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TGF-β1 factor in the cerebrovascular diseases of Alzheimer's disease

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Abstract. – Transforming growth factor betas (TGF-βs) belong to three isoforms (TGF-β1, TGF-β2 and TGF-β3) members of a large pleiotropic superfamily of around 100 distinct proteins participating in the regulation of key events of development and disease, and tissue repair. In the central nervous system (CNS), all the three isoforms are produced by both glial and neuronal cells and are involved in essential tissue functions such as cell-cycle control, regulation of early development and differentiation, neuronal survival and astrocytes differentiation. Recent findings have shown abnormally increase of the levels of TGF-β1 in the brain of patients suffering Alzheimer's disease (AD), an elderly pathology reaching individuals over 65-years-old which present well-known hallmarks, including cerebrovascular deficiency, abnormal deposition of amyloid beta (Aβ), cholinergic denervation, neuroinflammation, neurofibrillary tangles and progressive loss of memory. However, related to the pathological features of AD, the brain overexpression of TGF-β1 was associated with neuroinflammation, accumulation of extracellular matrix compounds and cerebrovascular stiffness, neuronal apoptosis along with the development of vascular hypertrophy. Consistent with these observations, transgenic mice model (TGF mice) overexpressing constitutively TGF-β1 fully mimicked AD-like cerebrovascular pathology. Taken altogether, these data suggest the involvement of TGF-β1in the pathogenesis of AD, particularly in the cerebrovascular pathology which is of interest in the present review that will discuss the contribution of TGF-β1 in the cerebrovascular physiopathology of AD.

Key Words:
TGF-β1, Cerebrovascular deficits, Neuroinflammation, Alzheimer's disease.

Introduction

Discovered in the early 1980s for its transforming properties[1,2], transforming growth factor betas (TGF-βs) soon appeared as pleiotropic cytokines orchestrating many critical physiological processes including embryogenesis, immune response, extracellular matrix metabolism as well as cell circle. Indeed, TGF-βs belong to a subfamily of a large family of more than 40 structurally related regulatory protein expressed in mammals among which are included bone morphogenetic proteins (BMPs), growth and differentiation factors (GDFs), Mullerian inhibitory factor (MIF), activins and inhibins[3,4] (Figure 1). TGF-βs subfamily express by human are three genetically distinct isoforms (TGF-β1, β2 and β3) with high homology, located on chromosomes 19q13, 1q41 and 14q24, respectively[5]. TGF-βs play pleiotropic roles in the growth organs and systems[6] including, cell-cycle control, differentiation, regulation of early development, extracellular matrix formation, angiogenesis, hematopoiesis and immune functions[7].

Brain TGF-β1 may have neuroprotective functions, but under some conditions[8,9], thereby preventing neuronal apoptosis through the inhibition of caspase-3[10] mitochondrial membrane potential and increases the expression of the antiapoptotic protein, Bcl-2 and Bcl-xl[11]. As well, TGF-β1 protects neurons against damage induced by excitotoxins, hypoxia/ischemia, deprivation of trophic factors, and aggregates of amyloid beta (Aβ)[12-14], a distinct feature of Alzheimer's disease (AD) which is a neurodegenerative disease affecting mostly individual over 65 year old, characterized by cerebrovascular deficiency, abnormally deposition and aggregation of amyloid beta (Aβ), cholinergic denervation, neuroinflammation, neurofibrillary tangles and the progressive loss of memory[15]. In line with the hallmarks of AD, recent findings have shown the increased of the levels of TGF-β1 inside of the brain and cerebral vessels tissues of patients suffering Alzheimer disease (AD)[16,17]. These increases of TGF-β1 were likely associated with the development of neuroinflammation, vascular hypertrophy, fibrosis, and the accumulation of extracellular matrix components[18-22] (Figure 2).

