Ageing Research Reviews 12 (2013) 67–75

Contents lists available at SciVerse ScienceDirect

Ageing Research Reviews

journal homepage: www.elsevier.com/locate/arr

Review article

A breach in the scaffold: The possible role of cytoskeleton dysfunction in the pathogenesis of major depression

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ARTICLE INFO

Article history:
Received 13 August 2012
Received in revised form 31 August 2012
Accepted 31 August 2012
Available online 17 September 2012

Keywords:
Depression
Cytoskeleton
Post-translational modification
Tubulin
Microtubule
Actin

ABSTRACT

Depression is one of the most common psychiatric disorders with inadequately understood disease mechanisms. It has long been considered that dendritic regression and decrease in the number of dendritic spines are involved in depression. Dendrites made up of microtubules and actin filaments form synapses with neighboring neurons, which come together as an important communication network. Cytoskeletal proteins undergo post-translational modifications to define their structure and function. In depression and other psychiatric disorders, post-translational modifications may be disrupted that can result in altered cytoskeletal functions. The disruption of microtubule and actin in terms of morphology and functions may be a leading cause of dendritic regression and decrease in dendritic spine in depression.

1. Introduction

Major depressive disorder (MDD) is one of the most common psychiatric disorders that leads to significant morbidities and medico-social burdens worldwide. It is typically characterized by persisting low mood, anhedonia, along with other behavioral changes including sleep pattern alteration, appetite change, and motivational deficit (Belmaker and Agam, 2008). Depressed individuals may also have feelings of worthlessness, hopelessness, and suicidal tendencies (Belmaker and Agam, 2008). This disorder affects more than 121 million people including 25% of women and 12% of men worldwide (Bromet et al., 2011; Gelenberg, 2010). Europe alone spends up to 118 billion Euros annually on health care related to MDD (Sobocki et al., 2006). The rapidly rising number of MDD patients has led to a 28% increase in the consumption of antidepressants during 2010, which in turn greatly strains the health care system (Guaiana et al., 2011).

MDD is a complex neuropsychiatric disorder with unclear etiology and many possible risk factors. It has a wide array of etiology ranging from genetic alteration (Ridder et al., 2005; Sallinen et al., 1999), monoamine-deficiency hypothesis (Delgado, 2000; Meyer et al., 2006), hypothalamic pituitary-adrenal (HPA) axis dysfunction (Belmaker and Agam, 2008; Swaab et al., 2005) and alterations in other excitatory and inhibitory neurotransmitters (aan het Rot et al., 2009; Krystal et al., 2002). Furthermore, new evidence has shown that histone deacetylase inhibitor (HDAC) (Covington et al., 2009; Gundersen and Blendy, 2009; Tsankova et al., 2004) and the p11 protein has antidepressant-like effects (Alexander et al., 2010; Svenningsson et al., 2006; Svenningsson and Greengard, 2007). Despite the appearance of new hypotheses, the exact cause of depression remains unclear.

MDD is typically marked by its repeated episodes of low mood, making treatment more complicated and costly (Nierenberg et al., 2003; Post, 1992; Simons et al., 1993). The most common pharmacotherapy for MDD is the use of antidepressants, which range from the earliest form of tricyclic antidepressants and monoamine oxidase inhibitors to serotonin or noradrenalin reuptake inhibitors (Hatzinger, 2010; Jackson et al., 2010). Despite the reduced side effects with the newer antidepressants, the efficacy has not improved significantly over time (Hatzinger, 2010). Many reports now show the importance of treatment until full remission (Nierenberg et al., 2003; Zajecka, 2003). Since MDD is marked by repeated episodes, long-term treatment with antidepressants

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1568-1637/$ – see front matter © 2012 Published by Elsevier B.V.
http://dx.doi.org/10.1016/j.arr.2012.08.004

would be needed, hence possibly causing financial burden. Additionally, a large proportion of patients are treatment-resistant, making treatment options difficult (Nelson, 2003). Deep brain stimulation (DBS) is one of the newest treatments for MDD patients, providing an alternative option for the treatment-resistant population (Kennedy et al., 2011). DBS allows progressive improvement in depression symptoms and behavior (Kennedy et al., 2011). However, it is a very invasive treatment with high surgery cost, risk of infection, and electrical defect (Malone, 2010).

MDD can be accompanied by many other psychiatric disorders such as anxiety disorders (Keenan et al., 2009), obsessive–compulsive disorder (Merrill et al., 2011), Alzheimer's disease (Aznar and Knudsen, 2011), and schizophrenia (Majadas et al., 2012). Taken together, there is an urgent need for researchers to reach a better understanding in the pathology of MDD in order to develop more effective treatments.

Accumulating evidence has shown that cytoskeletal abnormalities cause dendritic regression and decrease in dendritic spine in depressive disorder (Lee et al., 2002). Cytoskeletons are crucial structures in maintaining neuronal health (Gu and Zheng, 2009; Penzes et al., 2009). A number of post-translational modifications help to maintain function and stability of these cytoskeletons (Idriss, 2000; Saha et al., 2010; Sparaco et al., 2006; Westermann and Weber, 2003). The healthiness of the cytoskeleton can determine the fate of neurons in many neurological disorders including depression-associated neurodegeneration. Investigation of the relationship between cytoskeletal dysfunction and pathological observations in depression is therefore necessary.

