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Neurobiological links between depression and AD: the role of TGF-β1 signaling as a new pharmacological target

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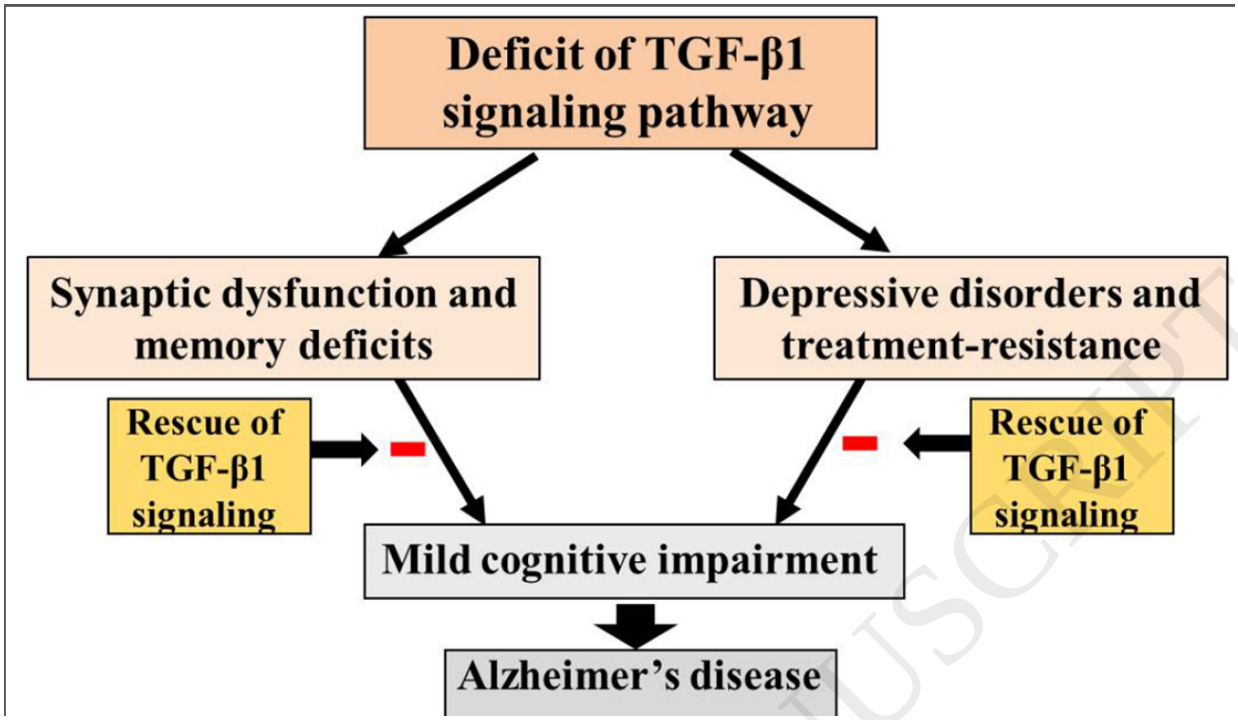
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Graphical Abstract



Abstract

In the last several years a large number of studies have demonstrated the neurobiological and clinical continuum between depression and Alzheimer's disease (AD). Depression is a risk factor for the development of AD, and the presence of depressive symptoms significantly increases the conversion of Mild Cognitive Impairment (MCI) into AD. Common pathophysiological events have been identified in depression and AD, including neuroinflammation with an aberrant Tumor Necrosis Factor-α (TNF-α) signaling, and an impairment of Brain-Derived Neurotrophic Factor (BDNF) and Transforming-Growth-Factor-β1 (TGF-β1) signaling.

TGF-β1 is an anti-inflammatory cytokine that exerts neuroprotective effects against amyloid-β (Aβ)-induced neurodegeneration, and it has a key role in memory formation and synaptic plasticity. TGF-β1 plasma levels are reduced in major depressed patients (MDD), correlate with depression severity and significantly contribute to treatment resistance in MDD. The deficit of Smad-dependent TGF-β1 signaling is also an early event in AD pathogenesis, which contributes to inflammaging and cognitive decline in AD. A long-term treatment with antidepressants such as

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selective-serotonin-reuptake inhibitors (SSRIs) is known to reduce the risk of AD in patients with depression and, SSRIs, such as fluoxetine, increase the release of TGF-β1 from astrocytes and exert relevant neuroprotective effects in experimental models of AD.

We propose the TGF-β1 signaling pathway as a common pharmacological target in depression and AD, and discuss the potential rescue of TGF-β1signaling by antidepressants as a way to prevent the transition from depression to AD.

Keywords: Alzheimer's disease, depression, amyloid-β, Transforming-Growth-Factor-β1, antidepressants.

1.Introduction

Alzheimer's disease (AD) is an incurable dementia affecting about 33 million people worldwide. Its incidence doubles every 5-10 years. AD is a neurodegenerative disorder characterized by memory loss, cognitive decline, and neuropsychiatric symptoms such as depression, agitation and psychosis that are common precipitants of institutional care [1].

Different cohort studies have demonstrated that depression is one the most frequent behavioral symptoms in AD [2] and the most prevalent comorbidity [3].

The old concept of "pseudodementia", defined as a late-life depression (LLD) with cognitive impairment, has been revised in light of the epidemiological links and the neurobiological continuum between major depressive disorder (MDD), in particular LLD, and AD [4-7]. Starting from a large epidemiological evidence, depression is now considered as a relevant risk factor for the development of AD. However, a still open question is to understand whether a history of depression acts simply as an independent risk factor for AD [8] or whether depressive disorders represent a prodromal symptom of AD, which increases the conversion of Mild Cognitive Impairment (MCI) to

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AD [9, 10]. The two hypotheses can probably co-exist and are not mutually exclusive, as suggested by epidemiological evidence and longitudinal studies in MCI and LLD patients, where depressive disorders act as prodromal symptoms of AD [8, 11-13], and by studies in earlier-life MDD patients, where depression occurring years before seems to be an independent risk factor for subsequent AD [4, 14].

The first systematic meta-analysis conducted by Ownby *et al*. [8] clearly demonstrated that the interval between the diagnosis of depression and AD was positively related to an increased risk of developing AD, suggesting that MDD was an independent risk factor for AD, rather than a prodromal symptom. Moreover, it is known that depression occurring early in life (more than 25 years before the diagnosis of AD) is associated with a late development of AD [15], and the rate of dementia increases by 13% with every affective episode leading to hospital admission for patients with depressive disorders [16].

Long-term epidemiological studies have demonstrated that the risk to develop AD is high in MDD patients receiving a diagnosis of MDD one year from dementia (depression as a prodrome of dementia). However, AD risk remains relatively high in MDD patients with different depressives episodes older than 10 years, suggesting that a history of MDD should be considered an independent risk for the development of AD [17, 18].

Recent studies in LLD and MCI patients [18-22] suggest that, when developing disease-modifying drugs able to prevent the transition from MCI to AD, it would be useful to focus on the neurobiological continuum between late-life depressive disorders on one side, MCI and AD on the other.

After briefly examining epidemiological and neurobiological data linking depression, MCI and AD, we will focus on TGF-β1, because recent evidence suggest that a deficient TGF-β1 signaling occurs in both major depression and AD, thus pointing to a pathophysiological event common to these two diseases. Finally, we will discuss the rescue of TGF-β1 signaling pathway as a way to prevent the transition from depression to AD.

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2.The mysterious links between depression and Alzheimer's disease: from epidemiological evidence to neurobiological continuum

LLD is known to be associated with prevalent MCI, an established risk factor for the progression of dementia [19, 22]. A recent meta-analysis found an overall prevalence of 32% for depression in MCI patients [1], with depressive symptoms more prevalent in hospital-based studies (44.3%) than in population-based studies (15.7%) [20]. A comorbidity with MCI was found in 25% to 50% of patients with LLD [4, 21-23]. MCI is considered a prodromal syndrome towards AD, although only a proportion of individuals with MCI patients (50-70%) develop dementia within the next 5 to 7 years [24]. MCI is characterized by a selective deficit of episodic memory (amnestic MCI) or other cognitive domains (non-amnestic MCI) [24]. Amnestic MCI is associated with an increased risk to develop AD [25], in particular when it is associated with clinically-relevant depressive symptoms [9, 26].

The first study that demonstrated the central role of depression as a risk factor for the conversion from MCI to AD was conducted by Modrego and Fernandez in 2004 [9]. In that 3-years prospective cohort study, 114 amnestic MCI outpatients were recruited in a community general hospital. The authors found that a high percentage of depressed MCI patients developed dementia (85%) in comparison with non-depressed MCI patients (32%) (relative risk, 2.6). Interestingly, MCI patients with a poor response to antidepressants showed an especially increased risk of developing dementia, suggesting that treatment-resistant depression (TRD) could be a prodromal sign of AD in MCI patients with depression.

The efficacy of antidepressants as first-line treatment of depression in AD is low because of the absence of benefit compared with placebo, and the increased risk of adverse events [27]. A recent meta-analysis of selective-serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs) treatment for depression in AD detected "small to null" effect sizes, with small responses in AD patients with subsyndromal depression [28]. Lack of

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treatment response in patients with LLD is also common, and it can be hypothesized that treatment-resistance in MCI patients might constitute a "potential" biological marker between LLD and prodromal AD [29].

Positron emission tomography (PET) imaging with ^{18}F-florbetapiris used to assess brain beta-amyloid (Aβ) deposition in the AD brain [30]. Treatment-resistance in elderly MDD patients is associated with increased Aβ accumulation in precuneus, parietal, temporal, and occipital regions as imaged by PET, and with the so-called "amyloid-related depression", a recently identified clinical phenotype characterized by a low response to "monoaminergic antidepressants" [31]. In amnestic MCI patients, a lifetime history of MDD is associated with an overall increased Aβ deposition and a regional Aβ distribution highly similar to the pattern observed in early AD patients [29]. Unfortunately, no studies have been yet conducted to assess Aβ(1-42) levels in CSF from MDD patients with amyloid-related depression, although a long-term longitudinal study has demonstrated that higher plasma Aβ(1-42) at baseline (>80 pg/ml) predicted the development of first episode of LLD and conversion of MCI to AD [32]. Future longitudinal studies are needed to assess whether treatment-resistance is associated with "amyloid-related depression" in amnestic MCI patients.

Recent studies have found that: i) the persistence of depression over two to three years in MCI patients significantly predicts cognitive deterioration to AD [33]; ii) depressive disorders in MCI patients predict greater atrophy in AD-related regions, such as frontal and temporal cortex [12], and significantly increase the conversion rate from MCI to AD [26, 34]. The primary role for depression as a risk factor for the conversion from MCI to AD has been validated in a meta-analysis including eighteen studies with a sample size of 10,861 MCI subjects [13]. Mourao *et al*. (2016) found that the pooled relative risk of progressing to dementia was 1.28 in the group of depressed MCI subjects, thus suggesting that depressive symptoms represent an additive risk factor for progression to dementia. We have recently proposed the evaluation of depressive symptoms as an early manifestation of AD in MCI patients, which combined with positive biomarkers both for Aβ and

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neuronal cell injury could improve the identification of MCI patients with a high risk of conversion into AD [35]. In particular, we suggested to include a thorough evaluation of depressive symptoms at baseline in future clinical trials designed to assess the clinical efficacy of disease-modifying drugs in MCI due to AD [35].

According to this scenario, the identification of common biological and neuropsychological markers in depression and AD represents an essential step for an early diagnosis and treatment of preclinical AD.

According to the amyloid hypothesis, overproduction or impaired clearance of Aβ causes AD as a result of the aggregation of monomeric Aβ species into higher-molecular-weight oligomers that result in neuronal loss [36]. Different studies suggest that elevated levels of cerebral soluble Aβ peptides, especially Aβ(1-42) oligomers, may also be associated with the development of amyloid-related depression [37-39]. Yasuno and coworkers found a positive correlation between depressive symptoms and cortical amyloid burden (as assessed by PET imaging) in cognitively intact MDD patients, which were more likely to have underlying AD neuropathology [40].

Soluble Aβ(1-42) possesses neuromodulatory actions, and directly interferes with monoaminergic systems [41]. The first demonstration that soluble Aβ induces a depressive-like state was obtained in rats [42], where Aβ(1-42) injected intra cerebroventricularly (i.c.v.) determined an increase in the immobility frequency, a typical state of "behavioral despair", assessed by the forced swimming test (FST). This depressive-like phenotype was associated with a significant reduction in cortical 5-HT, BDNF, and nerve growth factor (NGF) levels [42]. I.c.v. injection of Aβ(1-42) oligomers induced both cognitive and depression-like symptoms in mice [43], and induced neuroinflammatory phenomena, which play a central role in the pathophysiology of both depression and AD [44].

Schiavone *et al*. [39] recently demonstrated that Aβ induced a dysfunction of serotoninergic (i.e., reduced cortical 5-HT levels) and neurotrophin (i.e., BDNF, NGF) signaling, with related depressive-like behavior. This phenotype could be reverted in rats by fluoxetine and ketamine,

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which are able to increase the release of noradrenaline, a neurotransmitter known to exert strong neuroprotective effects against Aβ-induced neurotoxicity [39, 45].