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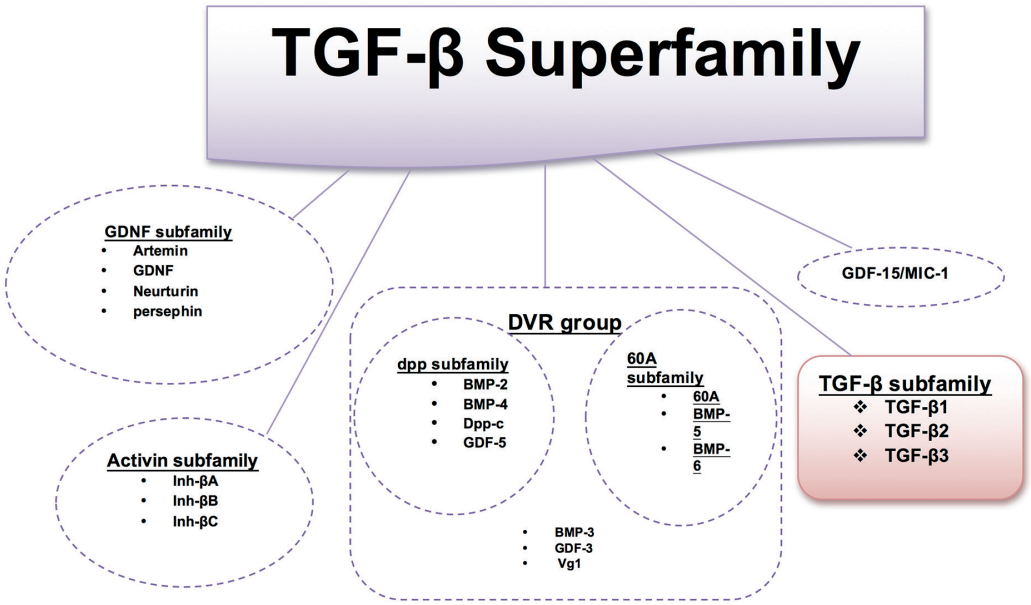

Figure 1. Representative members of the transforming growth factor beta (TGF-β) superfamily grouped according to sequence similarities. In red the TGF-β subfamily which is of interest in the study.

Accordingly, transgenic mice overexpressing a constitutive form of TGF-β1 (TGF mice) in astrocytes exhibited AD-like neuroinflammation and cerebrovascular dysfunction[23-27]. Consequently, more to suggest the involvement of TGF-β1in AD pathogenesis, these findings revealed a fundamental novel role and distinct mechanisms through which cerebral blood vessels and brain perfusion can be endangered. In this review, we will focus our attention on the involvement of TGF-β1 in the cerebrovascular disease physiopathology of AD.

Presence and Role of Transforming Growth Factor Beta (TGF-β) in the Mammalian Brain

In the central nervous system, (CNS) of animals and humans, from early embryonic stages, all three isoforms are expressed (mRNA and protein) by both glial and neuronal cells[7,28-30]. However, TGF-β2 and -β3, but not TGF-β1, and their respective receptors are expressed in early embryonic structures where they play essential role in the induction of midbrain dopaminergic neurons survival[31-33], acting in concert with other molecules such as Fibroblast Growth Factor (FGF2, FGF8) and glial cell line-derived neurotrophic factor (GDNF)[32]. TGF-β2 and -β3 are also localized in radial glial cells, neuronal cell bodies in the telencephalic cortex and cerebellum, suggesting a role in the regulation of neuronal migration and differentiation as well as glial cell proliferation and differentiation[34,35]. In addition, the expression of TGF-β2 and -β3 persists in the entire adult CNS areas including cortex, hippocampus, striatum, brainstem and cerebellum.

