Forkhead Box O Transcription Factors as Possible Mediators in the Development of Major Depression

Haitao Wang¹,², Rémi Quirion³, Peter J. Little⁴, Yufang Cheng¹, Zhong-Ping Feng⁵, Hong-Shuo Sun⁵, Jiangping Xu¹*, Wenhua Zheng²*

¹Guangdong Provincial Key Laboratory of New Drug Screening, School of Pharmaceutical Sciences, Southern Medical University, Guangzhou 510515, China;
²Faculty of Health Sciences, University of Macau, Taipa, Macau, China and Key Laboratory of Ophthalmology, Zhongshan Ophthalmic Center, Sun Yat-sen University, Guangzhou 510006, China.
³Douglas Mental Health University Institute, McGill University, Montreal, Canada;
⁴School of Pharmacy, The University of Queensland, QLD 4072, Australia;
⁵Department of Physiology, Faculty of Medicine, University of Toronto, Toronto, Ontario, Canada.

*Corresponding author
Prof. Jiangping Xu, Ph.D, MD.
Guangdong Provincial Key Laboratory of New Drug Screening, School of Pharmaceutical Sciences, Southern Medical University, Guangzhou 510515, PR China.
Tel./Fax:+86 20 6164 8236, E-mail address: jpx@smu.edu.cn

Prof. Wenhua Zheng, MD, PhD.
Faculty of Health Sciences, University of Macau
Room 4021, Building E12, Avenida de Universidade, Taipa, Macau. China
Tel: +853-88224919; Email: wenhuzheng@umac.mo
Abstract

Forkhead box O (FoxO) transcription factors play important roles in cellular physiology and biology. Recent findings indicate that FoxOs are also involved in the development of major depressive disorder. Alterations in the upstream molecules of FoxOs, such as brain derived neurotrophic factor or protein kinase B, have been linked to depression. Antidepressants, such as imipramine and venlafaxine, modify the FoxOs phosphorylation. Furthermore, FoxOs could be regulated by serotonin and norepinephrine receptor signaling as well as the hypothalamic-pituitary-adrenal axis, all of which are involved in the pathogenesis of depression. FoxOs also regulate neuronal morphology, synaptogenesis and adult hippocampal neurogenesis, which are viewed as candidate mechanisms for the etiology of depression. In this review, we emphasize the possible roles of FoxOs during the development of depression and make some strategic recommendations for future research. We propose that FoxOs and its signaling pathways may constitute potential therapeutic targets in the treatment of depression.

Keywords: FoxO, major depression, PI3K/Akt, neuronal atrophy, neurogenesis, antidepressants
1. Introduction

Major depression is one of the most severe and common psychiatric disorders with high rates of self-harm and suicide attempts (Hegerl et al., 2013). The causes of major depressive disorder are not well understood. A diverse contribution of genetic, neurochemical and environmental factors are involved in the onset and progression of depression. Besides the common monoamine hypotheses, the diathesis stress model is another attempt to explain the etiology of depressed behavior (Gold and Chrousos, 2013). Diathesis interacts with the subsequent stress response of an individual, especially some early life experiences which are known to increase the risk for depression (Kiejna et al., 2010). Antidepressants initially correct imbalances of neurotransmitters in the synapse cleft (Mahar et al., 2014; Werner and Coveñas, 2013), while the therapeutic response may result from above and the downstream adaptive changes that occur as a consequence of increased neuroplasticity. These subcellular events include synaptic transmission, gene expression, neuronal morphological changes and many other molecular events in the brain (Kavalali and Monteggia, 2012; Pilar-Cuéllar et al., 2012; Seo et al., 2014). However, some patients do not tolerate some of the undesirable effects associated with these agents such as nervousness, insomnia or sexual dysfunction (Sussman. 1994). Novel targets and new classes of antidepressant agents are required to improve the therapeutic arsenal for the treatment of depression. In addition, currently available antidepressants are prescribed for both moderately and severely depressed patients (Fournier et al., 2010), and for severe major depression, a combination of antidepressant medication and psychotherapy or electroconvulsive therapy are usually considered (Oudega et al., 2011; Hollon et al., 2014). Antidepressants have unusual temporal responses with many agents having a delayed onset of action since clinical improvement is observed several weeks after initiation of antidepressant drug and usually patients have to take antidepressants for months to get a stable maximal improvement (Kirsch et al., 2008; Mitchell. 2006). Antidepressants require a timescale of minutes to boost the synaptic concentration of serotonin and/or norepinephrine, whereas the onset of the therapeutic action is usually a few weeks after the initiation of therapy. The traditional view about the delayed
onset of current antidepressant action relies on neurobiological effects that develop slowly under chronic drug treatment, such as alterations of glucocorticoid receptor systems in patients with depression, and changes of gene and protein expression related to dendritic spines, production of brain derived neurotrophic factor (BDNF), adult hippocampal neurogenesis and enhanced synaptic plasticity (Hajszan et al., 2005; Anacker et al., 2011b; Malberg et al., 2000; Groves, 2007). The pathological mechanisms of depression need to be further explored and the controversy about the mechanism of current antidepressant agents to be resolved.

In recent years, the regulation of gene expression has been implicated in the etiology and treatment of depression; several genes such as BDNF, fibroblast growth factor receptor 1, NCAM1 neural cell adhesion molecule 1, and Calcium/Calmodulin-dependent Protein Kinase II have been identified to be of interest (Groves, 2007; Tochigi et al., 2008). Transcription factor DNA binding peptides are essential for the regulation of gene expression and are themselves regulated by phosphorylation and dephosphorylation. For example, phosphorylated cAMP-response element binding protein (CREB) transcription factor binds to the regulatory site on the BDNF promoter and increases BDNF protein levels, both of which have been associated with depression (Breuillaud et al., 2012). Transcription factors could serve as the intermediates between intracellular signaling cascades and gene expression, and therefore be involved in the pathophysiology of depression and represent potential targets for the pharmacotherapy.