Immune system activation and neuroinflammatory phenomena play a central role in the pathogenesis of depression [46] and AD [47]. Neuroinflammation has been defined as an innate immunological responses of the nervous system, involving microglia, astrocytes, cytokines, and chemokines. Activated microglia and astrocytes are the main source of cytokines in the brain [48], and elevated markers of microglial activation [measured by translocator protein (TSPO) binding *in vivo* with PET] have been found both in MDD [49] and AD patients [47]. Different preclinical studies have demonstrated that an increase in the expression of pro-inflammatory cytokines by astrocytes and microglia results in cognitive deficits and exacerbated sickness and depressive-like behavior [46, 50]. Neuroinflammation is strongly associated with a reduced response to the treatment with SSRIs [50, 51], and it may also account for the complex interaction of depression and cognitive deficits in older adults [52].

An increase of pro-inflammatory cytokines, such as interleukin-1β (IL-1β) and tumor necrosis factor-α (TNF-α), and a decrease of anti-inflammatory cytokines, such as interleukin-4 (IL-4), interleukin-10 (IL-10), and TGF-β1, has been observed in the hippocampus and in the cortex of animal models of depression [53]. Most importantly, MDD patients have high levels of pro-inflammatory cytokines, such as interleukin-1 (IL-1), interleukin-2 (IL-2), interleukin-6 (IL-6), interleukin-8 (IL-8), interleukin-12 (IL-12), interferon-γ (IFN-γ), and TNF-α [54]. Pro-inflammatory cytokines interfere with many of the pathophysiological mechanisms that characterize the pathogenesis of MDD, altering serotonin metabolism and reducing synaptic plasticity [50, 55]. Reduced levels of anti-inflammatory cytokines, such as IL-4, IL-10, and TGF-β1, have also been found in the plasma of depressed patients [56-59], an event that, along with increased TNF-α levels, can significantly contribute to treatment resistance in MDD [60].

Immune system activation and neuroinflammation have been proposed to contribute critically to the early phase of AD pathogenesis [61]. Aβ oligomers promote neuroinflammation and

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neurodegeneration in AD brain by eliciting the release of pro-inflammatory cytokines from microglia cells [61-63]. Neuroinflammation and microglial activation are critically linked to ectopic cell cycle activation in neurons, a primary event in the pathogenic cascade that leads to neuronal death in the AD brain [64]. Accordingly, chronic administration of non steroidal anti-inflammatory drugs (NSAIDs) in a transgenic mouse models of AD prevents both microglial activation and induction of neuronal ectopic cell cycle events (CCE) [65, 66]. In particular, microglial activation induced by Aβ oligomers promoted neuronal CCEs via the TNF-α and the c-Jun Kinase (JNK) signaling pathway [64].

TNF-α has been considered a relevant neurobiological link and a common pharmacological target between depression and AD [67]. Aβ oligomers induce microglial activation and an aberrant TNF-α signaling in mice. This aberrant activation of the brain innate immunity leads to a decreased serotonergic tonus, which plays a central role in Aβ-induced depressive-like behavior [67]. We can hypothesize that neuroinflammation and aberrant TNF-α signaling represent one of the possible neurobiological links among late-life depression, MCI, treatment-resistance to antidepressants, and AD.

Neuroinflammation can also contribute to the pathogenesis of depression and AD by impairing neurotrophin signaling function. Recently, we found, in Down syndrome patients with preclinical AD, a strong correlation among plasma TNF-α increase, NGF decline, and the rate of cognitive decline [68]. A deficit of NGF plays a central role in the pathophysiology of preclinical AD and the NGF pathway represents a new relevant pharmacological target for disease-modifying approaches in AD [69].

BDNF is the most widely distributed neurotrophic factor in human CNS, and is essential for maintenance of neuronal homeostasis and modulation of synaptic plasticity [70]. A deficit of BDNF signaling has been found both in depression [71] and AD [72]. Several studies have shown a significant BDNF decrease in stress-induced animal models of depression [73-75], as well as in selected brain structures and at peripheral level in MDD patients [76-78]. The impairment of BDNF

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signaling might be particularly relevant in MDD patients with a history of TRD [79]. An association has been found between a specific BDNF gene polymorphism (Val66Met), with Met carrier correlated with impaired intracellular trafficking and reduced activity-dependent release of BDNF [80], and an increased risk to develop TRD [81]. The Val66Met polymorphism of the BDNF gene has emerged as a possible inhibitor of hippocampal function. A recent study found a strong relationship in normal adults between BDNF gene polymorphism (Val66Met) and decreased spatial memory abilities [82]. The same polymorphism plays a relevant role also in AD pathogenesis, where Met carrier is correlated with lower BDNF concentrations, hippocampal atrophy, and impaired cognitive ability in AD patients [72]. The deficit of BDNF synthesis and secretion has been detected in an early stage of AD pathogenesis [72]. The levels of BDNF and of its receptor, tropomyosin receptor kinase B (TrkB), are reduced in AD brain [83]. Aβ-oligomers reduce BDNF signaling by impairing the axonal transport of BDNF in neurons of AD transgenic mice (Tg2576) [84]. Neuroinflammation and the ensuing release of pro-inflammatory cytokines, such as IL-1β, also render neurons vulnerable to degeneration by interfering with BDNF-induced neuroprotection [85]. The deficit of BDNF can induce abnormal accumulation of Aβ and synaptic dysfunction finally leading to cognitive decline [72]. According to this scenario, the presence of a Met-BDNF allele is associated with a higher risk of disease-progression in patients with MCI [86], and a significant and large decline in episodic memory and hippocampal volume in prodromal AD patients [87]. Interestingly, the presence of the functional single-nucleotide polymorphism (Val66Met), which impairs BDNF signaling, significantly increases the risk to develop depression in AD patients [88], thus suggesting that a deficit of BDNF release might be a common pathophysiological event both in depression and AD.

3. From depression to AD: the role TGF-β pathway

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TGF-β1 is a member of TGF-β superfamily, which includes several groups of highly conserved multifunctional cell-cell signalling proteins of key importance in the control of cell growth, differentiation, as well as immune suppression and repair after injury [89].

The mammalian TGF-β superfamily includes TGF-β1, -2 and, -3, which are synthesized as homodimeric pro-proteins (pro-TGF-β), and are then cleaved intracellularly by furin into a larger C-terminal pro-region, also known as latency-associated peptide (LAP), and a shorter N-terminal active peptide that forms the mature homodimers (25-kDa). The mature 25-kDa TGF-β dimer remains non-covalently associated with LAP before the complex is secreted [44, 90]. TGF-β1 activity is primarily regulated through the conversion of latent TGF-β1 to active TGF-β1 by a variety of proteases [91], among which Matrix Metalloproteinase 2 (MMP-2) and Matrix Metalloproteinase 9 (MMP-9) play a central role in this conversion [92]. Interestingly, TGF-β1 expression in the CNS is constitutive only in the meninges and choroid plexus, and it increases in microglia and astrocytes in response to injury. On the contrary, TGF-β2 and TGF-β3 are ubiquitously expressed [93]. Active TGF-β1 binds to a receptor complex constituted by the serine/threonine receptors ALK/TGF-β type I receptor (TβRI) and TGF-β type II receptor (TβRII), which are strongly expressed in the CNS [44, 89]. When TGF-β1 binds to TβRII it induces the assembly of type I and type II receptors into a complex, where type II receptor phosphorylates and activates type I receptors TβRI, in turn, phosphorylates the receptor-regulated Smad2 (R-Smad-2), thus promoting its interaction with the protein partner Smad-4. Smad protein complexes translocate into the nucleus, where they regulates the expression of different target genes involved in cell proliferation and neuronal survival. TGF-β1/Smad signalling cascade is regulated at many different levels. Inhibitory Smads, such as Smad-7,can bind to activated type I receptors, thus inhibiting the phosphorylation and the nuclear translocation of R-Smads [94]. Recently, Beclin 1 has been identified as a positive regulator of a TGF-β1 signaling pathway [95]. Beclin 1 is required for recycling of TβRI, and loss of beclin 1 results in neuronal death [95]. Besides Smad-mediated gene transcription, TGF-β1 activates Smad-independent pathways, including the extracellular-regulated

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kinase (ERK) [96, 97] and the phosphatidylinositol-3-kinase/protein kinase B (PI-3-K/Akt) pathways [98, 99]. The rescue of these Smad-independent signalling pathways could be relevant in the occurrence of a selective impairment of Smad signalling [100].

TGF-β1 is an anti-inflammatory cytokine that exerts neuroprotective effects in different models of neurodegenerative disorders [93], including amyloid-induced neurodegeneration [98, 101-103]. It also exert a key role in recognition memory formation, where it promotes the transition from early to late Long Term Potentiation (LTP) [104]. Hence, a deficit of TGF-β1 signaling can contribute to inflammaging and cognitive decline both in depression and AD [5].

As discussed earlier, the immune system activation is a primary event in the pathogenesis of MDD and AD. TGF-β1 is believed to be an important factor in regulating inflammatory responses by promoting the induction of T regulatory cells, and reducing both Th1 and Th2 responses [58].

Several studies carried out in MDD patients have demonstrated that plasma TGF-β1 levels are reduced in MDD patients and correlate with depression severity [57-59, 105]. A recent study using whole-exome sequencing identified variants of four genes belonging to TGF-β signaling pathway, which associate with suicidal behavior in MDD patients [106]. A reduction of TGF-β1 levels can significantly contribute to treatment resistance in MDD [58]. Interestingly, responder- and remitter-MDD patients had higher initial TGF-β1 levels at baseline, compared to non-responder patients [58]. In addition, melancholic depressed patients with a recent history of treatment resistance had lower levels of TGF-β1 and higher levels of the pro-inflammatory cytokine IL-6 than healthy controls [59].

In agreement with human studies, preliminary evidence in animal models suggests that an impairment of TGF-β1 signaling can promote the onset of a depression-like phenotype [107]. Rodents treated with inflammatory agents such as lipopolysaccharide (LPS) display depressive-like behaviors, with increased immobility in the FST and decreased sucrose preference [55]. Interestingly, these mice showed a long-term down-regulation of TGF-β1 expression in the hippocampus [108].

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Adult neurogenesis is reduced in MDD patients, and antidepressants seem to exert their clinical efficacy by increasing neurogenesis [109]. In rats, low hippocampal TGF-β1 levels correlate with reduced neurogenesis and reduced response to novelty [108], whereas chronic expression of TGF-β1 by adenoviral vectors enhances adult neurogenesis [110] and it increases social interaction and reduces depression-related behaviors in mice [107]. We have recently found that selective inhibition of Smad-dependent TGF-β1 signaling pathway with SB431542 induces a depressive-like phenotype in rats. Interestingly, SB431542 affected monoaminergic circuits, by reducing both noradrenaline and serotonin release in rat prefrontal cortex (unpublished data).

Moving from the evidence that TGF-β1 enhances the expression of both BDNF and TrkB [111], it is conceivable that a deficit of TGF-β1 signaling contributes to reduced BDNF levels in the hippocampus, an established marker of depression at least in rodents [112]. In addition, because a selective blockade of endogenous TGF-β1 signaling impairs synaptic plasticity and memory in mice [104], it is likely that a deficit of TGF-β1 contributes to cognitive deficits and treatment resistance in depressive disorders.

4. The TGF-β1pathway in MCI and AD

The deficit of TGF-ß1 signaling has been suggested as an early and primary event in AD pathogenesis over ten years ago [113]. AD patients with moderate to severe neurofibrillary tangles (NFT) show downregulated amounts of TGFβ-1 mRNA in their superior temporal gyrus, and this deficit negatively correlates with NFT formation [114]. Several studies have demonstrated a selective impairment of Smad signaling in AD brain [100, 113, 115, 116]. In particular, an ectopic localization of phosphorylated Smad2/3 has been detected in the cytoplasm of hippocampal neurons close to amyloid plaques, or overlapping with NFT [100, 116]. Studies in rat primary cortical cells demonstrated that increasing tau phosphorylation with okadaic acid prevents the nuclear translocation of Smad2/3 [117], suggesting that cytoplasmic and/or NFT sequestration of

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phosphorylated Smad2/3 can reduce the nuclear translocation of the proteins, and critically contribute to the loss of Smad-mediated signaling pathway in AD brain.

In AD animal models, different studies have validated the hypothesis that a deficiency of TGF-β1 signaling in neurons and astrocytes can significantly contribute to Aβ pathology and NFT formation in the AD brain [44, 113, 118-120]. Neuronal expression of the kinase-deficient TβRII in human amyloid precursor protein (hAPP) 20-month-old-transgenic mice promotes both cerebral Aβ accumulation and dendritic degeneration [120]. Interestingly, Wang *et al*. [119] demonstrated the correlation between the deficit of TGF-β1 signaling and the early stage of AD in transgenic animal models. The authors found an increased expression of micro RNA-106b, which decreases TβRII transcription, already in 3- to 9-month-old APPswe/ PSΔE9 mice compared to age-matched controls [119]. We have mimicked the impairment of TGF-β/Smad signaling cascade observed in AD brain, by using the selective inhibitor of Smad-dependent TGF-β1 signaling, SB431542, in rats injected with synthetic Aβ into the dorsal hippocampus [98]. In these conditions, a single hippocampal injection of Aβ produced only a small extent of neuronal loss, whereas the use of SB431542 significantly increased the vulnerability of hippocampal neurons to Aβ, resulting into a relevant extent of neuronal degeneration [98].