However, immunoreactive mRNA of TGF-β1 was observed in white matter astrocytes as well as neurons within the hippocampal pyramidal neuron, dentate gyrus granule cells, large cortical neurons within layer II, III and V, and a subpopulation of cerebellar Purkinje cells[36,37]. Although the distribution of TGF-β1 in the brain is controversial and restricted to meninges and choroid plexus in the intact brain and upon lesion, it is induced in neurons, astrocytes and microglia[38]. *In vivo* role of TGF-β1 in the unlesioned brain is supported by *in vitro* studies in neurons and astrocytes in culture[39]. Indeed, TGF-β1 has been widely considered as an injury-related cytokine which is a crucial regulator of nervous system physiology and its vasculature. It has been reported a reduction of cell-cell-contacts and increase focal contacts, thus inducing astrocytes motility[40]. However, TGF1-β1 production and release increase significantly in response to CNS lesions, with astrocytes and microglia as the major sources of TGF-β1 in the injured brain[12,41]. Indeed, an increase of TGF-β activation can be observed in response to injury and subsequent extracellular matrix perturbation. The TGF-βs activity is primarily regulated through the conversion of latent TGF-β to an active form by a var-

iety of molecules, from protons to proteases[42], and once released from its latent secreted complex[43], TGF-βs isoforms elicits their cell type-specific responses through the ligand-induced formation of heteromeric receptor complex between the serine/threonine kinase receptors. The subsequent functional complex of TGF-β family receptors at the cell surface consists of the activin-like kinase 5 (ALK5)/TGF-β type I (TβRI) receptor and the TGF-β type II (TβRII) subunits with the latter having serine/threonine kinase domain[44,45]. The consequently activated type I receptor phosphorylates selected Smads, and these receptor-activated Smads (R-Smads) then form a complex with Smad 4. Activated Smad complexes translocate into the nucleus where they regulate the expression of various target genes involving cell proliferation[44] (Figure 3). However, the TGF-β/Smad signaling cascade can be regulated at many levels. For example, inhibitory-Smads, namely Smad 6 and Smad 7, counteract the signaling of R-Smads through diverse mechanisms[45]. Particularly, Smad 7binds to activated type I receptors, thus inhibiting the phosphorylation and the following nuclear translocation of R-Smads[46]. The same way, Smad 7 can also target TGF-β receptors to the ubiquitin degradation pathway with the following inhibition of TGF-β/Smad signaling cascade[46]. Accordingly, the increase of Smad 7 protein could oppose the cell-cycle control operate by TGF-β or other protein or pathways[46]. In addition to Smad-mediated gene transcription, TGF-β can activate Smad-independent pathways including the extracellular-regulated kinase (ERK) pathway[44], the nuclear factor κB (NF-κB) pathways[47], and the PI-3-K/serine-threonine protein kinase (AKT) pathway[13]. TGF-β/Smad-independent pathways have a key role in mediating various biological effects of TGF-β, such as cell-cycle inhibition, epithelial-to-mesenchymal transdifferentiation, immune suppression, and neuroprotective effects[13,44].

However, in AD, impairment of TGF-β-activated Smad signaling has been demonstrated, particularly, an ectopic localization of phosphorylated Smad2/3 has been detected in the cytoplasm