Forkhead box O (FoxO) is a transcription factor, which plays a regulatory role in multiple biological and pathological systems, including the central nervous system (CNS). Recent discoveries indicate a role for FoxO in the pathogenesis of depression and other psychiatric disorders (Polter et al., 2009; Weeks et al., 2010; Zheng et al., 2013). Enhanced neurotrophins or serotonin neurotransmission in animal brain phosphorylate and inactivate FoxO3a (Zheng et al., 2002; Polter et al., 2009). BDNF, which is reduced in depression (Karege et al., 2005; Angelucci et al., 2005), promotes phosphorylation of the FoxO protein (Mojsilovic-Petrovic et al., 2009; Zhu et al., 2004); moreover, FoxO3a-deficient mice display an antidepressant-like behavior
(Zheng et al., 2002; Polter et al., 2009; Zheng and Quirion, 2004); Furthermore, both the serotonin-norepinephrine reuptake inhibitor antidepressant venlafaxine and the mood stabilizer lithium, suppress FoxO3a activity in mouse brain (Wang et al., 2013; Mao et al., 2007). FoxOs are under the control of neurotransmitters (Liang et al., 2006) and glucocorticoids (Qin et al., 2014). FoxOs also regulate signals for cellular atrophy (Jaitovich et al., 2015), cellular morphology (Aranha et al., 2009) and adult neurogenesis (Zhang et al., 2013) and all of these physiological or pathological conditions contribute to the development of depression (Borre et al., 2014; Mahar et al., 2014; Anacker et al., 2013). Although the role of FoxOs in the process of depression is only beginning to be unveiled, it is reasonable at this time to hypothesize that FoxO transcription factors will be found to be pivotal mediators in psychiatric disorders. In this review, cellular signaling cascades responsible for regulating FoxOs, the possible roles of FoxOs in the development of depression, the effects of antidepressants on the activity of FoxOs as well as the potential mechanistic pathways linking major depression and FoxOs will be discussed.

2. Overview of FoxO signaling pathway

Forkhead box (Fox) proteins are a family of transcription factors characterized by a conserved “forkhead” or “winged helix” DNA binding motif. Foxs bind to the regulatory sequence of the downstream target genes and play important roles in regulating the transcription of genes involved in cell growth, proliferation, differentiation, metabolism, apoptosis and drug resistance (Lam et al., 2013; Accili and Arden 2004). According to the sequence homology, Fox superfamily genes can be classified from FoxA to FoxS (Lam et al., 2013). Of the Fox subfamilies, the FoxO group is one of the most researched subgroups. FoxOs share a conserved DNA-binding domain, the binding sequence is 5’-TTGTTTAC-3’ (Brent et al., 2008). In mammals, there are four FoxO homologues, FoxO1, FoxO3a, FoxO4 and FoxO6. FoxO2 was shown to be same with FoxO3a and FoxO5 is the ortholog of FoxO3a in the zebrafish (Carter and Brunet, 2007). The activity of FoxO is regulated by post-translational modification, including phosphorylation, acetylation, methylation,
ubiquitination and glycosylation (Eijkelenboom and Burgering, 2013; Zhao et al., 2011). Phosphorylation of FoxO by protein kinases has been extensively studied. Protein kinase B (Akt), serum/glucocorticoid inducible kinase (SGK), AMP-activated protein kinase (AMPK), mitogen-activated protein kinases (MAPK), inhibitor of nuclear factor kappa-B kinase (IKK), cyclin-dependent kinase (CDK) and mammalian sterile 20-like kinase (MST) are common upstream kinases for FoxO (Boccitto and Kalb, 2011). Phosphatidylinositol 3-kinase (PI3K)/Akt signal pathway activated by insulin or growth factors mediates the major regulation of FoxO (Woodgett, 2005). Binding of insulin or other growth factors (such as nerve growth factor, BDNF or insulin like growth factor 1 (IGF-1) to their receptors leads to the autophosphorylation of the growth factor receptor and its subsequent activation (Zheng et al., 2002; Zheng and Quirion, 2004; Zheng and Quirion, 2009). Through regulation via the PI3K/Akt pathway, many of downstream target genes of FoxO (such as Btg-1, Bim-1, FasL, MnSOD, p27, PEPCK) are regulated and these gene products play roles in cell proliferation (p27), differentiation (Btg-1), metabolism (PEPCK), apoptosis (Bim-1, FasL) and drug resistance (Wen et al., 2012; van der Vos and Coffer, 2011; Hui et al., 2008). For example, sustained FoxO3a activation promotes drug resistance by activating and promoting the expression of ATP-binding cassette sub-family B member 1, which is a plasma membrane P-glycoprotein that functions as an efflux pump for various anticancer agents, including doxorubicin (Hui et al., 2008).

The PI3K pathway is a major regulator of FoxOs activity. Akt and SGK are two key downstream components of the PI3K pathway and both of them recognize the RXRXXS/T motif. Akt phosphorylates FoxO3a at Thr32, Ser253 and Ser315, while SGK phosphorylates FoxO3a at Thr32 and Ser315. For FoxO1, Akt phosphorylates it at Thr24, Ser256 and Ser319, while SGK phosphorylates it at Thr24 and Ser319 (Burgering and Kops, 2002). Phosphorylation of these sites leads to translocation of FoxOs from the nucleus to cytoplasm and inhibition of transcriptional activity (Chen et al., 2013; Huang and Tindall, 2007). What is important is that the C terminal of FoxO6 lacks the Akt phosphorylation site and thus it is constitutively nuclear (Jacobs et al., 2003). Extracellular regulated protein kinase (ERK) is a downstream
component of MEK and it has been shown to phosphorylate FoxO3a at Ser294, Ser344 and Ser425 (Yang et al., 2008), similarly, activation of IKK induces FoxO3a phosphorylation at Ser644 (Hu et al., 2004). Phosphorylation of FoxO3a by both ERK and IKK leads to nuclear exclusion and degradation. The serine/threonine kinases p38 and c-Jun N-terminal kinase (JNK) are other two major MAPK pathways relevant to FoxO function. p38 phosphorylates FoxO3a at Ser7 and promotes the nuclear translocation and activation of FoxO3a (Ho et al., 2012); JNK may repress the PI3K/Akt signal pathway, thereby activating FoxO3a indirectly, meanwhile, it may phosphorylate FoxO proteins in a direct way (Sunters et al., 2006). FoxOs may also play a critical role in the regulation of energy homeostasis when phosphorylated by the AMP-activated protein kinase (AMPK) at six sites (Greer et al., 2009). In contrast to the effect of the above kinases on FoxOs, MST binds to FoxO3a and phosphorylates it at Ser207; however, the phosphorylation of this site promotes its nuclear accumulation and subsequently the expression of proapoptotic genes (Sanphui and Biswas, 2013). Another interesting example is the role of CDK on FoxOs. CDK1 phosphorylates FoxO1 at Ser249 and enhances the content of FoxO1 in the nucleus and thus promotes cell death (Yuan et al., 2008), CDK2 phosphorylates FoxO1 at the same site, however, it leads to the accumulation of FoxO1 in the cytoplasm and the inhibition of FoxO1 (Huang et al., 2006). Figure 1 summarizes the above pathways regulating FoxO activity and subcellular localization.