A deficit of TGF-β1 can contribute to neurodegeneration in the AD brain through different mechanisms [44]. TGF-β1 is a strong inhibitor of cell cycle activation, and it is essential for maintenance of neuronal differentiation [44]. It induces the expression of cyclin-dependent-kinases (CDK) inhibitors (p21, p27), which induce G1 phase arrest [121, 122]. Cell cycle inhibition is one among the most relevant mechanisms by which TGF-β1 exerts its neuroprotective effects against Aβ toxicity [98], combined with the inhibition of GSK-3β and the prevention of Aβ-induced tau hyperphosphorylation [123]. Hence, neuronal cell cycle re-activation induced by Aβ could be facilitated by a specific impairment of Smad-dependent TGF-β1 signaling.

We should also consider the role of TGF-β1 in the context of neuroinflammation due to microglia activation, which contributes to the reactivation of the neuronal cell-cycle [47, 124]. In

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fact, TGF-β1 has a constitutive role in the suppression of inflammation, and appears to control the degree of microglial activation in the CNS [125, 126] in an age-dependent manner [127].

The role of TGF-β1 is quite complex and not unequivocal in AD models. Physiological concentrations of TGF-β1 range from 0.02 to 1 ng/ml, whereas the concentration of TGF-β1 in pathological conditions increase up to 10^{-10}- 10^{-9}M (>2ng/ml) [128]. Unfortunately, no data are available in the literature on CSF and plasma TGF-β1 levels from transgenic animal models of AD. It is known that mice overexpressing TGF-β1 develop AD-like vascular alterations [129, 130], and over-expression of TGF-β1 in AD transgenic mice seems to accelerate the deposition of Aβ in cerebral blood vessels [131]. Moreover, blockade of TGF-β/Smad 2/3 signaling in peripheral macrophages reduces cerebrovascular Aβ deposits in Tg2576 mice [132]. It has been hypothesized that vessel-derived TGF-β1 might contribute to inflammatory processes in the AD brain [133, 134], whereas glia-derived TGF-β1 might have beneficial effects in the brain parenchyma (see Fig.1). According to this hypothesis, overproduction of TGF-β1 by astrocytes reduces overall Aβ accumulation, with a decrease in the number of dystrophic neurites in APP transgenic mice [135]. Astrocyte-derived TGF-β1 also prevents memory deficits and synaptic loss induced by Aβ oligomers (Fig.1) [136].

TGF-β1 released by astrocytes stimulates Aβ uptake by microglia through Smad3-dependent mechanisms [137]. Activation of the TGF-β1-Smad3 pathway is impaired in aged mice compared to young mice, suggesting that the age-related impairment of TGF-β1-Smad3 signaling can reduce the protective activation of microglia cells, while facilitating its cytotoxic activation [127]. Huang *et al*. (2010) have demonstrated that TGF-β1 reduces chemotactic migration of microglial cells toward Aβ aggregates via Smad-dependent pathways, thus preventing microglia-mediated neuroinflammation [138] (Fig.1). Recently, it has been demonstrated that TβRII levels are lower in 9-months-old-APP/PS1 mouse hippocampus when compared to normal mouse hippocampus, and this event contributes to microglia-mediated neuroinflammation [139]. TGF-β1 also suppresses glial and T cell-mediated neuroinflammation, thereby alleviating amyloid-related neurodegeneration, in a

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rat model of AD [118]. Intranasal administration of TGF-β1, before i.c.v. Aβ(1-42) injection, prevented Aβ-induced increases in microglia-derived proinflammatory mediators (TNF-α, IL-1β and iNOS), thereby preventing amyloid-related neurodegeneration [118].

Coming back to MCI and AD patients, several studies have found a significant decrease in the plasma levels of the active (25 kDa) and inactive (50 kDa) forms of TGF-β1 in AD patients [140-142], as well as a reduced secretion of TGF-β1 from circulating peripheral blood mononuclear cells [143]. Interestingly, the deficit of TGF-β1 has been detected in the early phase of AD (preclinical AD) and, in particular, in amnestic MCI patients[144].

The link between the different single nucleotide polymorphisms (SNPs) of TGF-β1 gene and the deficit of this neurotrophic factor in AD plasma has not been definitively identified [145]. The TGF-β1 gene, located on chromosome 19q13.1-3, contains several SNPs upstream and in the transcript region, such as the SNP at codon +10 (T/C) and +25 (G/C) [146]. The SNP at codon +10 (T/C) is within the 29-amino acid signal sequence of TGF-β1 gene, and it might affect both the secretion and the conversion to active TGF-β1 [147]. The +10 CC genotype of TGF-ß1 gene increases the risk to develop Late-Onset AD (LOAD), and it is also associated with depressive symptoms in AD (>5-fold risk) [44]. We have preliminary evidence that TGF-β1 CC genotype is associated with a significantly increased rate of cognitive decline (-3.08 MMSE scores/year) compared to T/C (-1.9/year) and T/T (-1.03/year) carriers, as well as with reduced response to cholinesterase inhibitors in LOAD patients (unpublished data). Arosio *et al*. [148] found reduced serum levels of TGF-β1 in MCI-AD patients with the CC genotype, suggesting that low levels of this cytokine could facilitate neurodegeneration in the early stage of AD. We are currently examining in a cohort of 63 amnestic MCI patients with or without depressive symptoms, recruited for a 36 months-longitudinal observational study, whether the CC genotype can increases the rate of conversion into AD by increasing the risk to develop depressive symptoms. Preliminary data suggest that MCI patients with the CC genotype showed a significant reduction of basal TGF-β1 plasma levels, an increased severity of depressive symptoms, and a faster rate of cognitive decline

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compared to T/C and T/T carriers. So far, the hypothesis that a deficit of TGF-β1 can be a common pathophysiological event in depression and in preclinical AD remains to be validated.

5. Rescue of TGF-β1 signaling as a common pharmacological strategy in depression and AD: perspectives for drug development

Different drugs that cross the blood-brain-barrier, such estrogens, lithium, and agonists of group II metabotropic glutamate (mGlu) receptors, are able to increase the production of TGF-β1 by glial cells and have been described in a previous review [44]. Here, we will focus on antidepressants drugs, such as SNRIs (i.e., venlafaxine), and SSRIs (i.e., sertraline and fluoxetine), which significantly increase circulating TGF-β1 levels in MDD patients [105, 149]. It is known that high TGF-β1 levels are beneficial for the response to antidepressive treatment in MDD patients [58]. Both humans and rodent studies have been essential to identify the effects of antidepressants on TGF-β1 release [44]. Studies conducted in peripheral blood mononuclear cells (PBMC) from 16 healthy volunteers have shown that antidepressants, such as mianserin or imipramine, induce the release of TGF-β1 [150]. Therapeutic concentrations of venlafaxine prevent microglial activation, reduce pro-inflammatory cytokine secretion, and increase the release of TGF-β1 in an astroglia–microglia co-culture model [151]. *In vivo* studies conducted in animal models of stroke demonstrate that venlafaxine increases the mRNA and the protein of TGF-β1, thus reducing infarct volume [152]. No studies have been carried out so far in animal models of AD to examine whether venlafaxine can exert neuroprotective effects by rescue of TGF-β1 signalling.

An open question remains the clinical efficacy of second-generation antidepressants in prodromal AD patients, with clinically relevant depressive disorders. As discussed earlier, the clinical efficacy of antidepressants in moderate-severe AD is low, although a long-term treatment with antidepressants, such as SSRIs, reduce the risk to develop AD in patients with depression [153]. Long-term treatment with SSRIs also associates with lower cortical β-amyloid PET signal in cognitively normal elderly human subjects [154], and with some degree of protection against the

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negative effects of depression on cognition in AD patients [155]. Whether second-generation antidepressants, such as SSRIs and SNRIs, can be potentially neuroprotective in LLD and prodromal AD with depression, by rescuing TGF-β1 signalling, remains to be determined both in AD models and MCI-AD patients.

Evidence exists that fluoxetine prevents amyloid pathology, and reverses memory impairment in different animal models of AD [156, 157]. We have recently demonstrated that fluoxetine is neuroprotective against Aβ-induced neurodegeneration *via* a paracrine signalling mediated by TGF-β1, which, interestingly, does not depend on the SERT blockade [158]. Other SSRIs, such as fluvoxamine, increase the expression of TGF-β1 and reduce neuroinflammation in the striatum of parkinsonian rats, finally reverting anhedonia [159]. We found, in our experimental model of Aβ-induced neurodegeneration, that fluoxetine promoted the release of active TGF-β1 by favoring the activation of MMP-2, and the ensuing maturation of latent TGF-β1 [158]. Other molecular mechanisms might also contribute to the neuroprotective efficacy of fluoxetine in AD, such as: i) inhibition of glia-mediated oxidative stress [160] and reduced release of TNF-α, IL-1β from microglial cells [161]; ii) increased release of insulin-like growth factor 1 (IGF-1) and glial cell line-derived neurotrophic factor (GDNF) [162]; iii) an increased release of noradrenaline combined with BDNF release [39].

The endogenous neurotransmitter noradrenaline is known to exert potent anti-inflammatory effects in glial cells and to provide neuroprotection against inflammatory stimuli [163]. Noradrenaline (NA) prevents Aβ-induced toxicity *via* activation of β-adrenergic receptor signaling cascade [45, 164] and, interestingly, NA increases the expression of TGF-β1 [165, 166]. Hence, by increasing the levels of NA in the CNS, antidepressants might provide an unexpected advantage in depression, MCI and AD by rescuing TGF-β1 signaling. The specific contribute of NA in the neuroprotective efficacy of fluoxetine remains to be established in future studies. Secondary prevention strategies with fluoxetine in AD models are effective, and adolescent administration of

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fluoxetine prevents the increase of Aβ levels and improve learning and memory abilities in 6-month-old 3×TgAD mice [167].

In humans, the neuroprotective effects of fluoxetine has been demonstrated only in stroke patients [168]. Preliminary evidence in MCI patients show that fluoxetine improves global cognitive function and immediate and delayed logical memory [169]. Long-term (18 months) longitudinal studies should be conducted in depressed amnestic MCI patients with the CC genotype to assess whether a chronic treatment with fluoxetine can delay cognitive decline and reduce the risk of conversion from MCI into AD.

6. Conclusions

A large number of studies have demonstrated the epidemiological and neurobiological links between depression and AD. Depression significantly increases the conversion of MCI into AD. Recent studies in LLD or MCI patients strongly suggest the existence of a neurobiological and clinical continuum between late-life depressive disorders, MCI and AD, which should be borne in mind to develop disease-modifying drugs able to prevent the transition from MCI to AD. Aβ accumulation, neuroinflammation, aberrant TNF-α signaling, and a deficit of BDNF and TGF-β1 have been recognized as common pathophysiological events in depression and AD.

In the present review, we have focused on the TGF-β1 signaling pathway as a new pharmacological target across depression and AD (Fig.2). TGF-β1 plasma levels are reduced in MDD patients, correlate with depression severity, and significantly contribute to treatment resistance in MDD.

The +10 CC genotype of TGF-β1 gene, which reduces plasma TGF-β1 levels, increases the risk to develop LOAD, and also associates with depressive symptoms and increases the rate of cognitive decline in MCI. We hypothesize that the deficit of TGF-β1 might contribute to cognitive deficits and treatment resistance in LLD patients, by increasing Aβ accumulation and promoting the so called “amyloid-related depression” (Fig.2). Future longitudinal studies should be conducted in LLD and MCI patients with a “defective” CC genotype of TGF-β1 gene to assess whether

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antidepressant drugs, such as fluoxetine, can exert a disease-modifying activity and delay cognitive decline in preclinical AD by rescuing of TGF-β1 signaling.

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References

[1] K.L. Lanctot, J. Amatniek, S. Ancoli-Israel, S.E. Arnold, C. Ballard, J. Cohen-Mansfield, Z. Ismail, C. Lyketsos, D.S. Miller, E. Musiek, R.S. Osorio, P.B. Rosenberg, A. Satlin, D. Steffens, P. Tariot, L.J. Bain, M.C. Carrillo, J.A. Hendrix, H. Jurgens, B. Boot, Neuropsychiatric signs and symptoms of Alzheimer's disease: New treatment paradigms, Alzheimer's & dementia 3(3) (2017) 440-449 10.1016/j.trci.2017.07.001.

[2] M. Benoit, G. Berrut, J. Doussaint, S. Bakchine, S. Bonin-Guillaume, P. Fremont, T. Gallarda, P. Krolak-Salmon, T. Marquet, C. Mekies, F. Sellal, S. Schuck, R. David, P. Robert, Apathy and depression in mild Alzheimer's disease: a cross-sectional study using diagnostic criteria, Journal of Alzheimer's disease : JAD 31(2) (2012) 325-34 10.3233/JAD-2012-112003.