2. Evidence of cytoskeletal abnormality in depression and other psychiatric disorders

A number of psychiatric disorders have been reported to exhibit dendritic regression or decrease in dendritic spine number that may be related to cytoskeletal abnormality. For example, there is a decrease in mushroom-shaped spine in Down syndrome (Blanpied and Ehlers, 2004). In schizophrenia, microtubule-associated protein (MAP)-2 and -3 are found to be abnormally expressed and there is altered phosphorylation of MAP1B (Blanpied and Ehlers, 2004). Depletion of MAP6 can also cause impairment of cognitive function (Fournet et al., 2012). As a result, synaptic stability and proliferation are disrupted (Gozes, 2011). In Alzheimer's disease (AD), hyperphosphorylated tau causes impairment in the tubulin assembly, causing microtubules in dendrites to become structurally unstable (Jinwal et al., 2010). This could be the eventual cause of decreased dendritic spine number (Knafo et al., 2009). These examples illustrate a likely involvement of cytoskeleton in maintaining synapse and consequently communication among neurons in different psychiatric disorders.

Depression is related to many other psychiatric disorders as mentioned above; therefore, it is not surprising that similar cytoskeletal abnormality is also present in depression. Growing evidence has shown cytoskeleton-related alteration in depression. Chronic stress is one of the important risk factors for depression (Lin and Koleske, 2010; Pittenger and Duman, 2008). During stress, an increase in glucocorticoids has been shown to trigger stress-induced dendritic remodeling (Chen et al., 2008; Magarinos and McEwen, 1995; Pawlak et al., 2005), resulting in regression of dendrites and a decrease in spine density, which leads to a decreased synaptic connectivity (Chen et al., 2008). Chronic stress animal models also show alteration in post-translational modified tubulin isoforms, with a decrease in the ratio of tyrosinated tubulin and increase in the ratio of acetylated tubulin (Yang et al., 2009), which can modulate the dynamics of microtubules (Palazzo et al., 2004; Peris et al., 2006; Yang et al., 2009). In a proteomics study, genetic alteration in tubulin and actin has been reported in an animal model of depression (Piubelli et al., 2011). This disrupts the function and isoform ratio of these proteins (Beasley et al., 2006; English et al., 2009; Kojima and Shirao, 2007). Apart from tubulin and actin, changes in their associated proteins such as a reduction in dendritic MAP in the animal model of depression resulted in a reduction of dendritic spine number (Soetanto et al., 2010). The number of post-translational modified tubulin isoforms also decreased, suggesting a decrease in tubulin post-translational modification (Bianchi et al., 2005, 2009). In contrast, therapeutic approaches that are targeted to reverse these effects help decrease behavior immobility and recover recognition memory deficits in the animal model of depression (Bianchi and Baulieu, 2012).

Actin is another cytoskeletal protein that works hand in hand with microtubules. Many reports have shown the importance of its interaction in dendritic spine morphology and synaptic plasticity (Hoogenraad and Akhmanova, 2010). Similar to microtubules, actin malfunction can play a role in many psychiatric disorders. Decrease in spine head size and the number of dendritic spine due to morphological changes of actin is evident in depression and AD (Aguilera, 2011; Milzani et al., 1997; Sabens Liedhegner et al., 2012). In a stress model using primary cultures of hippocampal neurons to mimic depression, abnormalities have been shown in actin morphology in the dendritic spines (Minamide et al., 2000). The normal actin meshwork became rod forms (Medina et al., 2008; Minamide et al., 2000). Although some reports suggest that these actin rods appear to be neuroprotective (Medina et al., 2008), others show microtubules being displaced by these actin rods, which in turn disrupt dendrite morphology, transport and synaptic plasticity (Davis et al., 2011; Medina et al., 2008; Minamide et al., 2000). These phenomena are also observed in AD (Aguilera, 2011). Additional to the formation of actin rods, there is a decrease in actin turnover in AD, causing an accumulation of aggregated F-actin, contributing to an increase in reactive oxygen reagents and apoptosis.

The evidence above shows the range of cytoskeletal alterations in depression, which suggests their relation to dendritic regression and loss of dendritic spines observed in depression. Moreover, treatments targeting cytoskeleton related proteins are able to reverse pathological effects. This strongly suggests the importance of conducting thorough research in how cytoskeleton can influence the course of depression and provide new therapeutic pathways.