Fig.1. Effects of various upstream regulators on the activity and subcellular localization of
FoxO. Phosphorylation is one of the most common post-translational modifications. Kinases, such as Akt, IKK, SGK, ERK1/2 and CDK promote the export from the nucleus and inactivation of FoxO. While under stress conditions, MST, AMPK, p38MAPK and JNK induce the nuclear accumulation and activation of FoxO. In the nuclear, FoxO recognizes and binds to FRE (FoxO response element), activated FoxO thereby regulates the transcription activity of its downstream targets, which makes it possible to regulate many cellular processes, including proliferation, differentiation, metabolism, apoptosis and drug resistance.

3. FoxO expression patterns in the brain

FoxO is one of the substrates for Akt which is a pro-survival serine/threonine kinase. The PI3K/Akt signal pathway plays a critical role in mediating neuronal survival. FoxO regulates the expression of genes involved in neuronal cell apoptosis and oxidative stress, such as Bim-1, FasL, Catalase and MnSOD (Brunet et al., 2001a, Wen et al., 2012). The pattern of protein distribution related to FoxO functions points to the associated biological functions. Understanding the expression patterns of FoxO in the CNS should help us to understand the relationship between FoxO and neurodevelopment, neurodegeneration and potentially neuropsychiatric disorders. FoxOs are highly expressed in brain areas related to the regulation of mood and stress. FoxO1, FoxO3a and FoxO4 are each expressed during neurodevelopment and also in the adult, with distinct patterns ranging from ubiquitous to tissue-specific (Biggs et al., 2001). Among the FoxO subtypes expressed in brain, FoxO1 is mostly expressed in the hippocampus and the striatum (Zemva et al., 2012), its mRNA is expressed in part of the ventral region of the CA3 pyramidal neurons, however, no expression was observed in the dorsal CA3 neurons (Hoekman et al., 2006). FoxO3a shows the widest brain expression, whereas FoxO4 is expressed at very low levels in the brain and a FoxO4 probe did not reveal detectable expression in the adult murine brain (Salih et al., 2012). FoxO6 is mostly expressed during the developmental stage with a nuclear-predominant distribution (Jacobs et al., 2003). For FoxO6, both the protein and mRNA levels are highly expressed during the stage of neuronal development, and its expression decreases during maturity but then stays relatively constant. In the adult
brain, FoxO6 protein is expressed abundantly in hippocampus, amygdala and nucleus accumbens (Salih et al., 2012). Converging evidences suggest that the hippocampal complex may play a role in the pathology of major depression (Campbells and Macqueen, 2004). FoxO isoforms also have different patterns of expression in the hippocampus where FoxO1 is enriched in the dentate gyrus (DG) region of hippocampus, FoxO3a is present in all hippocampal areas but more highly expressed in the DG and CA3 regions than in the CA1 region. FoxO6 is enriched in the CA1 and CA3 hippocampal areas (Hoekman et al., 2006; Furuyama et al., 2000; Jacobs et al., 2003; Salih et al., 2012). The differential expression patterns suggest that FoxO isoforms may have specific and perhaps complementary or redundant roles in different physiological or pathological processes. In conclusion, spatial expression patterns of FoxO gene family members in the CNS, especially regions related to stress, implicate their biological functions in stress-related behavior regulation.

4. **FoxOs regulate the behavioral manifestation of depression**

The role of FoxOs in psychiatric disorders has recently drawn more attention even though the data in this area are somewhat limited at this time. FoxOs, especially FoxO6, are expressed abundantly in hippocampus, amygdala and nucleus accumbens which are important brain areas involved in aversive and rewarding responses to emotional stimuli (Accili and Arden, 2004; Hoekman et al., 2006). Thus FoxOs could mediate the inability to experience pleasure and lack of motivation that predominate in many patients with depression (Berton and Nestler, 2006). The subregional distributions of FoxOs could predict their roles in the regulation of mood and emotion. In a case-control association study in a Brazilian population, FoxO3a emerged as an gene candidate involved in bipolar disorder and related behaviors. Three single-nucleotide polymorphisms within the FoxO3a gene (rs1536057, rs2802292 and rs1935952) were associated with bipolar disorder (Magno et al., 2011). Mood-related behavioral disturbance, such as depression, is highly related to stress (Krishnan and Nestler, 2008). In a learned helplessness animal model, which is a commonly used model to mimic human depression (Muller et al., 2011), inescapable shocks
significantly reduced the phosphorylation of FoxO3a and induced the nuclear location of FoxO3a in the cerebral cortex, interestingly, learned helplessness behavior was markedly diminished in FoxO3a-deficient mice (Zhou et al., 2012). This research provides evidence that depression activates FoxO3a. These results was consistent with the previous report that FoxO3a influences behavioral processes linked to anxiety and depression and FoxO3a-deficient mice show a significant antidepressant-like behavior, but these animals didn't exhibit changes in general locomotor activity tested by open field test (Polter et al., 2009), suggesting that FoxO3a is a transcriptional target for mood disorder treatment. In contrast, a study using a knockout (KO) mouse model suggested that FoxO1 KO mice displayed reduced anxiety (Polter et al., 2009). Recently, disrupted rhythms are observed in psychiatric disorders, including depression (Emens et al., 2009). Association of Clock gene and major depressive disorder has also been suggested (Germain and Kupfer, 2008). Although the detailed etiologies still need to be unraveled, it is evident that there is a strong relationship between major depression and circadian disruption (Karatsoreos, 2014). Interestingly, clock is a transcriptional target of FoxO3a and the insulin-FoxO3a-Clock signaling pathway plays a key role in the modulation of circadian rhythms, for instance, knock down of FoxO3a dampens circadian amplitude (Chaves et al., 2014; Zheng et al., 2007). These studies revealed an important new role for FoxOs in the regulation of depressive behavior.