[3] M. Steinberg, C. Corcoran, J.T. Tschanz, C. Huber, K. Welsh-Bohmer, M.C. Norton, P. Zandi, J.C. Breitner, D.C. Steffens, C.G. Lyketsos, Risk factors for neuropsychiatric symptoms in dementia: the Cache County Study, International journal of geriatric psychiatry 21(9) (2006) 824-30 10.1002/gps.1567.

[4] T. Leyhe, C.F. Reynolds, 3rd, T. Melcher, C. Linnemann, S. Kloppel, K. Blennow, H. Zetterberg, B. Dubois, S. Lista, H. Hampel, A common challenge in older adults: Classification, overlap, and therapy of depression and dementia, Alzheimer's & dementia : the journal of the Alzheimer's Association 13(1) (2017) 59-71 10.1016/j.jalz.2016.08.007.

[5] F. Caraci, A. Copani, F. Nicoletti, F. Drago, Depression and Alzheimer's disease: neurobiological links and common pharmacological targets, European journal of pharmacology 626(1) (2010) 64-71 10.1016/j.ejphar.2009.10.022.

[6] J. Herbert, P.J. Lucassen, Depression as a risk factor for Alzheimer's disease: Genes, steroids, cytokines and neurogenesis - What do we need to know?, Frontiers in neuroendocrinology 41 (2016) 153-71 10.1016/j.yfrne.2015.12.001.

[7] L.E. Santos, D. Beckman, S.T. Ferreira, Microglial dysfunction connects depression and Alzheimer's disease, Brain, behavior, and immunity 55 (2016) 151-165 10.1016/j.bbi.2015.11.011.

[8] R.L. Ownby, E. Crocco, A. Acevedo, V. John, D. Loewenstein, Depression and risk for Alzheimer disease: systematic review, meta-analysis, and metaregression analysis, Archives of general psychiatry 63(5) (2006) 530-8 10.1001/archpsyc.63.5.530.

[9] P.J. Modrego, J. Ferrandez, Depression in patients with mild cognitive impairment increases the risk of developing dementia of Alzheimer type: a prospective cohort study, Archives of neurology 61(8) (2004) 1290-3 10.1001/archneur.61.8.1290.

[10] N.J. Donovan, D.C. Hsu, A.S. Dagley, A.P. Schultz, R.E. Amariglio, E.C. Mormino, O.I. Okereke, D.M. Rentz, K.A. Johnson, R.A. Sperling, G.A. Marshall, Depressive Symptoms and Biomarkers of Alzheimer's Disease in Cognitively Normal Older Adults, Journal of Alzheimer's disease : JAD 46(1) (2015) 63-73 10.3233/JAD-142940.

[11] D.C. Steffens, Depressive symptoms and mild cognitive impairment in the elderly: an ominous combination, Biological psychiatry 71(9) (2012) 762-4 10.1016/j.biopsych.2012.02.002.

[12] G.J. Lee, P.H. Lu, X. Hua, S. Lee, S. Wu, K. Nguyen, E. Teng, A.D. Leow, C.R. Jack, Jr., A.W. Toga, M.W. Weiner, G. Bartzokis, P.M. Thompson, I. Alzheimer's Disease Neuroimaging, Depressive symptoms in mild cognitive impairment predict greater atrophy in Alzheimer's disease-related regions, Biological psychiatry 71(9) (2012) 814-21 10.1016/j.biopsych.2011.12.024.

[13] R.J. Mourao, G. Mansur, L.F. Malloy-Diniz, E. Castro Costa, B.S. Diniz, Depressive symptoms increase the risk of progression to dementia in subjects with mild cognitive impairment: systematic review and meta-analysis, International journal of geriatric psychiatry 31(8) (2016) 905-11 10.1002/gps.4406.

ACCEPTED MANUSCRIPT

[14] D.E. Barnes, K. Yaffe, A.L. Byers, M. McCormick, C. Schaefer, R.A. Whitmer, Midlife vs late-life depressive symptoms and risk of dementia: differential effects for Alzheimer disease and vascular dementia, Archives of general psychiatry 69(5) (2012) 493-8 10.1001/archgenpsychiatry.2011.1481.
[15] P.H. Robert, S. Schuck, B. Dubois, J.P. Lepine, T. Gallarda, J.P. Olie, S. Goni, S. Troy, [Validation of the Short Cognitive Battery (B2C). Value in screening for Alzheimer's disease and depressive disorders in psychiatric practice], L'Encephale 29(3 Pt 1) (2003) 266-72 doi: http://www.ncbi.nlm.nih.gov/pubmed/12876552.
[16] L.V. Kessing, P.K. Andersen, Does the risk of developing dementia increase with the number of episodes in patients with depressive disorder and in patients with bipolar disorder?, Journal of neurology, neurosurgery, and psychiatry 75(12) (2004) 1662-6 10.1136/jnnp.2003.031773.
[17] W. Katon, H.S. Pedersen, A.R. Ribe, M. Fenger-Gron, D. Davydow, F.B. Waldorff, M. Vestergaard, Effect of depression and diabetes mellitus on the risk for dementia: a national population-based cohort study, JAMA psychiatry 72(6) (2015) 612-9 10.1001/jamapsychiatry.2015.0082.
[18] R. Rodrigues, R.B. Petersen, G. Perry, Parallels between major depressive disorder and Alzheimer's disease: role of oxidative stress and genetic vulnerability, Cell Mol Neurobiol 34(7) (2014) 925-49 10.1007/s10571-014-0074-5.
[19] E. Richard, C. Reitz, L.H. Honig, N. Schupf, M.X. Tang, J.J. Manly, R. Mayeux, D. Devanand, J.A. Luchsinger, Late-life depression, mild cognitive impairment, and dementia, JAMA neurology 70(3) (2013) 374-82 10.1001/jamaneurol.2013.603.
[20] F. Panza, V. Frisardi, C. Capurso, A. D'Introno, A.M. Colacicco, B.P. Imbimbo, A. Santamato, G. Vendemiale, D. Seripa, A. Pilotto, A. Capurso, V. Solfrizzi, Late-life depression, mild cognitive impairment, and dementia: possible continuum?, The American journal of geriatric psychiatry : official journal of the American Association for Geriatric Psychiatry 18(2) (2010) 98-116 10.1097/JGP.0b013e3181b0fa13.
[21] G. Adler, K. Chwalek, A. Jajcevic, Six-month course of mild cognitive impairment and affective symptoms in late-life depression, European psychiatry : the journal of the Association of European Psychiatrists 19(8) (2004) 502-5 10.1016/j.eurpsy.2004.09.003.
[22] J.S. Lee, G.G. Potter, H.R. Wagner, K.A. Welsh-Bohmer, D.C. Steffens, Persistent mild cognitive impairment in geriatric depression, International psychogeriatrics 19(1) (2007) 125-35 10.1017/S1041610206003607.
[23] O.L. Lopez, W.J. Jagust, S.T. DeKosky, J.T. Becker, A. Fitzpatrick, C. Dulberg, J. Breitner, C. Lyketsos, B. Jones, C. Kawas, M. Carlson, L.H. Kuller, Prevalence and classification of mild cognitive impairment in the Cardiovascular Health Study Cognition Study: part 1, Archives of neurology 60(10) (2003) 1385-9 10.1001/archneur.60.10.1385.
[24] R.C. Petersen, Early diagnosis of Alzheimer's disease: is MCI too late?, Current Alzheimer research 6(4) (2009) 324-30 doi: http://www.ncbi.nlm.nih.gov/pubmed/19689230.
[25] S.O. Bachurin, S.I. Gavrilova, A. Samsonova, G.E. Barreto, G. Aliev, Mild cognitive impairment due to Alzheimer disease: Contemporary approaches to diagnostics and pharmacological intervention, Pharmacological research : the official journal of the Italian Pharmacological Society (2017) 10.1016/j.phrs.2017.11.021.
[26] B. Moon, S. Kim, Y.H. Park, J.S. Lim, Y.C. Youn, S. Kim, J.W. Jang, I. Alzheimer's Disease Neuroimaging, Depressive Symptoms are Associated with Progression to Dementia in Patients with Amyloid-Positive Mild Cognitive Impairment, Journal of Alzheimer's disease : JAD 58(4) (2017) 1255-1264 10.3233/JAD-170225.
[27] S. Banerjee, J. Hellier, M. Dewey, R. Romeo, C. Ballard, R. Baldwin, P. Bentham, C. Fox, C. Holmes, C. Katona, M. Knapp, C. Lawton, J. Lindesay, G. Livingston, N. McCrae, E. Moniz-Cook, J. Murray, S. Nurock, M. Orrell, J. O'Brien, M. Poppe, A. Thomas, R. Walwyn, K. Wilson, A. Burns, Sertraline or mirtazapine for depression in dementia (HTA-SADD): a randomised,

ACCEPTED MANUSCRIPT

multicentre, double-blind, placebo-controlled trial, Lancet 378(9789) (2011) 403-11 10.1016/S0140-6736(11)60830-1.
[28] A.A. Sepehry, P.E. Lee, G.Y. Hsiung, B.L. Beattie, C. Jacova, Effect of selective serotonin reuptake inhibitors in Alzheimer's disease with comorbid depression: a meta-analysis of depression and cognitive outcomes, Drugs & aging 29(10) (2012) 793-806 10.1007/s40266-012-0012-5.
[29] J.K. Chung, E. Plitman, S. Nakajima, T.W. Chow, M.M. Chakravarty, F. Caravaggio, P. Gerretsen, E.E. Brown, Y. Iwata, B.H. Mulsant, A. Graff-Guerrero, I. Alzheimer's Disease Neuroimaging, Lifetime History of Depression Predicts Increased Amyloid-beta Accumulation in Patients with Mild Cognitive Impairment, Journal of Alzheimer's disease : JAD 45(3) (2015) 907-19 10.3233/JAD-142931.
[30] P.M. Doraiswamy, R.A. Sperling, R.E. Coleman, K.A. Johnson, E.M. Reiman, M.D. Davis, M. Grundman, M.N. Sabbagh, C.H. Sadowsky, A.S. Fleisher, A. Carpenter, C.M. Clark, A.D. Joshi, M.A. Mintun, D.M. Skovronsky, M.J. Pontecorvo, A.A.S. Group, Amyloid-beta assessed by florbetapir F 18 PET and 18-month cognitive decline: a multicenter study, Neurology 79(16) (2012) 1636-44 10.1212/WNL.0b013e3182661f74.
[31] P. Li, I.T. Hsiao, C.Y. Liu, C.H. Chen, S.Y. Huang, T.C. Yen, K.Y. Wu, K.J. Lin, Beta-amyloid deposition in patients with major depressive disorder with differing levels of treatment resistance: a pilot study, EJNMMI research 7(1) (2017) 24 10.1186/s13550-017-0273-4.
[32] I. Blasko, G. Kemmler, S. Jungwirth, I. Wichart, W. Krampla, S. Weissgram, K. Jellinger, K.H. Tragl, P. Fischer, Plasma amyloid beta-42 independently predicts both late-onset depression and Alzheimer disease, The American journal of geriatric psychiatry : official journal of the American Association for Geriatric Psychiatry 18(11) (2010) 973-82 10.1097/JGP.0b013e3181df48be.
[33] M. Houde, H. Bergman, V. Whitehead, H. Chertkow, A predictive depression pattern in mild cognitive impairment, International journal of geriatric psychiatry 23(10) (2008) 1028-33 10.1002/gps.2028.
[34] M. Defrancesco, J. Marksteiner, G. Kemmler, W.W. Fleischhacker, I. Blasko, E.A. Deisenhammer, Severity of Depression Impacts Imminent Conversion from Mild Cognitive Impairment to Alzheimer's Disease, Journal of Alzheimer's disease : JAD 59(4) (2017) 1439-1448 10.3233/JAD-161135.
[35] F. Caraci, S. Castellano, S. Salomone, F. Drago, P. Bosco, S. Di Nuovo, Searching for disease-modifying drugs in AD: can we combine neuropsychological tools with biological markers?, CNS & neurological disorders drug targets 13(1) (2014) 173-86 doi: http://www.ncbi.nlm.nih.gov/pubmed/24040795.
[36] D.J. Selkoe, J. Hardy, The amyloid hypothesis of Alzheimer's disease at 25 years, EMBO molecular medicine 8(6) (2016) 595-608 10.15252/emmm.201606210.
[37] M.G. Morgese, M. Colaianna, E. Mhillaj, M. Zotti, S. Schiavone, P. D'Antonio, A. Harkin, V. Gigliucci, P. Campolongo, V. Trezza, A. De Stradis, P. Tucci, V. Cuomo, L. Trabace, Soluble beta amyloid evokes alteration in brain norepinephrine levels: role of nitric oxide and interleukin-1, Frontiers in neuroscience 9 (2015) 428 10.3389/fnins.2015.00428.
[38] M.G. Morgese, S. Schiavone, L. Trabace, Emerging role of amyloid beta in stress response: Implication for depression and diabetes, European journal of pharmacology 817 (2017) 22-29 10.1016/j.ejphar.2017.08.031.
[39] S. Schiavone, P. Tucci, E. Mhillaj, M. Bove, L. Trabace, M.G. Morgese, Antidepressant drugs for beta amyloid-induced depression: A new standpoint?, Progress in neuro-psychopharmacology & biological psychiatry 78 (2017) 114-122 10.1016/j.pnpbp.2017.05.004.
[40] F. Yasuno, H. Kazui, N. Morita, K. Kajimoto, M. Ihara, A. Taguchi, A. Yamamoto, K. Matsuoka, J. Kosaka, T. Kudo, H. Iida, T. Kishimoto, K. Nagatsuka, High amyloid-beta deposition related to depressive symptoms in older individuals with normal cognition: a pilot study, International journal of geriatric psychiatry 31(8) (2016) 920-8 10.1002/gps.4409.