3. Actin filament, microtubule and their interplay

3.1. Actin filaments

Actin filaments are the thinnest amongst the three types of neuronal cytoskeleton with a length of 5–7 nm. They are made up of two subunits: monomeric globular actin (G-actin) and polymeric filamentous actin (F-actin). The actin filament consists of a fast-growing barbed end known as the "plus end", and a slow-growing pointed end known as the "minus end". Upon formation, monomer G-actin binds to ATP to assemble into an actin nuclei that serves as the seed for F-actin (Firat-Karalar and Welch, 2011; Hild et al., 2010). Once this filament becomes stabilized, polymerization occurs to allow filament elongation where free-floating G-actin can be added onto its plus end. Eventually, a steady state is reached when the amount of G-actin added onto the plus end is at equilibrium with the amount of F-actin lost on the minus end. These strands of actin filaments nucleate to form a branching network. Actin-related protein 2/3 (Arp2/3) is one of the actin-nucleating proteins that bind onto matured actin filaments, also known as the mother filament (Dent et al., 2011). Nucleation begins with the activation of Arp2/3 complex by nucleation promoting factors. Once activated, this complex causes a daughter filament to

branch out, forming a Y-branched network (Korobova and Svitkina, 2010). This nucleation process continues as the daughter filament matures into a mother filament, eventually forming a branching network that acts as the supporting architecture in neurons (Firat-Karalar and Welch, 2011). Actin filaments are found in presynaptic terminals and growth cones, but they are especially abundant in dendritic spines. Its dynamic characteristics to polymerize and form Y-branch networks are essential and are considered to be a determining factor for dendritic spine morphology (Frost et al., 2010; Fukazawa et al., 2003).

3.1.1. Actin filament in dendritic spines

Actin filaments are the main type of cytoskeleton found in dendritic spines (Korobova and Svitkina, 2010). They nucleate at the spine head roofs, forming a mesh of Y-branching networks. This mesh acts as structural support to the shape of the spine (Hotulainen et al., 2009; Pollard and Borisy, 2003). In addition, actin filaments polymerize and depolymerize during long-term potentiation (LTP) and long-term depression (LTD), causing the spines to enlarge or shrink, respectively (Fukazawa et al., 2003). The finely tuned ratio of F-actin and G-actin through post-translational modification is important in maintaining dendritic spine morphology (Hoogenraad and Akhmanova, 2010). Reports have shown that an increase in F-actin ratio increases dendritic spine volume, while an increase in G-actin ratio does the opposite (Fukazawa et al., 2003). The aforementioned properties of the actin filaments allow individual spines to have continuous morphological modifications throughout their lifetime (Frost et al., 2010).

3.2. Microtubules

Microtubules are hollow cylinders with a diameter of 25 nm that have a length ranging from 200 nm to 25 μm. They are formed at the centrosome into short polymers and transported to the neurites (Conde and Caceres, 2009). Microtubules contain a system of proteins including microtubule-associated proteins, microtubule plus end proteins (Hoogenraad and Akhmanova, 2010), motor proteins, and capping proteins (O'Rourke and Sharp, 2011). These interacting protein systems work together to maintain the stability, function, and dynamics of microtubules (Sept et al., 2003). Microtubules act as transport tracks, with two different "motor proteins", dynein and kinesin, running along the microtubular tracks, transporting vesicles to and from the cell body (Perlson et al., 2010).

Microtubules are made up of two isoforms of tubulin dimers: α- and β-tubulin. These two dimers form an αβ-tubulin heterodimer. Like the actin filament, microtubules contain a plus and minus end, allowing them to be highly dynamic by growing and disassembling rapidly (Conde and Caceres, 2009). During rapid growth, microtubule polymerizes and depolymerizes (Gu et al., 2008; Hoogenraad and Akhmanova, 2010). The minus end of a microtubule is often capped by a capping protein to maintain microtubule stability (O'Rourke and Sharp, 2011).

3.2.1. Microtubules in dendritic spines

Traditionally, microtubules were thought to locate only in the axons and dendrites. With advancing imaging techniques, many reports now show that microtubules can enter and exit dendritic spines through polymerization and depolymerization (Hu et al., 2008). The polymerization process appears to be triggered by microtubule plus end proteins (+TIP) (Akhmanova and Steinmetz, 2008; Penzes et al., 2009). Among different +TIPs, EB family proteins and Cap-Gly proteins work together in pulling the microtubule into the dendritic spine. Cap-Gly proteins including CLIP170, CLIP115 and $p150^{glued}$ bind onto the plus end of microtubule. In turn, their bindings allow EB family proteins including EB1, EB2, and EB3 to be attached onto the microtubule, thereby increasing microtubule polymerization and subsequent elongation into the dendritic spine (Akhmanova and Steinmetz, 2008; Penzes et al., 2009). Microtubules are responsible for transporting organelles into and out of the dendritic spine (Jaworski et al., 2009). An increase in neuron–neuron communication causes microtubules to enter the dendritic spine more frequently. Knock-out of EB3 in rat primary culture neurons caused a reduced number of dendritic spines and the number of mushroom-shaped spines in particular (Gu et al., 2008; Hu et al., 2008).

3.3. Actin filament and microtubule interaction in the dendritic spines

Actin filaments span the dendritic spine to maintain spine morphology and plasticity (Fischer et al., 1998; Hoogenraad and Akhmanova, 2010). One may question whether actin filaments and microtubules work together in regulating spine functioning as well. As previously discussed, microtubules enter dendritic spines by binding onto +TIP. It is now known that +TIP binds to actin and affects spine plasticity by modulating actin dynamics. It has been considered that cortactin activates Arp2/3 as a substrate of Src (Di Stefano et al., 2007; Jaworski et al., 2009). Upon activation, actin Y-branched network becomes stabilized and promotes formation of mushroom spine (Daly, 2004; Hering and Sheng, 2003). When +TIP EB3 is knocked-down by small hairpin ribonucleic acid (shRNA), a decrease of F-actin would be observed (Rao et al., 2009). This in turn changes dendritic spine morphology (Jaworski et al., 2009). On the contrary, an increase in microtubule invasion into the dendritic spines leads to an expansion of dendritic spine volume (Merriam et al., 2011). Such evidence demonstrates that interaction of actin filaments and microtubules is important in maintaining the proper functioning of dendrites and dendritic spines.