BDNF is a well known regulator involved in the pathophysiology of mood disorders and a recognized upstream effector of FoxOs. The role of BDNF in depression is well characterized. Depression, at least in its severe form, is associated with reduced neuronal plasticity and lower levels of BDNF, while antidepressants, such as fluoxetine, could reactivate BDNF-mediated neuronal plasticity (Castrén and Rantamäki, 2010). BDNF reduces FoxO transcriptional activity through activation of TrkB and downstream kinases including Akt, which is a candidate susceptibility gene related to schizophrenia (Emamian et al., 2004). The link between Akt and depression was also provided by both genetic studies and postmortem data (Hsiung et al., 2003; Pereira et al., 2014). In response to BDNF, active Akt phosphorylates and inactivates
FoxOs (except for FoxO6, which is constitutively nuclear) by facilitating their translocation out of the nucleus (Wen et al., 2012). In both invertebrate and vertebrate brain, FoxOs can be phosphorylated and inactivated by serotonin selective reuptake inhibitors or exogenous serotonin via a PI3K/Akt-dependent mechanism (Polter et al., 2009; Liang et al., 2006). All of data suggests that downregulation or inactivation of FoxOs are highly related to antidepressant-like effects.

5. Antidepressants regulate the activities of FoxOs

The classical view of depression is that a functional deficit in neurotransmitters, particularly decreased levels of serotonin and noradrenaline, are associated with the clinical symptoms of depression. Serotonin could be viewed as a regulator of the insulin/IGF-1-FoxO pathway in stress physiology and modulation of FoxO by serotonin represents a conserved feature of stress physiology. Acute stressful life events can lead to the recurrence of episodes of major depression and chronic stress is strongly associated with both onset and recurrence of depression (Kessler, 1997; Risch et al., 2009). Studies of C. elegans showed that serotonin-deficient mutants exhibited DAF-16 (the homologues of FoxO) nuclear accumulation in constitutive physiological stress states, while treatment with exogenous serotonin directly or with fluoxetine, an antidepressant known to increase synaptic levels of endogenous serotonin, prevented DAF-16 nuclear accumulation in wild-type animals under aversive conditions (Liang et al., 2006). This result was confirmed by experiments showing that serotonin and fluoxetine can partially suppress DAF-16 nuclear accumulation in wild type animals exposed to hypergravity in C elegans (Kim et al., 2007). These observations suggest that individual behavior and physiological or psychiatric responses to the environment in animals are likely accompanied by the changes of the subcellular location/function of FoxO protein.

The tricyclic antidepressant agent, imipramine, is a monoamine-regulating antidepressant. Chronic treatment with imipramine for 28 days in mice caused appreciable increases in phosphorylated FoxO1 (Ser256), FoxO3a (Ser253) and Akt (Thr308) in the cerebral cortex, hippocampus and striatum, but no changes in the level
of total FoxO1, FoxO3a and Akt were observed (Polter et al., 2009). Our previous results also indicated that the FoxO3a subtype in PC12 cells could be inactivated by the antidepressant venlafaxine via PI3K/Akt pathway. Venlafaxine, on one hand, induced the phosphorylation of Akt and FoxO3a by the PI3K/Akt pathway and on the other hand reversed the reduction of phosphorylated Akt and FoxO3a and the nuclear translocation of FoxO3a induced by corticosterone (Wang et al., 2013). Lithium, another well known therapeutic drug in the treatment of mood disorder, reduced FoxO3a transcriptional activity, gene expression and protein levels in both the cytosol and nucleus, and this effect was independent of Akt (Mao et al., 2007). Moreover, this effect of lithium was observed in SH-SY5Y neuroblastoma cells and mouse brain (cortex and hippocampus) after relevant lithium treatments, which indicate that this effect is likely therapeutically relevant (Mao et al., 2007). Amphetamine is a compound which can increase the concentration of dopamine in the synaptic gap and thus induce hyperactivity, reversal of its action by lithium is used to model mania in bipolar disorder. A study from our lab indicated that pretreatment of animals with lithium prevented an amphetamine-induced decrease in striatal phosphorylated Akt and FoxO1 levels (Zheng et al., 2013). Lithium also attenuated amphetamine-induced locomotor activity and decreased prepulse inhibition (Zheng et al., 2013). The modulation by lithium of FoxO and its upstream kinases (such as Akt) may be relevant to the treatment of neuropsychiatric disorders. Since FoxO3a can be regulated by BDNF-induced Akt activation, and phosphorylated by antidepressants, we hypothesize that FoxO3a is a candidate transcription factor that plays a role in mood disorders, including depression. Further studies are needed to elucidate the role of FoxO transcription factors in the neuropathology and treatment of mood disorders.

6. **FoxO as a regulator of serotonin and norepinephrine signaling**

   Decreased or abnormally low levels of serotonin and norepinephrine in the synaptic cleft is traditionally viewed as a common cause of mood disorders, including depression. These neurotransmitters play their roles by binding and activating their specific receptors. With the exception of the 5-HT3 receptor, which is a ligand-gated
ion channel, all other 5-HT receptors and adrenergic receptors are seven transmembrane G protein-coupled receptors (GPCRs) whose binding to serotonin or norepinephrine activates several intracellular second messenger cascades. Some of these cascades are related to FoxOs. For example, the serotonin 2A receptor (5-HT2AR) is highly expressed on pyramidal neurons in the frontal cortex and has been implicated in several psychiatric disorders, including depression. The density of 5-HT2R is higher in depressive patients than that in normal persons. Higher 5-HT2A binding in the prefrontal cortical region has been shown to be associated with greater gene expression in depression and youth suicide (López-Figueroa et al., 2004). Antidepressants (such as mirtazapine and mianserin) could occupy 5-HT2AR, block its role and augment the clinical response to SSRIs (Celada et al., 2004). Serotonin binds to 5-HT2AR and stimulates Akt phosphorylation in the frontal cortex and in primary cortical neurons through the activation of a PI3K/Akt cascade (Schmid and Bohn, 2010). FoxO transcription factors are downstream targets of PI3K/Akt, which is mainly regulated by receptor tyrosine kinases (such as IGF-1 receptor) and GPCRs. Serotonin is a regulator of the insulin/IGF-1 pathway in stress physiology and exogenous 5HT can suppress the nuclear accumulation of FoxO in wild-type animals under stress (Liang et al., 2006). Moreover, in the peripheral system, serotonin also influences the physiological actions of FoxO, for example, serotonin enhances the proliferation of hepatocellular carcinoma cells through upregulation of FoxO3a (Liang et al., 2013). Duodenum-derived serotonin is a critical regulator of bone mass during the process of bone formation, and importantly FoxO1 mediates this effect (Kode et al., 2012). High circulating serotonin levels prevent the association of FoxO1 with CREB, resulting in suppressed osteoblast proliferation (Kode et al., 2012). These results demonstrate that FoxO acts as an endogenous mediator of serotonin signaling which may have consequences for the role of FoxOs in psychiatric disorders associated with altered serotonin metabolism.