ACCEPTED MANUSCRIPT

[41] L. Trabace, K.M. Kendrick, S. Castrignano, M. Colaianna, A. De Giorgi, S. Schiavone, C. Lanni, V. Cuomo, S. Govoni, Soluble amyloid beta1-42 reduces dopamine levels in rat prefrontal cortex: relationship to nitric oxide, Neuroscience 147(3) (2007) 652-63 10.1016/j.neuroscience.2007.04.056.
[42] M. Colaianna, P. Tucci, M. Zotti, M.G. Morgese, S. Schiavone, S. Govoni, V. Cuomo, L. Trabace, Soluble beta amyloid(1-42): a critical player in producing behavioural and biochemical changes evoking depressive-related state?, British journal of pharmacology 159(8) (2010) 1704-15 10.1111/j.1476-5381.2010.00669.x.
[43] J.H. Ledo, E.P. Azevedo, J.R. Clarke, F.C. Ribeiro, C.P. Figueiredo, D. Foguel, F.G. De Felice, S.T. Ferreira, Amyloid-beta oligomers link depressive-like behavior and cognitive deficits in mice, Molecular psychiatry 18(10) (2013) 1053-4 10.1038/mp.2012.168.
[44] F. Caraci, S. Spampinato, M.A. Sortino, P. Bosco, G. Battaglia, V. Bruno, F. Drago, F. Nicoletti, A. Copani, Dysfunction of TGF-beta1 signaling in Alzheimer's disease: perspectives for neuroprotection, Cell and tissue research 347(1) (2012) 291-301 10.1007/s00441-011-1230-6.
[45] X. Liu, K. Ye, D. Weinshenker, Norepinephrine Protects against Amyloid-beta Toxicity via TrkB, Journal of Alzheimer's disease : JAD 44(1) (2015) 251-60 10.3233/JAD-141062.
[46] A. Bhattacharya, N.C. Derecki, T.W. Lovenberg, W.C. Drevets, Role of neuro-immunological factors in the pathophysiology of mood disorders, Psychopharmacology 233(9) (2016) 1623-36 10.1007/s00213-016-4214-0.
[47] D. Knezevic, R. Mizrahi, Molecular imaging of neuroinflammation in Alzheimer's disease and mild cognitive impairment, Progress in neuro-psychopharmacology & biological psychiatry 80(Pt B) (2018) 123-131 10.1016/j.pnpbp.2017.05.007.
[48] S. Hashioka, T. Miyaoka, R. Wake, M. Furuya, J. Horiguchi, Glia: an important target for anti-inflammatory and antidepressant activity, Current drug targets 14(11) (2013) 1322-8 doi: http://www.ncbi.nlm.nih.gov/pubmed/24020976.
[49] E. Setiawan, A.A. Wilson, R. Mizrahi, P.M. Rusjan, L. Miler, G. Rajkowska, I. Suridjan, J.L. Kennedy, P.V. Rekkas, S. Houle, J.H. Meyer, Role of translocator protein density, a marker of neuroinflammation, in the brain during major depressive episodes, JAMA psychiatry 72(3) (2015) 268-75 10.1001/jamapsychiatry.2014.2427.
[50] M. Maes, G. Nowak, J.R. Caso, J.C. Leza, C. Song, M. Kubera, H. Klein, P. Galecki, C. Noto, E. Glaab, R. Balling, M. Berk, Toward Omics-Based, Systems Biomedicine, and Path and Drug Discovery Methodologies for Depression-Inflammation Research, Molecular neurobiology 53(5) (2016) 2927-2935 10.1007/s12035-015-9183-5.
[51] K.M. Kulmatycki, F. Jamali, Drug disease interactions: role of inflammatory mediators in depression and variability in antidepressant drug response, Journal of pharmacy & pharmaceutical sciences : a publication of the Canadian Society for Pharmaceutical Sciences, Societe canadienne des sciences pharmaceutiques 9(3) (2006) 292-306 doi: http://www.ncbi.nlm.nih.gov/pubmed/17207413.
[52] R.L. Ownby, Neuroinflammation and cognitive aging, Current psychiatry reports 12(1) (2010) 39-45 10.1007/s11920-009-0082-1.
[53] Z. You, C. Luo, W. Zhang, Y. Chen, J. He, Q. Zhao, R. Zuo, Y. Wu, Pro- and anti-inflammatory cytokines expression in rat's brain and spleen exposed to chronic mild stress: involvement in depression, Behavioural brain research 225(1) (2011) 135-41 10.1016/j.bbr.2011.07.006.
[54] L. Capuron, A.H. Miller, Immune system to brain signaling: neuropsychopharmacological implications, Pharmacology & therapeutics 130(2) (2011) 226-38 10.1016/j.pharmthera.2011.01.014.
[55] J.L. Remus, R. Dantzer, Inflammation Models of Depression in Rodents: Relevance to Psychotropic Drug Discovery, The international journal of neuropsychopharmacology 19(9) (2016) 10.1093/ijnp/pyw028.

ACCEPTED MANUSCRIPT

[56] M. Maes, Major depression and activation of the inflammatory response system, Advances in experimental medicine and biology 461 (1999) 25-46 10.1007/978-0-585-37970-8_2.
[57] A.M. Myint, B.E. Leonard, H.W. Steinbusch, Y.K. Kim, Th1, Th2, and Th3 cytokine alterations in major depression, Journal of affective disorders 88(2) (2005) 167-73 10.1016/j.jad.2005.07.008.
[58] R. Musil, M.J. Schwarz, M. Riedel, S. Dehning, A. Cerovecki, I. Spellmann, V. Arolt, N. Muller, Elevated macrophage migration inhibitory factor and decreased transforming growth factor-beta levels in major depression--no influence of celecoxib treatment, Journal of affective disorders 134(1-3) (2011) 217-25 10.1016/j.jad.2011.05.047.
[59] G. Rush, A. O'Donovan, L. Nagle, C. Conway, A. McCrohan, C. O'Farrelly, J.V. Lucey, K.M. Malone, Alteration of immune markers in a group of melancholic depressed patients and their response to electroconvulsive therapy, Journal of affective disorders 205 (2016) 60-68 10.1016/j.jad.2016.06.035.
[60] R. Strawbridge, D. Arnone, A. Danese, A. Papadopoulos, A. Herane Vives, A.J. Cleare, Inflammation and clinical response to treatment in depression: A meta-analysis, European neuropsychopharmacology : the journal of the European College of Neuropsychopharmacology 25(10) (2015) 1532-43 10.1016/j.euroneuro.2015.06.007.
[61] R. Businaro, M. Corsi, R. Asprino, C. Di Lorenzo, D. Laskin, R.M. Corbo, S. Ricci, A. Pinto, Modulation Of Inflammation As A Way Of Delaying Alzheimer's Disease Progression: The Diet's Role, Current Alzheimer research (2017) 10.2174/1567205014666170829100100.
[62] L.E. Rojo, J.A. Fernandez, A.A. Maccioni, J.M. Jimenez, R.B. Maccioni, Neuroinflammation: implications for the pathogenesis and molecular diagnosis of Alzheimer's disease, Archives of medical research 39(1) (2008) 1-16 10.1016/j.arcmed.2007.10.001.
[63] A. Okello, P. Edison, H.A. Archer, F.E. Turkheimer, J. Kennedy, R. Bullock, Z. Walker, A. Kennedy, N. Fox, M. Rossor, D.J. Brooks, Microglial activation and amyloid deposition in mild cognitive impairment: a PET study, Neurology 72(1) (2009) 56-62 10.1212/01.wnl.0000338622.27876.0d.
[64] K. Bhaskar, N. Maphis, G. Xu, N.H. Varvel, O.N. Kokiko-Cochran, J.P. Weick, S.M. Staugaitis, A. Cardona, R.M. Ransohoff, K. Herrup, B.T. Lamb, Microglial derived tumor necrosis factor-alpha drives Alzheimer's disease-related neuronal cell cycle events, Neurobiology of disease 62 (2014) 273-85 10.1016/j.nbd.2013.10.007.
[65] N.H. Varvel, K. Bhaskar, M.Z. Kounnas, S.L. Wagner, Y. Yang, B.T. Lamb, K. Herrup, NSAIDs prevent, but do not reverse, neuronal cell cycle reentry in a mouse model of Alzheimer disease, The Journal of clinical investigation 119(12) (2009) 3692-702 10.1172/JCI39716.
[66] K. Herrup, R. Neve, S.L. Ackerman, A. Copani, Divide and die: cell cycle events as triggers of nerve cell death, The Journal of neuroscience : the official journal of the Society for Neuroscience 24(42) (2004) 9232-9 10.1523/JNEUROSCI.3347-04.2004.
[67] J.H. Ledo, E.P. Azevedo, D. Beckman, F.C. Ribeiro, L.E. Santos, D.S. Razolli, G.C. Kincheski, H.M. Melo, M. Bellio, A.L. Teixeira, L.A. Velloso, D. Foguel, F.G. De Felice, S.T. Ferreira, Cross Talk Between Brain Innate Immunity and Serotonin Signaling Underlies Depressive-Like Behavior Induced by Alzheimer's Amyloid-beta Oligomers in Mice, The Journal of neuroscience : the official journal of the Society for Neuroscience 36(48) (2016) 12106-12116 10.1523/JNEUROSCI.1269-16.2016.
[68] M.F. Iulita, A. Ower, C. Barone, R. Pentz, P. Gubert, C. Romano, R.A. Cantarella, F. Elia, S. Buono, M. Recupero, C. Romano, S. Castellano, P. Bosco, S. Di Nuovo, F. Drago, F. Caraci, A.C. Cuello, An inflammatory and trophic disconnect biomarker profile revealed in Down syndrome plasma: Relation to cognitive decline and longitudinal evaluation, Alzheimer's & dementia : the journal of the Alzheimer's Association 12(11) (2016) 1132-1148 10.1016/j.jalz.2016.05.001.
[69] C. Faustino, P. Rijo, C.P. Reis, Nanotechnological strategies for nerve growth factor delivery: Therapeutic implications in Alzheimer's disease, Pharmacological research : the official journal of the Italian Pharmacological Society 120 (2017) 68-87 10.1016/j.phrs.2017.03.020.