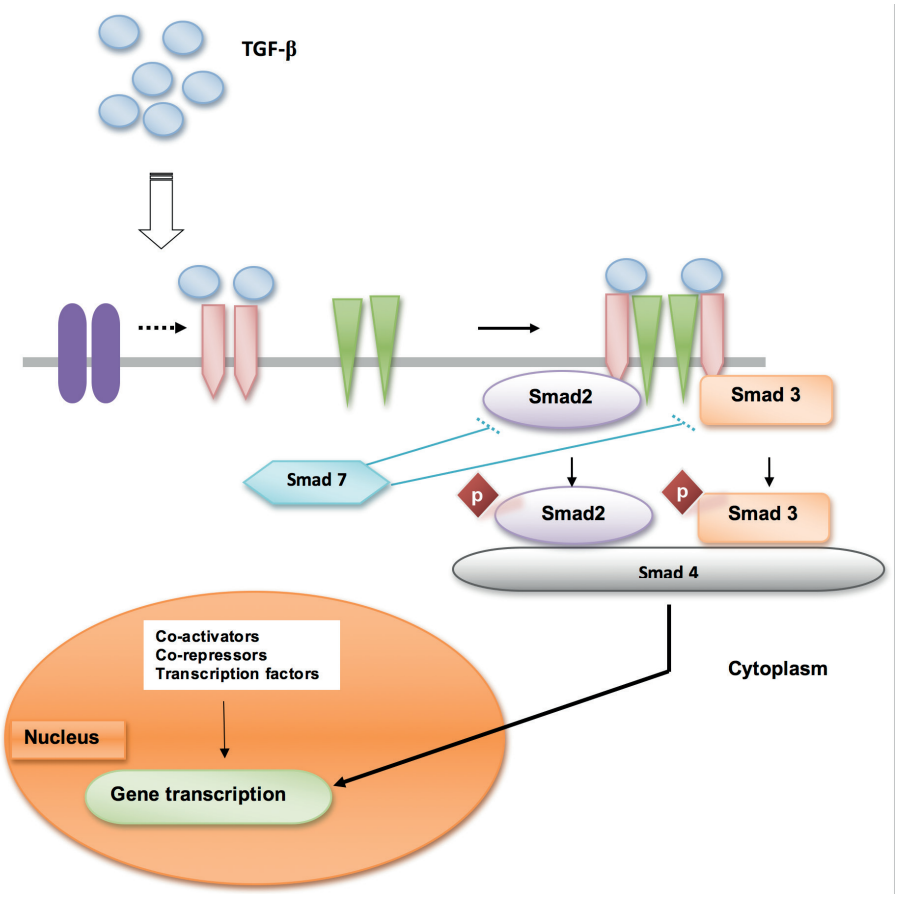

Figure 2. The main TGF-β signaling pathways.

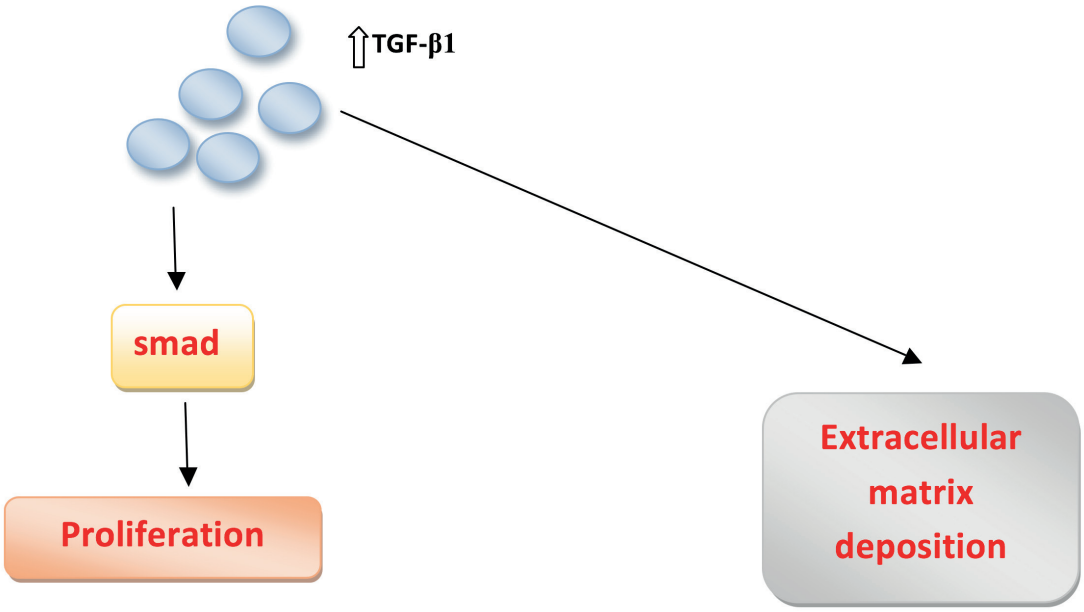

Figure 3. Through activation of MAPK/PI3K and Smads pathway TGF-β binds to the receptors Tβ-RII which benefit for the presence of Tβ-RIII to be enhanced. Thereafter Tβ-RII recruits and phosphorylates Tβ-RI that lead to the activation of Smad 2 and Smad 3 by phosphorylation, a process inhibited by Smad 7. The activated Smad 2 and 3 subsequently form heterodimers with Smad 4 and translocate to the nucleus where, together with co-activators, co-repressors and other transcription factors, the Smad complex regulate gene expression.