As mentioned above, the 5-HT$_3$ receptor is a ligand-gated ion channel whereas other receptors for serotonin are GPCRs. Serotonergic GPCRs can be classified on the basis of their associated G$_{\alpha}$ proteins into Gs-protein coupled receptors (5-HT$_4$, 5-HT$_6$, 5-HT$_7$).
5-HT₇), Gi-protein coupled receptors (5-HT₁, 5-HT₃), and Gq/G11-protein coupled receptors (5-HT₂). As for norepinephrine receptors, the adrenergic α₁ receptor is a Gq coupled receptor whereas the adrenergic α₂ is a Gi coupled receptor. Activation of Gs-protein coupled receptors leads to activation of adenylate cyclase and an increase in cellular levels of cAMP, while activation of Gi-protein coupled receptors results in decreased levels of cAMP. cAMP is a second messenger important in many biological processes, including mood/emotional regulation. Downstream effectors of cAMP include cAMP-dependent protein kinase (PKA) and exchange factor directly activated by cAMP (Epac). Deficits in cAMP/PKA or cAMP/ERK signaling are viewed as one of the mechanisms for the behavioral symptoms in depression (Breuillaud et al., 2012; Musazzi et al., 2010). There is interplay between the PI3K/Akt/FoxO and cAMP/PKA signaling pathways (Chen et al., 2007). FoxO1 is a direct substrate for PKA and PKA phosphorylates FoxO1 at Thr24, Ser256, and Ser319, three known Akt phosphorylation sites (Lee et al., 2011). Epac is an exchange protein activated by cAMP. Both Epac and PKA induce ERK phosphorylation, and ERK in turn phosphorylates FoxO3a at Ser294, Ser344 and Ser425 (Yang et al., 2008), and FoxO1 at Ser246, Ser284, Ser295, Ser326, Ser413, Ser415, Ser429, Ser467 and Ser475 (Asada et al., 2007) resulting in degradation of FoxO proteins (Fig.2). These results show that the binding of ligands or agonists to the serotonin or norepinephrine receptors results in the alteration of intracellular cAMP, which affect the cAMP/PKA or cAMP/ERK signal pathway, and might influence the biological functions of FoxOs.
Fig. 2. FoxO as a regulator of serotonin signaling. 5-HT receptor is a G protein coupled receptor, when 5-HT binds, the receptor activates the coupled G protein, which can diffuse along the membrane surface and directly activate PI3K/Akt signal pathway, leading to inactivation of FoxO proteins. On the other hand, 5-HT receptor may also stimulate adenylyl cyclase/PKA and Epac/ERK1/2 signal transduction, both PKA and ERK1/2 enhance the phosphorylation of FoxO, which lead to inactivation of FoxO. Catalytic subunit of PKA translocates into nuclear and promote the activation of CREB, which is also highly related with depression.

7. FoxO as an effector of Hypothalamic-pituitary-adrenal axis

The activated hypothalamic-pituitary-adrenal (HPA) axis stimulates the secretion of adrenocorticotropic hormone (ACTH) from the pituitary, which ultimately promotes the secretion of glucocorticoids from the adrenal cortex. Depression has been associated with hyperactivity of the HPA axis and increased levels of glucocorticoid in the serum where continuously high glucocorticoid levels attenuate the responsiveness and number of glucocorticoid receptors on hippocampal granule cells thus leading to impaired negative feedback suppression of glucocorticoid secretion and an even higher level of circulating corticosteroid (Anacker et al., 2011a; Anacker et al., 2011b; Raison and Miller, 2003). A schematic presentation of how the amygdala and the hippocampus regulate the HPA axis and the stress response is presented in Figure 3. Recent evidence suggests that FoxO plays a crucial role in the
pathophysiological hyperactivity of the HPA axis (Lutzner et al., 2012; Lutzner et al., 2012). Glucocorticoids activate FoxO signaling, and FoxO signaling is a major contributor to the mechanism of glucocorticoid-induced muscle atrophy (Sandri et al., 2004; Zhao et al., 2007). FoxO1 and FoxO3a expression (both mRNA and protein) are up-regulated by glucocorticoid treatment in hippocampal neurons and muscle cells (Anacker et al., 2011a; Poulsen et al., 2011). Induction of FoxO3a expression requires glucocorticoid receptor-binding steroids and is reversed by concomitant treatment with the glucocorticoid receptor antagonist RU-486 (Lutzner et al., 2012). Importantly, recent data indicate that FoxO3a is a direct glucocorticoid receptor target, as there are two potential glucocorticoid response elements within the promoter region of FoxO3a. These glucocorticoid hormones may induce transcriptional activation of FoxO3a directly (Lutzner et al., 2012). These results indicate that glucocorticoids regulate FoxO3a on a transcriptional level. Further evidence indicates that glucocorticoids regulate FoxO3a post-translationally. Glucocorticoids induce the expression of SGK, a serine/threonine kinase and activation and phosphorylation of SGK (Thr-256, Ser-422) is dependent upon PI3K activity (Buse et al., 1999). Activated SGK can promote cell survival through phosphorylating FoxO3a at sites Thr-32 and Ser-253 (Brunet et al., 2001b). When given in relatively high doses, glucocorticoids inhibit PI3K/Akt signaling, thereby reducing the phosphorylation of FoxO (Wang et al., 2013; Stitt et al., 2004). Moreover, consistent with the notion that overload of glucocorticoids is crucial to the development of depression (Anacker et al., 2013; Anacker et al., 2011b), antidepressant treatment antagonizes the role of glucocorticoids (Budziszewska et al., 2000; David et al., 2009) and additionally increases the level of phosphorylated FoxO3a and PI3K/Akt (Wang et al., 2013).
Fig. 3. Regulation of HPA axis by the amygdala and hippocampus in normal and stress conditions. The corticotropin-releasing hormone neurons are regulated by both the amygdala and the hippocampus. Activation of amygdala promotes the release of cortisol through HPA axis. Mineralocorticoid receptors and glucocorticoid receptors are abundant in the hippocampus, both of which respond to and regulate the level of cortisol in the serum by glucocorticoid negative feedback. In stress condition, inappropriate activation of the amygdala extensively stimulates the HPA axis, resulting in high level of cortisol in the body. Chronic exposure of hippocampus to excessive glucocorticoid leads to neuronal loss and morphological atrophy, and thus the negative feedback becomes weaken or disrupted, which leads to much higher level of cortisol. Chronic stress induces nuclear localization of GR, which binds to glucocorticoid response element (GRE) and promotes the transcription of FoxO, GR may also activate SGK and subseqently inhibit the activity of FoxO.