ACCEPTED MANUSCRIPT

[70] B. Lu, G. Nagappan, X. Guan, P.J. Nathan, P. Wren, BDNF-based synaptic repair as a disease-modifying strategy for neurodegenerative diseases, Nature reviews. Neuroscience 14(6) (2013) 401-16 10.1038/nrn3505.
[71] J.C. Zhang, W. Yao, K. Hashimoto, Brain-derived Neurotrophic Factor (BDNF)-TrkB Signaling in Inflammation-related Depression and Potential Therapeutic Targets, Current neuropharmacology 14(7) (2016) 721-31 doi: http://www.ncbi.nlm.nih.gov/pubmed/26786147.
[72] J.H. Song, J.T. Yu, L. Tan, Brain-Derived Neurotrophic Factor in Alzheimer's Disease: Risk, Mechanisms, and Therapy, Molecular neurobiology 52(3) (2015) 1477-1493 10.1007/s12035-014-8958-4.
[73] A. Berry, P. Panetta, A. Luoni, V. Bellisario, S. Capoccia, M.A. Riva, F. Cirulli, Decreased Bdnf expression and reduced social behavior in periadolescent rats following prenatal stress, Developmental psychobiology 57(3) (2015) 365-73 10.1002/dev.21297.
[74] F. Calabrese, R. Molteni, G. Racagni, M.A. Riva, Neuronal plasticity: a link between stress and mood disorders, Psychoneuroendocrinology 34 Suppl 1 (2009) S208-16 10.1016/j.psyneuen.2009.05.014.
[75] F. Calabrese, R.H. van der Doelen, G. Guidotti, G. Racagni, T. Kozicz, J.R. Homberg, M.A. Riva, Exposure to early life stress regulates Bdnf expression in SERT mutant rats in an anatomically selective fashion, Journal of neurochemistry 132(1) (2015) 146-54 10.1111/jnc.12846.
[76] F. Karege, G. Vaudan, M. Schwald, N. Perroud, R. La Harpe, Neurotrophin levels in postmortem brains of suicide victims and the effects of antemortem diagnosis and psychotropic drugs, Brain research. Molecular brain research 136(1-2) (2005) 29-37 10.1016/j.molbrainres.2004.12.020.
[77] V. Reinhart, S.E. Bove, D. Volfson, D.A. Lewis, R.J. Kleiman, T.A. Lanz, Evaluation of TrkB and BDNF transcripts in prefrontal cortex, hippocampus, and striatum from subjects with schizophrenia, bipolar disorder, and major depressive disorder, Neurobiology of disease 77 (2015) 220-7 10.1016/j.nbd.2015.03.011.
[78] E. Shimizu, K. Hashimoto, N. Okamura, K. Koike, N. Komatsu, C. Kumakiri, M. Nakazato, H. Watanabe, N. Shinoda, S. Okada, M. Iyo, Alterations of serum levels of brain-derived neurotrophic factor (BDNF) in depressed patients with or without antidepressants, Biological psychiatry 54(1) (2003) 70-5 doi: http://www.ncbi.nlm.nih.gov/pubmed/12842310.
[79] A.P. Allen, M. Naughton, J. Dowling, A. Walsh, F. Ismail, G. Shorten, L. Scott, D.M. McLoughlin, J.F. Cryan, T.G. Dinan, G. Clarke, Serum BDNF as a peripheral biomarker of treatment-resistant depression and the rapid antidepressant response: A comparison of ketamine and ECT, Journal of affective disorders 186 (2015) 306-11 10.1016/j.jad.2015.06.033.
[80] M.F. Egan, M. Kojima, J.H. Callicott, T.E. Goldberg, B.S. Kolachana, A. Bertolino, E. Zaitsev, B. Gold, D. Goldman, M. Dean, B. Lu, D.R. Weinberger, The BDNF val66met polymorphism affects activity-dependent secretion of BDNF and human memory and hippocampal function, Cell 112(2) (2003) 257-69 doi: http://www.ncbi.nlm.nih.gov/pubmed/12553913.
[81] S. Anttila, K. Huuhka, M. Huuhka, R. Rontu, M. Hurme, E. Leinonen, T. Lehtimaki, Interaction between 5-HT1A and BDNF genotypes increases the risk of treatment-resistant depression, Journal of neural transmission 114(8) (2007) 1065-8 10.1007/s00702-007-0705-9.
[82] H. Banner, V. Bhat, N. Etchamendy, R. Joober, V.D. Bohbot, The brain-derived neurotrophic factor Val66Met polymorphism is associated with reduced functional magnetic resonance imaging activity in the hippocampus and increased use of caudate nucleus-dependent strategies in a human virtual navigation task, The European journal of neuroscience 33(5) (2011) 968-77 10.1111/j.1460-9568.2010.07550.x.
[83] C.W. Cotman, The role of neurotrophins in brain aging: a perspective in honor of Regino Perez-Polo, Neurochemical research 30(6-7) (2005) 877-81 10.1007/s11064-005-6960-y.
[84] W.W. Poon, M. Blurton-Jones, C.H. Tu, L.M. Feinberg, M.A. Chabrier, J.W. Harris, N.L. Jeon, C.W. Cotman, beta-Amyloid impairs axonal BDNF retrograde trafficking, Neurobiology of aging 32(5) (2011) 821-33 10.1016/j.neurobiolaging.2009.05.012.

ACCEPTED MANUSCRIPT

[85] L. Tong, R. Balazs, R. Soiampornkul, W. Thangnipon, C.W. Cotman, Interleukin-1 beta impairs brain derived neurotrophic factor-induced signal transduction, Neurobiology of aging 29(9) (2008) 1380-93 10.1016/j.neurobiolaging.2007.02.027.
[86] O.V. Forlenza, B.S. Diniz, A.L. Teixeira, E.B. Ojopi, L.L. Talib, V.A. Mendonca, G. Izzo, W.F. Gattaz, Effect of brain-derived neurotrophic factor Val66Met polymorphism and serum levels on the progression of mild cognitive impairment, The world journal of biological psychiatry : the official journal of the World Federation of Societies of Biological Psychiatry 11(6) (2010) 774-80 10.3109/15622971003797241.
[87] Y.Y. Lim, V.L. Villemagne, S.M. Laws, D. Ames, R.H. Pietrzak, K.A. Ellis, K. Harrington, P. Bourgeat, A.I. Bush, R.N. Martins, C.L. Masters, C.C. Rowe, P. Maruff, A.R. Group, Effect of BDNF Val66Met on memory decline and hippocampal atrophy in prodromal Alzheimer's disease: a preliminary study, PloS one 9(1) (2014) e86498 10.1371/journal.pone.0086498.
[88] B. Borroni, S. Archetti, C. Costanzi, M. Grassi, M. Ferrari, A. Radeghieri, L. Caimi, C. Caltagirone, M. Di Luca, A. Padovani, I.W. Group, Role of BDNF Val66Met functional polymorphism in Alzheimer's disease-related depression, Neurobiology of aging 30(9) (2009) 1406-12 10.1016/j.neurobiolaging.2007.11.023.
[89] P. ten Dijke, C.S. Hill, New insights into TGF-beta-Smad signalling, Trends in biochemical sciences 29(5) (2004) 265-73 10.1016/j.tibs.2004.03.008.
[90] J. Taipale, J. Saharinen, J. Keski-Oja, Extracellular matrix-associated transforming growth factor-beta: role in cancer cell growth and invasion, Advances in cancer research 75 (1998) 87-134 doi: http://www.ncbi.nlm.nih.gov/pubmed/9709808.
[91] J.P. Annes, J.S. Munger, D.B. Rifkin, Making sense of latent TGFbeta activation, Journal of cell science 116(Pt 2) (2003) 217-24 doi: http://www.ncbi.nlm.nih.gov/pubmed/12482908.
[92] G. Jenkins, The role of proteases in transforming growth factor-beta activation, The international journal of biochemistry & cell biology 40(6-7) (2008) 1068-78 10.1016/j.biocel.2007.11.026.
[93] D. Vivien, C. Ali, Transforming growth factor-beta signalling in brain disorders, Cytokine & growth factor reviews 17(1-2) (2006) 121-8 10.1016/j.cytogfr.2005.09.011.
[94] M.A. Briones-Orta, A.C. Tecalco-Cruz, M. Sosa-Garrocho, C. Caligaris, M. Macias-Silva, Inhibitory Smad7: emerging roles in health and disease, Current molecular pharmacology 4(2) (2011) 141-53 doi: http://www.ncbi.nlm.nih.gov/pubmed/21222648.
[95] C.E. O'Brien, L. Bonanno, H. Zhang, T. Wyss-Coray, Beclin 1 regulates neuronal transforming growth factor-beta signaling by mediating recycling of the type I receptor ALK5, Molecular neurodegeneration 10 (2015) 69 10.1186/s13024-015-0065-0.
[96] Y. Zhu, G.Y. Yang, B. Ahlemeyer, L. Pang, X.M. Che, C. Culmsee, S. Klumpp, J. Krieglstein, Transforming growth factor-beta 1 increases bad phosphorylation and protects neurons against damage, The Journal of neuroscience : the official journal of the Society for Neuroscience 22(10) (2002) 3898-909 20026373.
[97] F. Caraci, E. Gili, M. Calafiore, M. Failla, C. La Rosa, N. Crimi, M.A. Sortino, F. Nicoletti, A. Copani, C. Vancheri, TGF-beta1 targets the GSK-3beta/beta-catenin pathway via ERK activation in the transition of human lung fibroblasts into myofibroblasts, Pharmacological research : the official journal of the Italian Pharmacological Society 57(4) (2008) 274-82 10.1016/j.phrs.2008.02.001.
[98] F. Caraci, G. Battaglia, C. Busceti, F. Biagioni, F. Mastroiacovo, P. Bosco, F. Drago, F. Nicoletti, M.A. Sortino, A. Copani, TGF-beta 1 protects against Abeta-neurotoxicity via the phosphatidylinositol-3-kinase pathway, Neurobiology of disease 30(2) (2008) 234-42 10.1016/j.nbd.2008.01.007.
[99] R. Derynck, Y.E. Zhang, Smad-dependent and Smad-independent pathways in TGF-beta family signalling, Nature 425(6958) (2003) 577-84 10.1038/nature02006.
[100] U. Ueberham, E. Ueberham, H. Gruschka, T. Arendt, Altered subcellular location of phosphorylated Smads in Alzheimer's disease, The European journal of neuroscience 24(8) (2006) 2327-34 10.1111/j.1460-9568.2006.05109.x.

ACCEPTED MANUSCRIPT

[101] J.H. Prehn, V.P. Bindokas, J. Jordan, M.F. Galindo, G.D. Ghadge, R.P. Roos, L.H. Boise, C.B. Thompson, S. Krajewski, J.C. Reed, R.J. Miller, Protective effect of transforming growth factor-beta 1 on beta-amyloid neurotoxicity in rat hippocampal neurons, Molecular pharmacology 49(2) (1996) 319-28 doi: http://www.ncbi.nlm.nih.gov/pubmed/8632765.
[102] R.F. Ren, D.B. Hawver, R.S. Kim, K.C. Flanders, Transforming growth factor-beta protects human hNT cells from degeneration induced by beta-amyloid peptide: involvement of the TGF-beta type II receptor, Brain research. Molecular brain research 48(2) (1997) 315-22 doi: http://www.ncbi.nlm.nih.gov/pubmed/9332729.
[103] E.S. Kim, R.S. Kim, R.F. Ren, D.B. Hawver, K.C. Flanders, Transforming growth factor-beta inhibits apoptosis induced by beta-amyloid peptide fragment 25-35 in cultured neuronal cells, Brain research. Molecular brain research 62(2) (1998) 122-30 doi: http://www.ncbi.nlm.nih.gov/pubmed/9813276.
[104] F. Caraci, W. Gulisano, C.A. Guida, A.A. Impellizzeri, F. Drago, D. Puzzo, A. Palmeri, A key role for TGF-beta1 in hippocampal synaptic plasticity and memory, Scientific reports 5 (2015) 11252 10.1038/srep11252.
[105] K.M. Lee, Y.K. Kim, The role of IL-12 and TGF-beta1 in the pathophysiology of major depressive disorder, International immunopharmacology 6(8) (2006) 1298-304 10.1016/j.intimp.2006.03.015.
[106] D. Tombacz, Z. Maroti, T. Kalmar, Z. Csabai, Z. Balazs, S. Takahashi, M. Palkovits, M. Snyder, Z. Boldogkoi, High-Coverage Whole-Exome Sequencing Identifies Candidate Genes for Suicide in Victims with Major Depressive Disorder, Scientific reports 7(1) (2017) 7106 10.1038/s41598-017-06522-3.
[107] A.M. Depino, L. Lucchina, F. Pitossi, Early and adult hippocampal TGF-beta1 overexpression have opposite effects on behavior, Brain, behavior, and immunity 25(8) (2011) 1582-91 10.1016/j.bbi.2011.05.007.
[108] M. Graciarena, A.M. Depino, F.J. Pitossi, Prenatal inflammation impairs adult neurogenesis and memory related behavior through persistent hippocampal TGFbeta1 downregulation, Brain, behavior, and immunity 24(8) (2010) 1301-9 10.1016/j.bbi.2010.06.005.
[109] J.E. Malberg, Implications of adult hippocampal neurogenesis in antidepressant action, Journal of psychiatry & neuroscience : JPN 29(3) (2004) 196-205 doi: http://www.ncbi.nlm.nih.gov/pubmed/15173896.
[110] P. Mathieu, A.P. Piantanida, F. Pitossi, Chronic expression of transforming growth factor-beta enhances adult neurogenesis, Neuroimmunomodulation 17(3) (2010) 200-1 10.1159/000258723.
[111] A. Sometani, H. Kataoka, A. Nitta, H. Fukumitsu, H. Nomoto, S. Furukawa, Transforming growth factor-beta1 enhances expression of brain-derived neurotrophic factor and its receptor, TrkB, in neurons cultured from rat cerebral cortex, Journal of neuroscience research 66(3) (2001) 369-76 10.1002/jnr.1229.
[112] I. Zaletel, D. Filipovic, N. Puskas, Hippocampal BDNF in physiological conditions and social isolation, Reviews in the neurosciences 28(6) (2017) 675-692 10.1515/revneuro-2016-0072.
[113] I. Tesseur, K. Zou, L. Esposito, F. Bard, E. Berber, J.V. Can, A.H. Lin, L. Crews, P. Tremblay, P. Mathews, L. Mucke, E. Masliah, T. Wyss-Coray, Deficiency in neuronal TGF-beta signaling promotes neurodegeneration and Alzheimer's pathology, The Journal of clinical investigation 116(11) (2006) 3060-9 10.1172/JCI27341.
[114] J.D. Luterman, V. Haroutunian, S. Yemul, L. Ho, D. Purohit, P.S. Aisen, R. Mohs, G.M. Pasinetti, Cytokine gene expression as a function of the clinical progression of Alzheimer disease dementia, Archives of neurology 57(8) (2000) 1153-60 doi: http://www.ncbi.nlm.nih.gov/pubmed/10927795.
[115] H.G. Lee, M. Ueda, X. Zhu, G. Perry, M.A. Smith, Ectopic expression of phospho-Smad2 in Alzheimer's disease: uncoupling of the transforming growth factor-beta pathway?, Journal of neuroscience research 84(8) (2006) 1856-61 10.1002/jnr.21072.

