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Authors: Filippo Caraci, Simona Federica Spampinato, Maria Grazia Morgese, Fabio Tascedda, Maria Grazia Salluzzo, Maria Concetta Giambirtone, Giuseppe Caruso, Antonio Munafò, Sebastiano Alfio Torrisi, Gian Marco Leggio, Luigia Trabace, Ferdinando Nicoletti, Filippo Drago, Maria Angela Sortino, Agata Copani

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

Filippo Caraci[1,2*], Simona Federica Spampinato[3], Maria Grazia Morgese[4], Fabio Tascedda[5], Maria Grazia Salluzzo[2], Maria Concetta Giambirtone[2], Giuseppe Caruso[2], Antonio Munafò[1], Sebastiano Alfio Torrisi[3], Gian Marco Leggio[3], Luigia Trabace[4], Ferdinando Nicoletti[6,7,] Filippo Drago[3], Maria Angela Sortino[3] & Agata Copani[1,8]

[1]Department of Drug Sciences, University of Catania, 95125, Catania, Italy; [2]IRCCS Associazione Oasi Maria S.S., Institute for Research on Mental Retardation and Brain Aging, Troina, Enna, Italy; [3]Department of Biomedical and Biotechnological Sciences, University of Catania, Catania, Italy; [4]Department of Clinical and Experimental Medicine, University of Foggia, Via Napoli 20, 71122 Foggia, Italy; [5]Department of Life Sciences, University of Modena and Reggio Emilia, Modena, Italy; [6]I.N.M. Neuromed, Località Camerelle, 86077, Pozzilli, Italy; [7]Department of Human Physiology and Pharmacology, University of Rome Sapienza, 00185 Rome; [8]I.B.B., CNR-Catania, 95125, Catania, Italy.

Corresponding author:

Filippo Caraci, MD

Department of Drug Sciences,

University of Catania,

Viale Andrea Doria 6

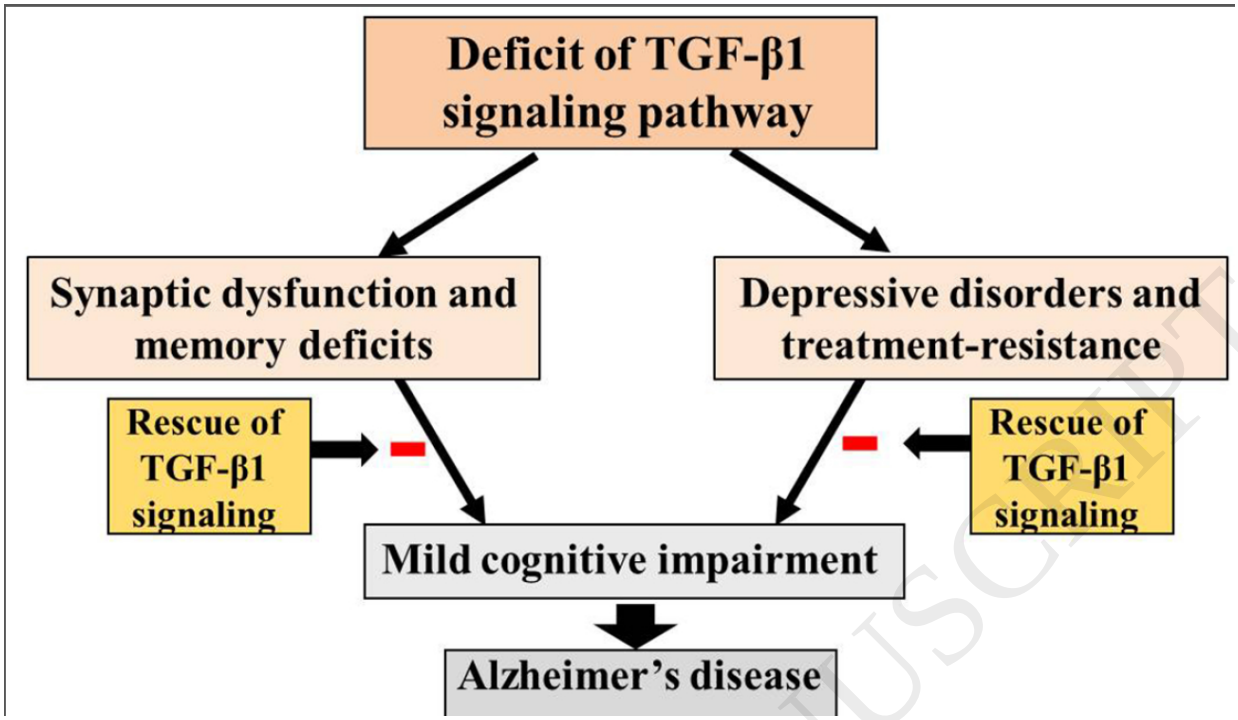
95125, Catania, Italy

Phone: + 39-095-7384251

Fax : + 39-095-7384238

E-mail: carafil@hotmail.com

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

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

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.

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

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

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,

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

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

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

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

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].

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

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

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

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

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

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

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

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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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.

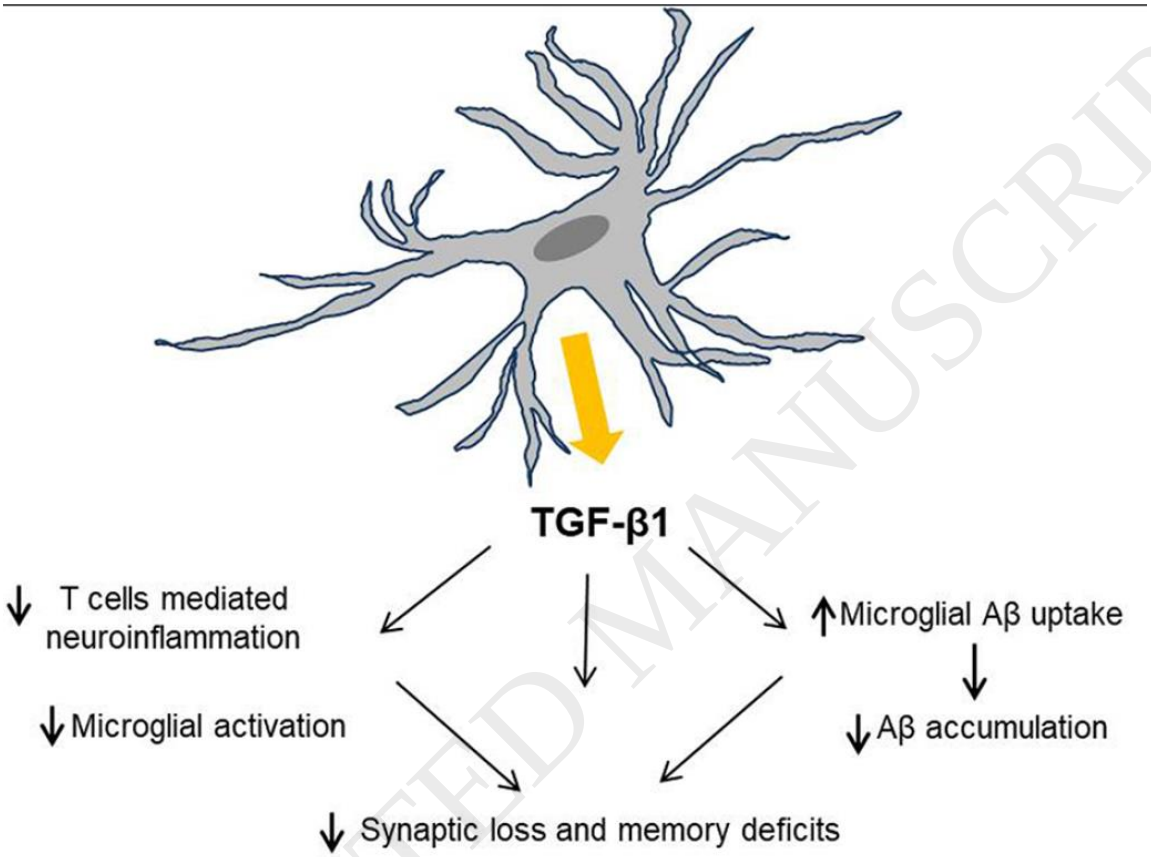

Figure 2. The deficit of TGF-β1signaling pathway as a common pathophysiological event in depression and AD. Different molecular events can contribute to the deficit of TGF-β1signaling pathway, which leads to memory deficits, depressive disorders and treatment-resistance. This deficit can then promote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