4. Aberrant post-translational modification in cytoskeletal abnormality in relation to depression

Post-translational modifications refer to a number of processes that modify specific amino acids in a protein after translation. Actin and microtubules undergo post-translational modification constantly (Westermann and Weber, 2003; Wloga and Gaertig, 2010). Since post-translational modification has a central influence on cytoskeletal functions, it is plausible that disturbance in this process causes cytoskeletal dysfunction associated with neuropsychiatric disorders including depression.

4.1. Actin arginylation

Actin arginylation involves the addition of arginine onto β-actin by the enzyme arginyltransferase (Ate) (Saha et al., 2010). It is a process that maintains actin polymer levels by increasing overall actin polymerization (Decca et al., 2006; Wong et al., 2007). Another important role of actin arginylation is to present proteins for ubiquitin-dependent degradation, which prevents actin from forming aggregates (Bachmair et al., 1986; Karakozova et al., 2006). Actin arginylation also strengthens the actin Y-branch network, which is the main architecture that supports the dendritic spine morphology (Hoogenraad and Akhmanova, 2010; Hotulainen et al., 2009; Karakozova et al., 2006).

In Ate knock-out mice, increase of actin nucleation was observed (Kwon et al., 2002; Saha et al., 2010). Although actin nucleation helps create a strong Y-branch network that supports the synapse, the overall actin polymerization rate was slower in the absence of Ate (Kwon et al., 2002; Saha et al., 2010). In turn, these actin filaments no longer elongated as much, and each filament was 1.4 times shorter on average (Saha et al., 2010). The consequence was that the actin Y-branch in these knockout mice eventually

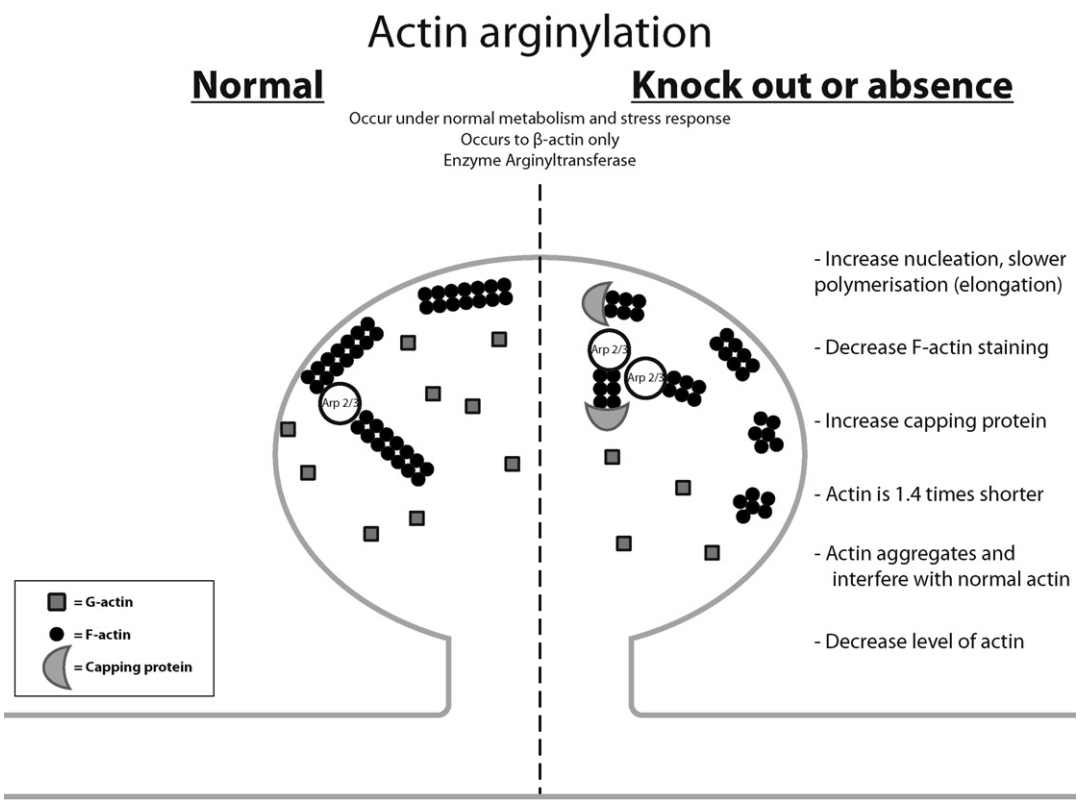

Fig. 1. Actin arginylation plays an important role in regulating actin polymer level (G- and F-actin) and its overall polymerization. On the left 'Normal' side of the dendritic spine, Arp 2/3 is recruited to the mother actin filament strand allowing nucleation to occur, forming a Y-branch. On the right 'Knock out or absence' side, no arginylation is taking place. Although there is an increase in Arp 2/3 recruitment causing increased formation of Y-branches, each strand is shorter. These Y-branches eventually aggregate and interfere with other normally functioning actin filaments. The knock-out model also has an increase in capping protein that prevents actin from carrying out its normal function in altering dendrite spine morphology.

aggregated into actin rods and interfered with the remaining non-aggregated actin (Fig. 1) (Kwon et al., 2002; Saha et al., 2010). The actin rods not only lose their ability to treadmill, they displace microtubules in the dendrite and disrupt transport as seen in depression (Karakozova et al., 2006).