ACCEPTED MANUSCRIPT

[116] K.A. Chalmers, S. Love, Neurofibrillary tangles may interfere with Smad 2/3 signaling in neurons, Journal of neuropathology and experimental neurology 66(2) (2007) 158-67 10.1097/nen.0b013e3180303b93.
[117] S. Baig, Z. van Helmond, S. Love, Tau hyperphosphorylation affects Smad 2/3 translocation, Neuroscience 163(2) (2009) 561-70 10.1016/j.neuroscience.2009.06.045.
[118] J.H. Chen, K.F. Ke, J.H. Lu, Y.H. Qiu, Y.P. Peng, Protection of TGF-beta1 against neuroinflammation and neurodegeneration in Abeta1-42-induced Alzheimer's disease model rats, PloS one 10(2) (2015) e0116549 10.1371/journal.pone.0116549.
[119] H. Wang, J. Liu, Y. Zong, Y. Xu, W. Deng, H. Zhu, Y. Liu, C. Ma, L. Huang, L. Zhang, C. Qin, miR-106b aberrantly expressed in a double transgenic mouse model for Alzheimer's disease targets TGF-beta type II receptor, Brain Res 1357 (2010) 166-74 10.1016/j.brainres.2010.08.023.
[120] I. Tesseur, T. Wyss-Coray, A role for TGF-beta signaling in neurodegeneration: evidence from genetically engineered models, Current Alzheimer research 3(5) (2006) 505-13 doi: http://www.ncbi.nlm.nih.gov/pubmed/17168649.
[121] M. Stander, U. Naumann, W. Wick, M. Weller, Transforming growth factor-beta and p-21: multiple molecular targets of decorin-mediated suppression of neoplastic growth, Cell and tissue research 296(2) (1999) 221-7 doi: http://www.ncbi.nlm.nih.gov/pubmed/10382266.
[122] U. Ueberham, I. Hilbrich, E. Ueberham, S. Rohn, P. Glockner, K. Dietrich, M.K. Bruckner, T. Arendt, Transcriptional control of cell cycle-dependent kinase 4 by Smad proteins--implications for Alzheimer's disease, Neurobiology of aging 33(12) (2012) 2827-40 10.1016/j.neurobiolaging.2012.01.013.
[123] A. Caricasole, A. Copani, F. Caraci, E. Aronica, A.J. Rozemuller, A. Caruso, M. Storto, G. Gaviraghi, G.C. Terstappen, F. Nicoletti, Induction of Dickkopf-1, a negative modulator of the Wnt pathway, is associated with neuronal degeneration in Alzheimer's brain, The Journal of neuroscience : the official journal of the Society for Neuroscience 24(26) (2004) 6021-7 10.1523/JNEUROSCI.1381-04.2004.
[124] K. Herrup, Reimagining Alzheimer's disease--an age-based hypothesis, The Journal of neuroscience : the official journal of the Society for Neuroscience 30(50) (2010) 16755-62 10.1523/JNEUROSCI.4521-10.2010.
[125] T.C. Brionne, I. Tesseur, E. Masliah, T. Wyss-Coray, Loss of TGF-beta 1 leads to increased neuronal cell death and microgliosis in mouse brain, Neuron 40(6) (2003) 1133-45 doi: http://www.ncbi.nlm.nih.gov/pubmed/14687548.
[126] M. Makwana, L.L. Jones, D. Cuthill, H. Heuer, M. Bohatschek, M. Hristova, S. Friedrichsen, I. Ormsby, D. Bueringer, A. Koppius, K. Bauer, T. Doetschman, G. Raivich, Endogenous transforming growth factor beta 1 suppresses inflammation and promotes survival in adult CNS, The Journal of neuroscience : the official journal of the Society for Neuroscience 27(42) (2007) 11201-13 10.1523/JNEUROSCI.2255-07.2007.
[127] J.E. Tichauer, B. Flores, B. Soler, L. Eugenin-von Bernhardi, G. Ramirez, R. von Bernhardi, Age-dependent changes on TGFbeta1 Smad3 pathway modify the pattern of microglial cell activation, Brain, behavior, and immunity 37 (2014) 187-96 10.1016/j.bbi.2013.12.018.
[128] M. Fogel-Petrovic, J.A. Long, N.L. Misso, P.S. Foster, K.D. Bhoola, P.J. Thompson, Physiological concentrations of transforming growth factor beta1 selectively inhibit human dendritic cell function, International immunopharmacology 7(14) (2007) 1924-33 10.1016/j.intimp.2007.07.003.
[129] R.F. Gaertner, T. Wyss-Coray, D. Von Euw, S. Lesne, D. Vivien, P. Lacombe, Reduced brain tissue perfusion in TGF-beta 1 transgenic mice showing Alzheimer's disease-like cerebrovascular abnormalities, Neurobiology of disease 19(1-2) (2005) 38-46 10.1016/j.nbd.2004.11.008.
[130] B. Ongali, N. Nicolakakis, C. Lecrux, T. Aboulkassim, P. Rosa-Neto, P. Papadopoulos, X.K. Tong, E. Hamel, Transgenic mice overexpressing APP and transforming growth factor-beta1 feature cognitive and vascular hallmarks of Alzheimer's disease, The American journal of pathology 177(6) (2010) 3071-80 10.2353/ajpath.2010.100339.

ACCEPTED MANUSCRIPT

[131] T. Wyss-Coray, E. Masliah, M. Mallory, L. McConlogue, K. Johnson-Wood, C. Lin, L. Mucke, Amyloidogenic role of cytokine TGF-beta1 in transgenic mice and in Alzheimer's disease, Nature 389(6651) (1997) 603-6 10.1038/39321.
[132] T. Town, Y. Laouar, C. Pittenger, T. Mori, C.A. Szekely, J. Tan, R.S. Duman, R.A. Flavell, Blocking TGF-beta-Smad2/3 innate immune signaling mitigates Alzheimer-like pathology, Nature medicine 14(6) (2008) 681-7 10.1038/nm1781.
[133] P. Grammas, R. Ovase, Cerebrovascular transforming growth factor-beta contributes to inflammation in the Alzheimer's disease brain, The American journal of pathology 160(5) (2002) 1583-7 doi: http://www.ncbi.nlm.nih.gov/pubmed/12000710.
[134] E. Hamel, Cerebral circulation: function and dysfunction in Alzheimer's disease, Journal of cardiovascular pharmacology 65(4) (2015) 317-24 10.1097/FJC.0000000000000177.
[135] T. Wyss-Coray, C. Lin, F. Yan, G.Q. Yu, M. Rohde, L. McConlogue, E. Masliah, L. Mucke, TGF-beta1 promotes microglial amyloid-beta clearance and reduces plaque burden in transgenic mice, Nature medicine 7(5) (2001) 612-8 10.1038/87945.
[136] L.P. Diniz, V. Tortelli, I. Matias, J. Morgado, A.P. Bergamo Araujo, H.M. Melo, G.S. Seixas da Silva, S.V. Alves-Leon, J.M. de Souza, S.T. Ferreira, F.G. De Felice, F.C.A. Gomes, Astrocyte Transforming Growth Factor Beta 1 Protects Synapses against Abeta Oligomers in Alzheimer's Disease Model, The Journal of neuroscience : the official journal of the Society for Neuroscience 37(28) (2017) 6797-6809 10.1523/JNEUROSCI.3351-16.2017.
[137] J.E. Tichauer, R. von Bernhardi, Transforming growth factor-beta stimulates beta amyloid uptake by microglia through Smad3-dependent mechanisms, Journal of neuroscience research 90(10) (2012) 1970-80 10.1002/jnr.23082.
[138] W.C. Huang, F.C. Yen, F.S. Shie, C.M. Pan, Y.J. Shiao, C.N. Yang, F.L. Huang, Y.J. Sung, H.J. Tsay, TGF-beta1 blockade of microglial chemotaxis toward Abeta aggregates involves SMAD signaling and down-regulation of CCL5, Journal of neuroinflammation 7 (2010) 28 10.1186/1742-2094-7-28.
[139] L. Song, Y. Gu, J. Jie, X. Bai, Y. Yang, C. Liu, Q. Liu, Dab2 attenuates brain injury in APP/PS1 mice via targeting transforming growth factor-beta/SMAD signaling, Neural regeneration research 9(1) (2014) 41-50 10.4103/1673-5374.125328.
[140] B. Juraskova, C. Andrys, I. Holmerova, D. Solichova, D. Hrnciarikova, H. Vankova, T. Vasatko, J. Krejsek, Transforming growth factor beta and soluble endoglin in the healthy senior and in Alzheimer's disease patients, The journal of nutrition, health & aging 14(9) (2010) 758-61 doi: http://www.ncbi.nlm.nih.gov/pubmed/21085906.
[141] A. Mocali, S. Cedrola, N. Della Malva, M. Bontempelli, V.A. Mitidieri, A. Bavazzano, R. Comolli, F. Paoletti, C.A. La Porta, Increased plasma levels of soluble CD40, together with the decrease of TGF beta 1, as possible differential markers of Alzheimer disease, Experimental gerontology 39(10) (2004) 1555-61 10.1016/j.exger.2004.07.007.
[142] B. De Servi, C.A. La Porta, M. Bontempelli, R. Comolli, Decrease of TGF-beta1 plasma levels and increase of nitric oxide synthase activity in leukocytes as potential biomarkers of Alzheimer's disease, Experimental gerontology 37(6) (2002) 813-21 doi: http://www.ncbi.nlm.nih.gov/pubmed/12175481.
[143] C. Luppi, M. Fioravanti, B. Bertolini, M. Inguscio, A. Grugnetti, F. Guerriero, C. Rovelli, F. Cantoni, P. Guagnano, E. Marazzi, E. Rolfo, D. Ghianda, D. Levante, C. Guerrini, R. Bonacasa, S.B. Solerte, Growth factors decrease in subjects with mild to moderate Alzheimer's disease (AD): potential correction with dehydroepiandrosterone-sulphate (DHEAS), Archives of gerontology and geriatrics 49 Suppl 1 (2009) 173-84 10.1016/j.archger.2009.09.027.
[144] L. Huang, J. Jia, R. Liu, Decreased serum levels of the angiogenic factors VEGF and TGF-beta1 in Alzheimer's disease and amnestic mild cognitive impairment, Neuroscience letters 550 (2013) 60-3 10.1016/j.neulet.2013.06.031.

ACCEPTED MANUSCRIPT

[145] W.W. Chang, L. Zhang, Y.L. Jin, Y.S. Yao, Meta-analysis of the transforming growth factor-beta1 polymorphisms and susceptibility to Alzheimer's disease, Journal of neural transmission 120(2) (2013) 353-60 10.1007/s00702-012-0850-7.
[146] P. Bosco, R. Ferri, M.G. Salluzzo, S. Castellano, M. Signorelli, F. Nicoletti, S.D. Nuovo, F. Drago, F. Caraci, Role of the Transforming-Growth-Factor-beta1 Gene in Late-Onset Alzheimer's Disease: Implications for the Treatment, Current genomics 14(2) (2013) 147-56 10.2174/1389202911314020007.
[147] M.R. Awad, A. El-Gamel, P. Hasleton, D.M. Turner, P.J. Sinnott, I.V. Hutchinson, Genotypic variation in the transforming growth factor-beta1 gene: association with transforming growth factor-beta1 production, fibrotic lung disease, and graft fibrosis after lung transplantation, Transplantation 66(8) (1998) 1014-20 doi: http://www.ncbi.nlm.nih.gov/pubmed/9808485.
[148] B. Arosio, L. Bergamaschini, L. Galimberti, C. La Porta, M. Zanetti, C. Calabresi, E. Scarpini, G. Annoni, C. Vergani, +10 T/C polymorphisms in the gene of transforming growth factor-beta1 are associated with neurodegeneration and its clinical evolution, Mechanisms of ageing and development 128(10) (2007) 553-7 10.1016/j.mad.2007.07.006.
[149] L. Sutcigil, C. Oktenli, U. Musabak, A. Bozkurt, A. Cansever, O. Uzun, S.Y. Sanisoglu, Z. Yesilova, N. Ozmenler, A. Ozsahin, A. Sengul, Pro- and anti-inflammatory cytokine balance in major depression: effect of sertraline therapy, Clinical & developmental immunology 2007 (2007) 76396 10.1155/2007/76396.
[150] A. Szuster-Ciesielska, A. Tustanowska-Stachura, M. Slotwinska, H. Marmurowska-Michalowska, M. Kandefer-Szerszen, In vitro immunoregulatory effects of antidepressants in healthy volunteers, Polish journal of pharmacology 55(3) (2003) 353-62 doi: http://www.ncbi.nlm.nih.gov/pubmed/14506314.
[151] P. Vollmar, A. Haghikia, R. Dermietzel, P.M. Faustmann, Venlafaxine exhibits an anti-inflammatory effect in an inflammatory co-culture model, The international journal of neuropsychopharmacology 11(1) (2008) 111-7 10.1017/S1461145707007729.
[152] R. Zepeda, V. Contreras, C. Pissani, K. Stack, M. Vargas, G.I. Owen, O.M. Lazo, F.C. Bronfman, Venlafaxine treatment after endothelin-1-induced cortical stroke modulates growth factor expression and reduces tissue damage in rats, Neuropharmacology 107 (2016) 131-145 10.1016/j.neuropharm.2016.03.011.
[153] L.V. Kessing, L. Sondergard, J.L. Forman, P.K. Andersen, Antidepressants and dementia, Journal of affective disorders 117(1-2) (2009) 24-9 10.1016/j.jad.2008.11.020.
[154] J.R. Cirrito, B.M. Disabato, J.L. Restivo, D.K. Verges, W.D. Goebel, A. Sathyan, D. Hayreh, G. D'Angelo, T. Benzinger, H. Yoon, J. Kim, J.C. Morris, M.A. Mintun, Y.I. Sheline, Serotonin signaling is associated with lower amyloid-beta levels and plaques in transgenic mice and humans, Proceedings of the National Academy of Sciences of the United States of America 108(36) (2011) 14968-73 10.1073/pnas.1107411108.
[155] L. Rozzini, B.V. Chilovi, M. Conti, E. Bertoletti, M. Zanetti, M. Trabucchi, A. Padovani, Efficacy of SSRIs on cognition of Alzheimer's disease patients treated with cholinesterase inhibitors, International psychogeriatrics 22(1) (2010) 114-9 10.1017/S1041610209990184.
[156] L. Jin, L.F. Gao, D.S. Sun, H. Wu, Q. Wang, D. Ke, H. Lei, J.Z. Wang, G.P. Liu, Long-term Ameliorative Effects of the Antidepressant Fluoxetine Exposure on Cognitive Deficits in 3 x TgAD Mice, Molecular neurobiology 54(6) (2017) 4160-4171 10.1007/s12035-016-9952-9.
[157] J. Wang, Y. Zhang, H. Xu, S. Zhu, H. Wang, J. He, H. Zhang, H. Guo, J. Kong, Q. Huang, X.M. Li, Fluoxetine improves behavioral performance by suppressing the production of soluble beta-amyloid in APP/PS1 mice, Current Alzheimer research 11(7) (2014) 672-80 doi: http://www.ncbi.nlm.nih.gov/pubmed/25115542.
[158] F. Caraci, F. Tascedda, S. Merlo, C. Benatti, S.F. Spampinato, A. Munafo, G.M. Leggio, F. Nicoletti, N. Brunello, F. Drago, M.A. Sortino, A. Copani, Fluoxetine Prevents Abeta1-42-Induced Toxicity via a Paracrine Signaling Mediated by Transforming-Growth-Factor-beta1, Frontiers in pharmacology 7 (2016) 389 10.3389/fphar.2016.00389.