8. FoxOs regulate neuronal morphology and possibly mediate neuronal atrophy

Neuroimaging studies with magnetic resonance imaging scanning demonstrated that compared with healthy individuals, depressed patients had an increased volume of the lateral ventricles and smaller volumes of the basal ganglia, thalamus, hippocampus, and frontal lobe (Arnone et al., 2012). The decreased cerebral size may be attributed to the loss and atrophy of neurons. In fact, clinical and preclinical studies have revealed that prolonged stress and major depression are associated with decreased neuronal synapses, neuronal atrophy of the PFC and the hippocampus
(Duman and Aghajanian, 2012; Ota et al., 2014; Sheline et al., 2003; Sheline et al., 1996). Compared with normal controls, depressed patients showed decreased cortical thickness, neuronal size, and neuronal and glial densities in the prefrontal cortical regions (Rajkowska et al., 1999), but the molecular mechanisms underlying these morphological alterations have not yet been identified.

FoxO transcription factors are important mediators of the effects of IGF-1/PI3K/Akt signaling. Withdrawal of IGF-1 causes reduced size of white matter structures in brain due to a decreased numbers of axons (Beck et al., 1995), while overexpression of IGF-1 leads to increased brain size due to an increase in cell size and apparently in cell number (Carson et al., 1993). As FoxOs are important key mediators of insulin and IGF-1 signaling (Kennedy et al., 2013), it is possible that FoxOs mediates the effect of IGF-1 in this process. Since overexpression of FoxO3a leads to reduced brain size and a decrease in neural progenitor number (Schmidt-Strassburger et al., 2012) and consistently, decreased FoxO activity has been reported to result in larger brain size and increased neural progenitor proliferation (Paik et al., 2009; Renault et al., 2009). Akt, one of the pivotal upstream kinases regulating the function of FoxO, has been shown to play a role in regulating cell size, a response which shares mechanisms with cellular atrophy or hypertrophy.

Constitutively active Akt increases muscle fiber size and prevents denervation atrophy in regenerating and adult rat muscle (Pallafacchina et al., 2002). In 2004, Stitt et al., (Stitt et al., 2004) reported that the IGF-1/PI3K/Akt pathway plays an important role in preventing skeletal muscle atrophy by inhibiting the expression of muscle-specific ubiquitin ligases MAFbx and MuRF1. Interestingly, this effect involves Akt-mediated inhibition of the FoxO transcription factors as mutation of FoxO1 attenuated the activation of Akt thereby preventing Akt-mediated inhibition of muscle atrophy (Stitt et al., 2004). This research extended the function of FoxO to the regulation of cellular atrophy and the role of FoxO in cell atrophy and hypertrophy has since been extensively studied. As in skeletal muscle, overexpression of FoxO3a also caused a significant reduction in cardiomyocyte size in mouse hearts in vivo and the induction of atrogin-1 by FoxO3a accounts for this effect (Skurk et al., 2005). The
role of FoxO transcription factors in mediating the muscle atrophy has been widely studied (Castets and Ruegg, 2013; Sanchez et al., 2014; Lee et al., 2012), however, the specific role of FoxO in neuronal atrophy is largely unknown. The four FoxO members found in humans, FoxO1, FoxO3a, FoxO4, and FoxO6, are all expressed in the CNS (Biggs et al., 2001; Salih et al., 2012). The IGF-1/PI3K/Akt signaling pathway is a key pathway for neuronal homeostasis (Rafalski and Brunet, 2011a). FoxOs are the classic downstream targets of the IGF-1/Akt pathway and both IGF-1/PI3K/Akt and FoxO have been identified in the regulation of cell atrophy. From this perspective, it is likely that FoxO mediates neuronal atrophy in the CNS and this effect is related to the etiology of depression. This speculation is worthy of further investigation potentially leading to a better understanding of the precise functions of FoxO transcription factors in the regulation of neuronal cell size and this might lead to the development of completely novel therapeutic approaches to the prevention or limitation of the morphological alterations that prevail in ageing and pathological states, such as depression and schizophrenia.

9. FoxOs play a inhibitory role in neurogenesis and synaptogenesis

Preclinical evidence showed that adult hippocampal neurogenesis may contribute to the mechanism of antidepressant drug action and BDNF is probably involved in this effect (Malberg et al., 2000; Guilloux et al., 2013; Sairanen et al., 2005). In fact BDNF has been implicated in regulating adult neurogenesis in the subgranular zone of the DG and is important for the regulation of the basal level of neurogenesis in adult mice (Lee et al., 2002; Waterhouse et al., 2012). FoxOs are downstream effector molecules of BDNF since BDNF activates a variety of signaling cascades, including PI3K/Akt, Ras/MAPK and cAMP/PKA pathways and activation of these pathways phosphorylates and inhibits the functioning of FoxOs (Kwon et al., 2011; de la Torre-Ubieta and Bonni, 2011). The regulatory effects of BDNF on FoxOs and its target genes play a significant role in the BDNF-mediated neurogenesis, neuronal survival and plasticity (Zhu et al., 2004).

FoxO transcription factors coordinately regulate diverse pathways to govern
neural stem cell or progenitor cell homeostasis in the brain (Paik et al., 2009; Renault et al., 2009). Given the importance of neural stem cells and progenitor cells for the generation of new neurons, the role of FoxO in the regulation of neurogenesis from neural stem cells has attracted attention. Genetic manipulation producing a transgenic mice expressing a constitutively active FoxO3a leads to mice having smaller brains accompanied with a loss of neurons in the olfactory bulbs, the cortex, the striatum, thalamic regions, and most notably the DG (Schmidt-Strassburger et al., 2012). Both the olfactory bulbs and the DG region are the sites for neurogenesis in adult, whilst neurogenesis assessed in adult FoxO3−/− and FoxO3+/+ mice revealed that FoxO3a deficiency in vivo led to an appreciable increase in the production of new neurons in the olfactory bulbs (Webb et al., 2013). However, the role of FoxOs in adult hippocampal neurogenesis remains to be investigated. FoxOs are classic downstream substrate of Akt (Zheng et al., 2002), these findings were quite consistent with earlier investigations showing that inhibition of 3-phosphoinositide-dependent protein kinase 1/Akt signaling reduces neurogenesis in neural progenitor cells, whereas constitutive activation of Akt or phosphatase and tensin homolog deletion promotes neurogenesis (Oishi et al., 2009; Gregorian et al., 2009). These results support the argument that FoxO negatively regulates neurogenesis in the brain.