The actin rod accumulation due to altered arginylation may contribute to a reduction of dendritic spine size (Saha et al., 2010) as the absence of arginylation weakens the actin Y-branch network. As mentioned, actin is important in supporting the mushroom shape of a mature dendrite. A decrease in arginylation can result in either a decrease in the size or complete collapse of dendritic spines, leading to a decrease in total spine number (Saha et al., 2010). Reduction of spines in their size and number is often observed in animal models of depression (Calabrese et al., 2006; Fiala et al., 2002; Glantz and Lewis, 2001). The disrupted dendritic transport caused by actin rods can be observed in depression models, resulting in dendritic dieback due to lack of protein supply (Manji et al., 2012; Perlson et al., 2010).

4.2. Actin glutathionylation

Glutathionylation is a reversible process that refers to the addition of glutathione through a disulfide bond, turning glutathione into glutathione disulfide. Glutathionylation is an important physiological process to defend cells from oxidative stress (Schulz et al., 2000). Dysregulation of this process is considered to play an important role in many neurodegenerative diseases (Sabens Liedhegner et al., 2012). Normally, the ratio between glutathione and glutathione disulfide is about 9:1 (Sparaco et al., 2006). However, glutathionylation increases during oxidative stress. Conversion from glutathione to glutathione disulfide can neutralize reactive oxygen species (Fig. 2).

Glutationylation of actin is important for maintaining its dynamic morphology by preventing oxidative modifications (Dalle-Donne et al., 2005; Milzani et al., 1997). Increased oxidative stress has been observed in neurons of depressed patients (Sarandol et al., 2007). Oxidative modifications of actin in depression models cause permanent changes in actin structure by altering the F-actin and G-actin ratio (Milzani et al., 1997). The ratio shifts F-actin to G-actin and the decrease of the efficiency of polymerizing G-actin into F-actin greatly affects the actin Y-branch network (Dalle-Donne et al., 2005; Hoogenraad and Akhmanova, 2010; Milzani et al., 1997; Wang et al., 2003). When glutathionylation is reversed, there is an increase of transforming G-actin into F-actin to promote polymerization of actin (Wang et al., 2003). On the other hand, significant increase in actin glutathionylation can also lead to actin filament disarrangement (Pastore et al., 2003; Sabens Liedhegner et al., 2012). This suggests the importance of keeping a balance between glutathione and glutathione disulfide for optimal actin function.

4.3. Microtubule acetylation and deacetylation

Most post-translational modifications occur on α-tubulin. Acetylation is a reversible process that occurs on the K40 residue of the α-tubulin subunit after polymerization of microtubules (Bulinski, 2007). Acetylation involves the addition of an acetyl group, while deacetylation involves the removal of an acetyl group by histone deacetylase (HAD)-6 and sirtuin-2 (Perdiz et al., 2011; Sudo and Baas, 2010). Since acetylation occurs on more stable polymerized microtubules, the process can therefore act as a marker of mature microtubules (Perdiz et al., 2011). After acetylation,