ACCEPTED MANUSCRIPT

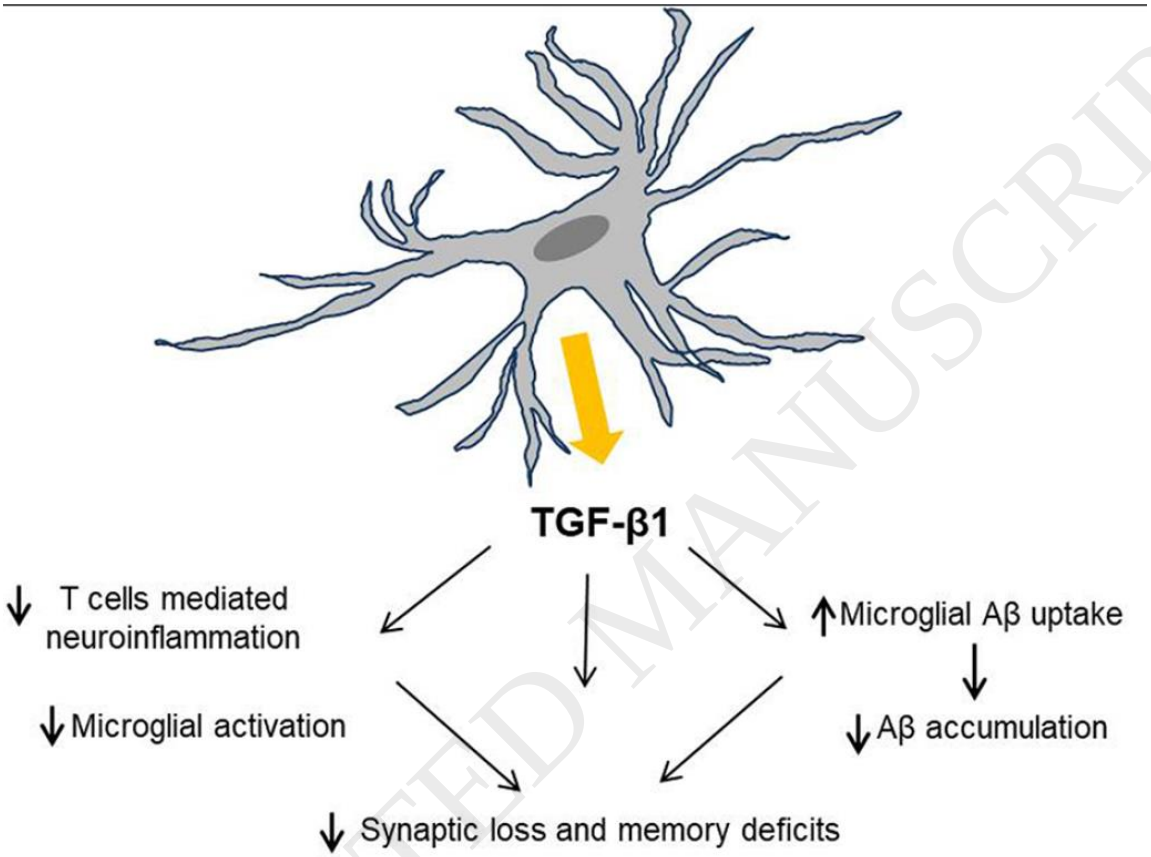
[159] E. Dalle, W.M. Daniels, M.V. Mabandla, Fluvoxamine maleate normalizes striatal neuronal inflammatory cytokine activity in a Parkinsonian rat model associated with depression, Behavioural brain research 316 (2017) 189-196 10.1016/j.bbr.2016.08.005.
[160] Y.C. Chung, S.R. Kim, J.Y. Park, E.S. Chung, K.W. Park, S.Y. Won, E. Bok, M. Jin, E.S. Park, S.H. Yoon, H.W. Ko, Y.S. Kim, B.K. Jin, Fluoxetine prevents MPTP-induced loss of dopaminergic neurons by inhibiting microglial activation, Neuropharmacology 60(6) (2011) 963-74 10.1016/j.neuropharm.2011.01.043.
[161] F. Zhang, H. Zhou, B.C. Wilson, J.S. Shi, J.S. Hong, H.M. Gao, Fluoxetine protects neurons against microglial activation-mediated neurotoxicity, Parkinsonism & related disorders 18 Suppl 1 (2012) S213-7 10.1016/S1353-8020(11)70066-9.
[162] Y. Tizabi, Duality of Antidepressants and Neuroprotectants, Neurotoxicity research 30(1) (2016) 1-13 10.1007/s12640-015-9577-1.
[163] E. Galea, M.T. Heneka, C. Dello Russo, D.L. Feinstein, Intrinsic regulation of brain inflammatory responses, Cell Mol Neurobiol 23(4-5) (2003) 625-35 doi: http://www.ncbi.nlm.nih.gov/pubmed/14514020.
[164] S.E. Counts, E.J. Mufson, Noradrenaline activation of neurotrophic pathways protects against neuronal amyloid toxicity, Journal of neurochemistry 113(3) (2010) 649-60 10.1111/j.1471-4159.2010.06622.x.
[165] Z.G. Ren, P. Porzgen, J.M. Zhang, X.R. Chen, S.G. Amara, R.D. Blakely, M. Sieber-Blum, Autocrine regulation of norepinephrine transporter expression, Molecular and cellular neurosciences 17(3) (2001) 539-50 10.1006/mcne.2000.0946.
[166] S.Y. Tsai, K.S. Schluns, P.T. Le, J.A. McNulty, TGF-beta1 and IL-6 expression in rat pineal gland is regulated by norepinephrine and interleukin-1beta, Histology and histopathology 16(4) (2001) 1135-41 doi: http://www.ncbi.nlm.nih.gov/pubmed/11642733.
[167] D.S. Sun, L.F. Gao, L. Jin, H. Wu, Q. Wang, Y. Zhou, S. Fan, X. Jiang, D. Ke, H. Lei, J.Z. Wang, G.P. Liu, Fluoxetine administration during adolescence attenuates cognitive and synaptic deficits in adult 3xTgAD mice, Neuropharmacology 126 (2017) 200-212 10.1016/j.neuropharm.2017.08.037.
[168] T. Siepmann, A.I. Penzlin, J. Kepplinger, B.M. Illigens, K. Weidner, H. Reichmann, K. Barlinn, Selective serotonin reuptake inhibitors to improve outcome in acute ischemic stroke: possible mechanisms and clinical evidence, Brain and behavior 5(10) (2015) e00373 10.1002/brb3.373.
[169] A. Mowla, M. Mosavinasab, A. Pani, Does fluoxetine have any effect on the cognition of patients with mild cognitive impairment? A double-blind, placebo-controlled, clinical trial, Journal of clinical psychopharmacology 27(1) (2007) 67-70 10.1097/JCP.0b013e31802e0002.

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Figure Legends

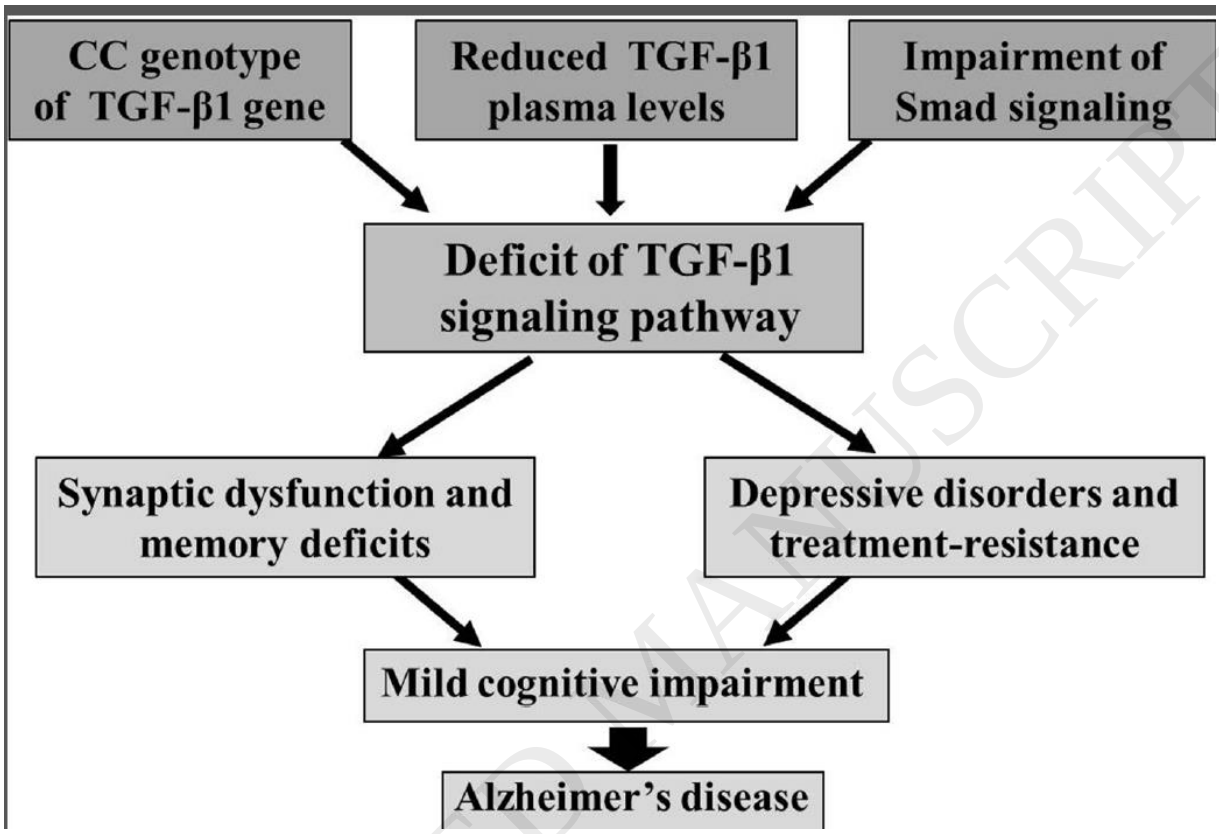
Figure 1. Effects of TGF-β1 to preventAβ induced neuronal damage. TGF-β1 released by astrocytes prevents Aβ-induced microglia activation, stimulates Aβ uptake by microglia thus preventing synaptic loss and memory deficits in AD brain.



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Figure 2. The deficit of TGF-β1signaling pathway as a common pathophysiological event in depression and AD. Different molecular events can contribute to the deficit of TGF-β1signaling pathway, which leads to memory deficits, depressive disorders and treatment-resistance. This deficit can then promote the transition from MCI to AD.



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