Reduced synaptogenesis could be observed in the prefrontal cortex and hippocampus of patients with depression whereas normal synaptogenesis restores the synapse connections in the brain that may deteriorate under stress and depression (Bambico and Belzung, 2013). Mammalian target of rapamycin (mTOR) is a ubiquitous protein kinase involved in protein synthesis and synaptogenesis. Activation of mTOR by PI3K/Akt promotes protein synthesis and synaptogenesis (Ayuso et al., 2010). However, FoxOs play a role in protein degradation (White et al., 2013). Moreover, it has been shown that FoxO1 inhibits mTOR signaling and protein synthesis. Activation of constitutively active FoxO1 reduces the phosphorylation of 4E binding protein 1 (Thr-37/46) and by consequence the phosphorylation of the downstream protein p70S6 kinase leading ultimately to an attenuation of protein production (Southgate et al., 2007). This inhibition of protein synthesis affects
proteins (such as post-synaptic density protein 95 and synaptophysin) involved in synapse formation. On the other hand, recent studies suggest that the rapid-acting antidepressant and synaptogenic effects of ketamine are dependent upon mTOR activity in the medial prefrontal cortex (Li et al., 2010). This finding fits our hypothesis well. As mentioned previously, FoxOs inhibit mTOR signaling (Southgate et al., 2007), under this condition, inactivation of FoxOs may be beneficial for the antidepressant effect of ketamine. Microtubule architecture in neurons is an essential element in the regulation of neuronal morphology and motility as well as synaptogenesis (Conde and Caceres, 2009). FoxO loss-of-function models display increased stability of microtubule and overexpression of wild-type FoxO moderately destabilizes microtubules (Nechipurenko and Broihier, 2012). Thus, it is conceivable that FoxOs negatively regulate synaptic microtubule stability and thus negatively regulate synaptogenesis. The roles of FoxOs in the regulation of cellular atrophy, neurogenesis and synaptogenesis are depicted schematically in Figure 4.

![Figure 4](image-url)

**Fig. 4.** The roles of FoxOs in the regulation of cellular morphology. Neurotrophic factors or growth factors, such as BDNF or IGF-1, play a pivotal role in the maintenance of normal cellular morphology. IGF-1 binds to its receptor and activates several signaling pathways. FoxOs are the classic downstream targets of IGF-1/PI3K/Akt pathway. Both IGF-1/PI3K/Akt and FoxOs are involved in the regulation of cell size. Activated Akt phosphorylates and inactivates FoxO proteins, it also phosphorylate and activate mTOR, which subsequently phosphorylates eukaryotic
translational initiation factor 4E binding protein 1 (4E-BP1), 70kDa ribosomal protein S6 kinase (p70S6K), and thereby promotes protein translation. Active FoxOs suppress the phosphorylation of 4E-BP1 and p70S6 kinase and thus limit protein synthesis. In addition, FoxO transcription factors induce the expression of atrophy-related ubiquitin ligase atrogin-1 and cause cellular atrophy, this effect possibly account for the neural atrophy implicated in the process of depression. FoxO may also suppress neurogenesis through inhibiting Wnt signaling. Furthermore, FoxOs limit the stability of microtubules, all of which contribute to the morphological changes (such as neuronal atrophy, decreased neurogenesis and synaptogenesis) occurring in the depressed individuals.

Down-regulated adult hippocampal neurogenesis and synaptogenesis in the prefrontal cortex and hippocampus have been linked to major depressive disorder. Chronic stress leads to decreased neuronal/progenitor cell proliferation within the specific region of the brain, neuronal spines and neuronal plasticity are also reduced in this condition (Bambico and Belzung, 2013). Interestingly, this process is reversible. Administration of antidepressants will produce an increase in the number of new-born neurons within the hippocampus (Malberg et al., 2000; Guilloux et al., 2013; Sairanen et al., 2005). The observation that current antidepressant drugs promote adult hippocampal neurogenesis provides a much stronger evidence on this link (Mahar et al., 2014; Zunszain et al., 2013). These findings suggest a link between depression and adult neurogenesis in the hippocampus and, as discussed previously, many antidepressants repress the activation of FoxO. In this context, it can be speculated that the inactivation of FoxO3a by the PI3K/Akt signaling pathway achieves a more potent induction of adult hippocampal neurogenesis and synaptogenesis.

10. Conclusions and Prospective

FoxOs are recently discovered transcription factors which play a role in the onset or duration of psychiatric disorders. Results from cellular studies and animal models support the idea that FoxOs are potential mediators in the pathogenesis of depression
(Polter et al., 2009; Wang et al., 2013; Liang et al., 2006). Given the considerations to target FoxO proteins as a novel therapeutic strategy for major depression, it becomes essential to further investigate whether specific FoxO family members should be targeted. Activation and upregulation of upstream molecules of FoxOs, including growth factors (such as BDNF, fibroblast growth factor and IGF-1), receptor tyrosine kinases, Akt and ERK1/2 produce beneficial effects against depression (Shi et al., 2012; Evans et al., 2004; Krogh et al., 2014; Mikoteit et al., 2014; Musazzi et al., 2010). In this condition, over inhibition of FoxOs through activation of its upstream molecules increases the risk of cancer should be taken into consideration. The roles of FoxO transcription factors in major depression are summarized schematically (Fig. 5). However, the possibility of FoxOs and their signaling pathways being potential therapeutic targets in depression requires considerable experimental exploration and validation. Their nature as transcription factors and the difficulty to target them directly suggest that targeting the signaling pathways rather than the FoxOs themselves may be preferred strategy towards efficacious therapeutic agents. At present, most of the information about FoxOs is derived from cellular and animal models. Direct data from individuals diagnosed with major depression are still in great need. It will be desirable that future work should be carried out to study the alteration of FoxOs in depressive individuals and post mortem brain tissues. Studies of the genetic linkage of FoxOs and depression also provide evidence to support a role of FoxOs in this very important area of human pathophysiology.