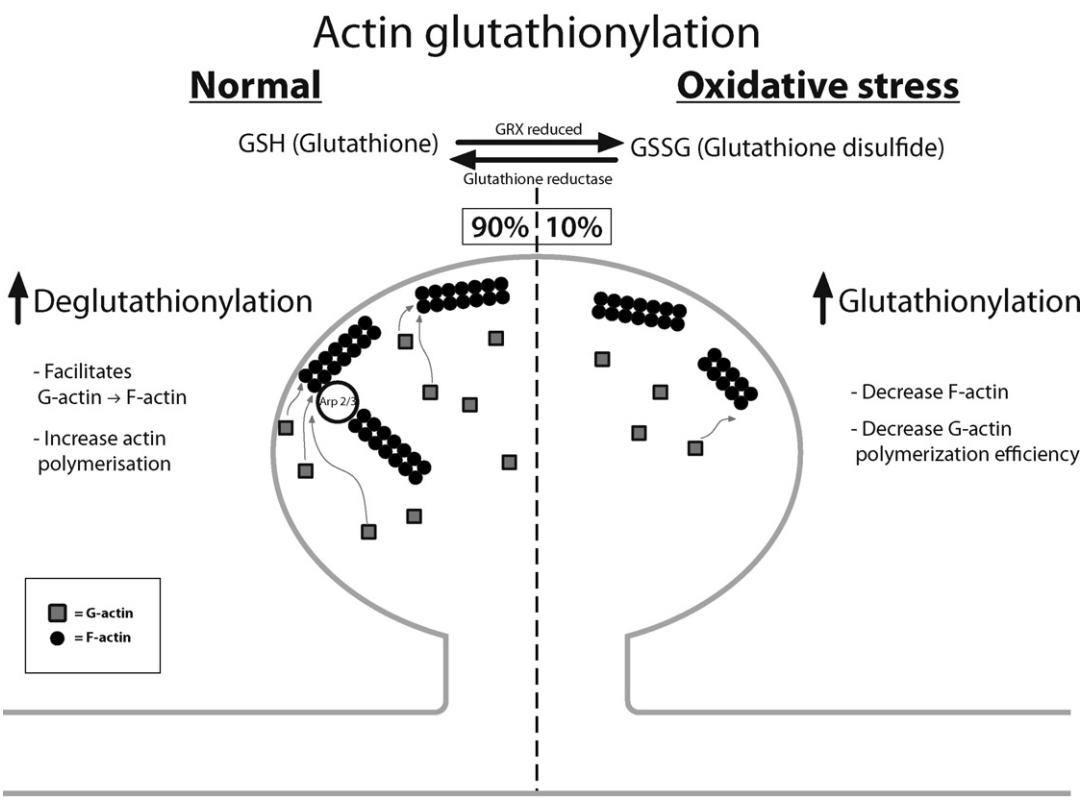

Fig. 2. Glutathionylation is a protective pathway that is activated during oxidative stress. Under physiological conditions, G actin is recruited to F actin. This allows actin polymerization and nucleation forming Y-branches. GSH to GSSG is kept at a constant 9:1 ratio. However, during oxidative stress, there is an increase of GSSG causing activation in glutathionylation. This results in a decrease in F-actin level, which may be due to a decrease in actin polymerization, as less G-actin is being recruited to form F-actin.

microtubules become less dynamic and have increased structural stability (Palazzo et al., 2004).

It has been shown that acetylation of microtubules increases the binding affinities of motor proteins kinesin-1 and dynein onto microtubules, resulting in increasing vesicular transport along the dendrites (Fig. 3) (Bulinski, 2007; Reed et al., 2006). Microtubules that are acetylated are more prone to be severed (Roll-Mecak and Vale, 2006; Sudo and Baas, 2010). When microtubules are assembled into stable structures, they must be severed to regulate the length of microtubules (Yu et al., 2008), allowing microtubules to be dynamic with free ends as well as increasing the total number of microtubules within a cell (Conde and Caceres, 2009).

Dendritic regression is observed in depression (Chen et al., 2008) and other psychiatric disorders like AD (Mattson, 2003). Since microtubules are the main architectural structure of the dendrite, their regression can be an indication of microtubule instability. Acetylation causes microtubules to become more stable, leading to efficient dendritic transport and microtubule severing. Nevertheless, reports have shown that the key to maintaining microtubule health is in the equilibrium of acetylation and deacetylation, rather than favoring either process (Bianchi et al., 2003; Mattson, 2003). A decrease in acetyated tubulin was observed in neurons of AD patients, causing impaired axonal function (Mattson, 2003). Acetylation of tubulin is also important in Huntington's disease (HD) (Hempen and Brion, 1996; Lai et al., 2009). The neurotoxic effect seen in HD is shown to be caused by faulty microtubule transport due to reduced acetylation (Dompierre et al., 2007; Gardiner and Marc, 2010). It is plausible that the same occurs in depression, thereby causing a disruption in the normal transport and a possible breakdown in the neuron–neuron communication system. A vast increase in acetylated tubulin was found in chronic stress rat brains resulting in failed neuronal plasticity and dendritic retraction in the hippocampus (Bianchi et al., 2003). The same result was observed in another chronic stress rat model (Yang et al., 2009). These contrasting results illustrate the importance in the ratio of acetylated and deacetylated tubulin for microtubule health. Modulation of this ratio has shown to rescue defective axonal transport (Medina et al., 2008).

4.4. Microtubule tyrosination and detyrosination

Tyrosination and detyrosination of microtubules is a balanced cycle. Tyrosination refers to the addition of a tyrosine in the C-terminal of α-tubulin, and detyrosination is the removal of this tyrosine (Idriss, 2000). Both tyrosination and detyrosination occur under normal physiological circumstances and involve two enzymes called tubulin tyrosine ligase (TTL) and tubulinyl tyrosine carboxypeptidase. Microtubules that contain tyrosinated tubulin are often very dynamic and less stable in structure. This is because tyrosination increases the likelihood of recruiting CAP-Gly to the microtubule plus-end. Recruited CAP-Gly assists the binding of EB3 and increases microtubule dynamics (Fig. 3) (Peris et al., 2006). Conversely, detyrosinated microtubules are more stable and are observed to increase with age (Cumming et al., 1984). The determining factor of the balance between tyrosination and detyrosination is the exchange between non-assembled tubulin and microtubules. If polymerization of microtubules is slow, there will be an increase in detyrosination (Barra et al., 1988).

