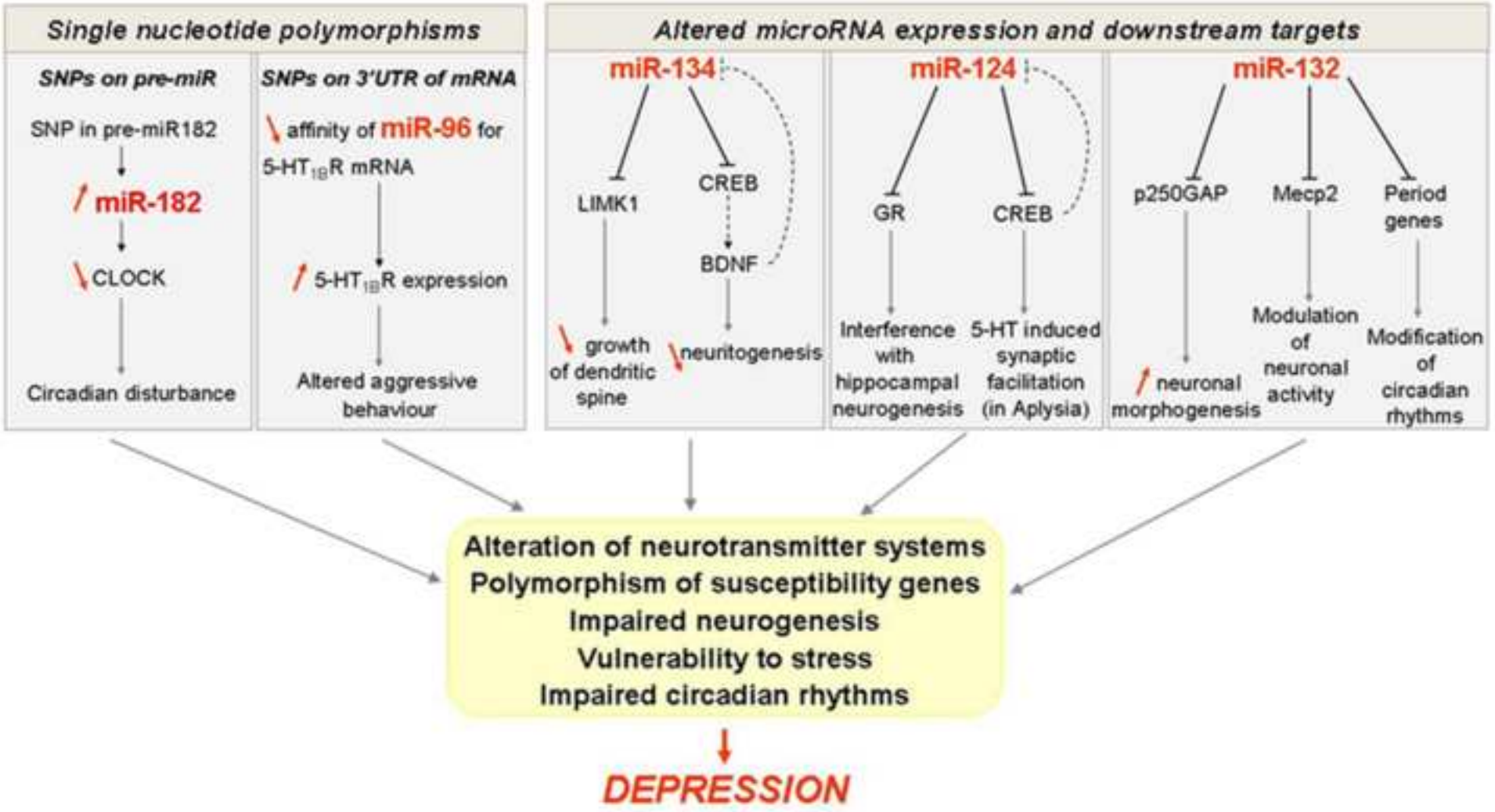

Figure 2

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