Fig. 5. The roles of FoxOs in major depression. Chronic stress causes imbalances of

---

23
neurotransmitters (such as 5-HT and NE), decreased production of growth factors (such as BDNF and IGF-1) and hyperactivation of HPA axis. The interaction of neurotransmitters with their postsynaptic receptors and binding of growth factors to their receptor tyrosine kinases (RTKs) inactivate FoxOs through cAMP/PKA, PKC, PI3K/Akt or MEK/ERK signaling. Hyperactive HPA axis promotes the nuclear location and activation of FoxOs. Released glucocorticoid also bind to the GRE in the promoter of FoxOs and enhance the production of FoxOs. As a result, chronic stress leads to the activation of FoxO, which inhibits neurogenesis/synaptogenesis and promotes neuronal atrophy. Consequently, all of these cause behavioral manifestations related to depression.

FoxOs have been linked to skeletal muscle atrophy and control of cardiomyocyte size in numerous models (Sandri et al., 2004; Skurk et al., 2005) so it is reasonable to speculate that the Akt-FoxO pathway may participate in neuronal atrophy, impairment of synaptogenesis/neurogenesis and control of brain size in depression. Currently there is little evidence to support this intriguing possibility, but it is worth studying the effect of FoxOs on the regulation of neuronal cell size and exploring the mechanisms of decreased cerebral volume in depressed individuals. However, there are always benefits and short comings to everything, what we should keep in mind is that since FoxOs affect cell size, there are possible unwanted side effects of targeting FoxO in treatment of depression, such as muscle hypertrophy. Moreover, abnormalities observed in major depression most commonly occur in the raphe nuclei, nucleus accumbens, anterior cingulated cortex, amygdala and hippocampus (Goffer et al., 2013; Tripp et al., 2011; Underwood et al., 1999; Andrus et al., 2012), but we still need to elucidate whether the change of FoxOs and their related signal pathways could be altered in region specific manner.

Despite the usefulness of currently available antidepressant medications, the limitations of both efficacy and tolerability are nonetheless evident. A better understanding of the underlying neurobiology and neuropathophysiology of depression will help us to discover novel targets for pharmacological interventions. In this review, we have outlined the involvement of FoxOs and related molecules in the pathogenesis of depression. Targeting FoxO proteins might attenuate neuronal
apoptosis and play a neuroprotective effects in the central nervous system, which might be considered beneficial to block degenerative disorders. However, whether or not this can yield therapeutic target and the generation of a novel class of agents for the treatment of major depression will depend upon further research which reveals the importance of FoxOs in the physiological and particular processes of major depression.

Acknowledgements

This research was supported by National Natural Science Foundation of China (No. 81301099, No. 81373384 and No. 31371088), Natural Science Foundation of Guangdong Province (No. S2013040014202), China Postdoctoral Science Foundation (No. 2013M542192), and the Science and Technology Development Fund (FDCT) of Macao (FDCT 021/2015/A1).

Conflict of Interest Disclosures
The authors declare no conflict of interest.
References:


David, D.J., Samuels, B.A., Rainer, Q., Wang, J.W., Marsteller, D., Mendez, I., Drew, M., Craig, D.A., 
Leonardo, E.D., Hen, R., 2009. Neurogenesis-dependent and -independent effects of fluoxetine in 

de la Torre-Ubieta, L., Bonni, A., 2011. Transcriptional regulation of neuronal polarity and 

Duman, R.S., Aghajanian, G.K., 2012. Synaptic dysfunction in depression: potential therapeutic targets. 
Science 338, 68-72.


for impaired AKT1-GSK3beta signaling in schizophrenia. Nat. Genet. 36, 131-137.


R.C., Meng, F., Stead, J.D., Walsh, D.M., Myers, R.M., Bunney, W.E., Watson, S.J., Jones, E.G., 

Fournier, J.C., DeRubeis, R.J., Hollon, S.D., Dimidjian, S., Amsterdam, J.D., Shelton, R.C., Fawcett, J., 
2010. Antidepressant drug effects and depression severity: a patient-level meta-analysis. JAMA. 
303, 47-53.

patterns of mRNAs and consensus binding sequences for mouse DAF-16 homologues. Biochem. J. 
349, 629-634.

23, 571-585.

Goffer, Y., Xu, D., Eberle, S.E., D'amour, J., Lee, M., Tukey, D., Froemke, R.C., Ziff, E.B., Wang, J., 
2013. Calcium-permeable AMPA receptors in the nucleus accumbens regulate depression-like 

pathophysiological entities: CRH, neural circuits, and the diathesis for anxiety and depression. Mol. 
Psychiatry 18, 632-634.


Gregorian, C., Nakashima, J., Le Belle, J., Ohab, J., Kim, R., Liu, A., Smith, K.B., Groszer, M., Garcia, 

Groves, J.O., 2007. Is it time to reassess the BDNF hypothesis of depression? Mol. Psychiatry 12, 
1079-1088.

Guilloux, J.P., Mendez-David, I., Pehrson, A., Guiard, B.P., Repérant, C., Orvoën, S., Gardier, A.M., 
Hen, R., Ebert, B., Miller, S., Sanchez, C., David, D.J., 2013. Antidepressant and anxiolytic potential of the multimodal antidepressant vortioxetine (Lu AA21004) assessed by behavioural and 
neurogenesis outcomes in mice. Neuropharmacology 73,147-159.

Hajszan, T., MacLusky, N.J., Leranth, C., 2005. Short-term treatment with the antidepressant


Kennedy, L.M., Pham, S.C., Grishok, A., 2013. Nonautonomous regulation of neuronal migration by


Muller, J.M., Morelli, E., Ansorge, M., Gingrich, J.A., 2011. Serotonin transporter deficient mice are vulnerable to escape deficits following inescapable shocks. Genes Brain Behav. 10, 166-175.


Sairanen, M., Lucas, G., Ernfors, P., Castrén, M., Castrén, E., 2005. Brain-derived neurotrophic factor and antidepressant drugs have different but coordinated effects on neuronal turnover, proliferation, and survival in the adult dentate gyrus. J. Neurosci. 25, 1089-1094.


Sanphui, P., Biswas, S.C., 2013. FoxO3a is activated and executes neuron death via Bim in response to
beta-amyloid. Cell Death Dis. 4: e625
2013. The role of Akt/FoxO3a in the protective effect of venlafaxine against corticosterone-induced cell death in PC12 cells. Psychopharmacology (Berl) 228, 129-141.


Highlights
FoxO transcription factors regulate the behavioral manifestation of depression
Antidepressants regulate the phosphorylation/activities of FoxOs
FoxOs are regulated by serotonin and norepinephrine receptor signaling and HPA axis
FoxOs induce cell atrophy and this effect may affect neuronal morphology