The tyrosination and detyrosination cycle has been shown to be disturbed under pathological conditions. In a depression rat model, a 90% decrease in tyrosinated tubulin led to dendritic retraction and failure in neuronal plasticity (Bianchi et al., 2003), possibly due to decreased CAP-Gly microtubule interaction with actin (Hoogenraad and Akhmanova, 2010). Shifts in the cycle's

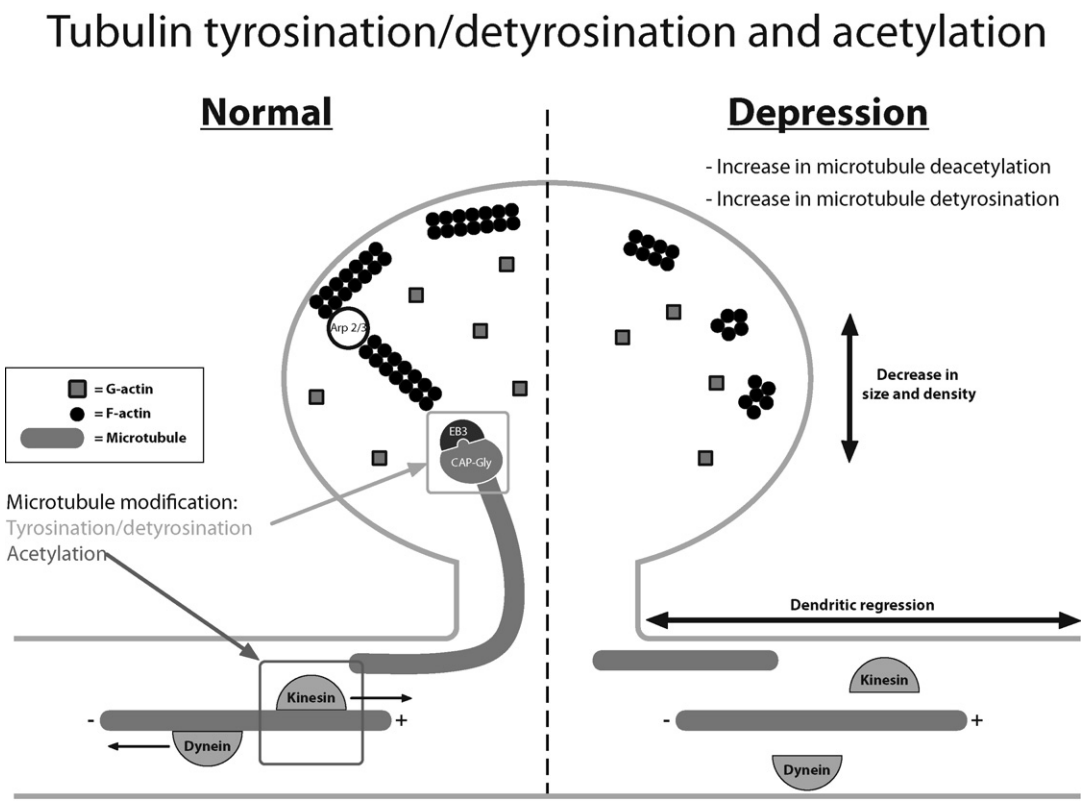

Fig. 3. Acetylation increases the binding of kinesin to microtubules. Kinesin is a motor protein that is very important in transporting nutrients to maintain cell viability and signaling for effective neuronal communication. It is speculated that under pathological conditions when there is an increase in microtubule deacetylation, the efficiency of neuronal communication becomes dysfunctional. In return, this may cause dendritic regression as seen in depression. On the other hand, microtubule tyrosination and detyrosination is a balanced cycle under physiological conditions. Tyrosination attracts the CAP-Gly domain to be recruited to the plus-end of the microtubule, which assists EB3 binding. When EB3 is bound, the microtubule is facilitated to move in and out of the dendritic spine to interact with actin – a process that is thought to be important to dendritic spine plasticity. In depression, detyrosination may increase, thereby causing the balance to be lost. This decreases EB3 binding to the microtubule, causing a decrease in dynamics of the microtubule. Without the interaction between actin and the microtubule, dendritic spines may therefore decrease in size and number as seen in many depression models. This may eventually cause dendritic regression.

equilibrium have been observed in both sleep deprivation and AD animal models (Basheer et al., 2005). In sleep-deprived rats, there is a 28% increase in tyrosinated α-tubulin – an indication of increased unstable, more dynamic microtubules – and decreased synaptosomal-associated protein 25 (SNAP25) were observed (Basheer et al., 2005). Although more dynamic microtubules can signify improved synaptic plasticity due to increased microtubule–actin interactions, the observed decrease in SNAP25 intensity indicated decreased overall synaptic activity. While the precise indication of these findings is yet to be better understood, they do indicate the potential relevance of microtubule tyrosination–detyrosination balance in neuropsychiatric disorders.

5. Other possible causes of dendritic regression and decrease in dendritic spines in depression

MDD patients have been shown to have a translocation of the Disrupted In Schizophrenia 1 (DISC1) (Chubb et al., 2008; Hashimoto et al., 2006). Translocation of DISC1 leads to reduced hippocampal gray matter and functional engagement in a mouse model (Singh et al., 2011). DISC1 plays a role in regulating neurogenesis, axon and dendrite growth, synaptogenesis, and microtubule dynamics (Hashimoto et al., 2006; Hayashi-Takagi et al., 2010; Shinoda et al., 2007). Genetic variation in MDD may therefore affect synaptic plasticity and dendrite morphology through interference with microtubule dynamics. DISC1 regulates these processes through modulation of the wingless-int (Wnt) signaling via inhibition of glycogen synthase kinase 3 beta (GSK-3β) (Singh et al., 2011). More importantly, one of the Wnt downstream signaling proteins is MAP1B, which directly affects microtubule stability and organization (Budnik and Salinas, 2011). DISC1 can also directly inhibit GSK-3β (Singh et al., 2011), leading to activation of β-catenin, which translocates into the nucleus and associates with transcription factors needed for cell proliferation (Okamoto et al., 2010). The reverse causes GSK-3β to phosphorylate β-catenin and degradation by ubiquitination or proteosome (Okamoto et al., 2010).

The importance of Wnt signaling in dendrite structure and synaptic assembly has become more evident. Wnt signaling activates futsch – a protein that stabilizes microtubules during microtubule loop formation at synaptic terminals (Hall et al., 2000; Purro et al., 2008; Roos et al., 2000). This process is essential for synaptic formation (Roos et al., 2000). Wnt also recruits synaptic vesicles and stimulates clustering of postsynaptic density protein 95 (Farias et al., 2009). The increase in Wnt receptor – frizzled (Fz) – in the hippocampus signifies an increase in synapse formation (Sahores et al., 2010). In MDD, variants in DISC1 lead to disruption of Wnt/GSK-3β signaling (Singh et al., 2011), interrupting neural progenitor cell proliferation, and inhibits neuronal migration, as the cytoskeletons are no longer stabilized by Wnt signaling (Budnik and Salinas, 2011; Singh et al., 2011). In a chronic stress animal model that mimics depression, Wnt signaling is significantly downregulated, while activity of GSK-3β is significantly increased (Wilkinson et al., 2011). These changes resulted in depression phenotypes such as decreased mobility (Wilkinson et al., 2011).

There is no study showing the direct changes of cytoskeletons after the modification of DISC1 and Wnt signaling in MDD. However, microarrays show that many antidepressants regulate the expression of Wnt and Fz in rodent hippocampus, improving learning and mobility tasks (Okamoto et al., 2010). It is clear that the alteration of DISC1 and Wnt in MDD can lead to a cascade of changes to their downstream signaling pathways, which in turn compromise cytoskeleton stability and synaptic function.

6. Conclusion

Cytoskeletal abnormalities are evident in MDD, causing dendritic regression and decrease in dendritic spines (Chen et al., 2008; Lee et al., 2002; Soetanto et al., 2010). These phenomena translate into learning deficits and immobility in animal models of depression (Bianchi and Baulieu, 2012; Calabrese et al., 2006). Cytoskeletal abnormalities are not only seen in MDD, but also in AD and schizophrenia (English et al., 2009; Lin and Koleske, 2010). Similar to animal models of depression, animal models of AD and schizophrenia also present learning deficits and immobility (Bolton et al., 2012; Fournet et al., 2012). This is a good illustration of the common phenotype resulting from cytoskeletal abnormalities. AD is one of the most common forms of dementia affecting 35.6 million people globally. The World Health Organization predicted this number to double in year 2030 and triple in year 2050. AD has also been considered to have many pathological similarities to MDD (Wuwongse et al., 2010). Schizophrenia is another devastating psychiatric disorder, affecting 24 million people globally where 90% of these people remain untreated.

Posttranslational modification is indeed one important process in defining the structure and function of microtubules and actin. Studying posttranslational modification alone only contributes to a small part in understanding cytoskeletal abnormalities, as cytoskeletal morphology and function are controlled by other processes as well. Microtubules before maturation are severed at the nucleus to a suitable size before being transported to the appropriate location in the dendrite (Yu et al., 2008). If this process becomes abnormal, it will give rise to multiple short segments of microtubules, causing functional disruption (Quarmby and Lohret, 1999; Sudo and Baas, 2011; Yu et al., 2008). Actin nucleation, as mentioned earlier, is important in maintaining synapse morphology (Firat-Karalar and Welch, 2011). The equilibrium between actin nucleation and recycling is controlled by Arp2/3 and cofilin (Firat-Karalar and Welch, 2011; Minamide et al., 2000). A tip in the balance can change the structure of its Y-branched network, and in turn compromise synaptic morphology (Minamide et al., 2000).

Cytoskeletal abnormalities are common denominators for MDD, AD, and schizophrenia. Treatment plans and interventions for these psychiatric disorders are difficult, as their causes remain unclear. Through understanding the causes of or contributing factors to cytoskeletal abnormality, the progression of these psychiatric disorders could be more predictable. A great deal of work needs to be done to explore different contributing factors causing these observed cytoskeletal abnormalities. The anticipated findings will eventually provide more in depth understanding of MDD, AD, and schizophrenia.

Acknowledgements

Experimental work in these laboratories regarding the cytoskeleton dysfunction in the pathogenesis of major depression is supported by The University of Hong Kong (HKU) Alzheimer's Disease Research Network under Strategic Research Theme on Healthy Aging, HKU Seed Funding for Basic Science Research (201111159160) and (201011159118).

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