of hippocampal neurons, within Aβ plaques[48]. One of the specific features arriving in the earlier course of AD, but not in other neurodegenerative conditions, is the reduction of neuronal expression of TβRII[49]. This suggests that a dysfunction of TGF-β signaling is probably a causal factor in AD progression. Accordingly, neuronal expression of the kinase deficient TβRII in AD transgenic mice promotes both Aβ deposition and dendritic loss[49]. In turn, Aβ might decrease the expression of TβRII through the induction of the micro RNA-106β[50]. *In vitro* studies have demonstrated that TGF-β1 prevents Aβ-challenged cortical neurons from entering the S-phase of the cell cycle[13]. The cell-cycle inhibition is one of the mechanisms by which TGF-β1exerts it neuroprotective effects against Aβ toxicity[13] or preventing Aβ-inducing τ hyperphosphorylation[51] through a mechanism involving PI-3K- promoted inhibition of the τ-phosphorylating enzyme GSK-3β[13]. Another important mechanism is the capacity of TGF-β1 to synergize with neurotrophins which required for full neuroprotective activity of brain-derived neurotrophic factor (BDNF) and glial-derived neurotrophic factor (GDNF)[52,53]. In AD, TGF-β1 reduces the chemotactic migration of microglial cells toward Aβ aggregates through Smad-dependent pathways to prevent microglia-mediated neuroinflammation[54,55]. The anti-inflammatory effects are seemingly mediated by the inhibition of the NADPH oxidase (PHOX) subunit P47phox from cytosol to the membrane in microglia[9]. However, in animal models of AD, TGF-β1 has been found to block the TGF-β/Smad 2/3 signaling in peripheral macrophages and to reduce cerebrovascular Aβ deposits in Tg2576 mice, while mice overexpressing TGF-β1 develop AD-like vascular alterations, and the overexpression of TGF-β1 in AD transgenic mice seems to accelerate the deposition of Aβ in cerebral blood vessels also termed cerebral amyloid angiopathy (CAA)[56]. These data suggest that vessel-derived TGF-β1 might contribute to inflammatory processes in AD brain[16,17].

Involvement of TGF-β1 in the Cerebrovascular Pathology of Alzheimer's disease

The deregulation of TGF-β1 signaling pathways are involved in several pathological conditions[57,58], including Alzheimer's disease (AD)[24]. Indeed, in AD brain, cytokines, chemokines, and free radicals emanating from activated glial cells recruited at the site of plaques may promote an inflammatory, oxidative state and chronic overproduction of TGF-β1may promote microvascular degener-

ation[59]. The overexpressed TGF-β1 inside of the brain and cerebral vessels tissues of Alzheimer disease (AD) patients[17,56] is associated with the release of pro-inflammatory cytokines IL-1β and TNF-α that induce inflammatory cycle in astroglial cells and neuronal apoptosis along with the development of vascular hypertrophy, fibrosis, and the accumulation of extracellular matrix components[18-22]. Likewise in the injured central nervous system (CNS), astrocytes which appear as a key component of reactive gliosis characterized the response of the nervous system to many kinds of lesions such as ischemia, excitotoxic lesion and several neurodegenerative diseases[60] and particularly AD[61]. Similar to what happen in CNS injury with the induction of a dramatic increase of TGF-β1 by astrocyte[62], the overexpression of a constitutive form of TGF-β1 in astrocytes of transgenic mice (TGF mice) resulted in AD-like neuroinflammation and cerebrovascular dysfunction[26,59,63]. The cerebrovascular dysfunction includes structural abnormalities associated with increased levels of extracellular matrix proteins, thickening of the blood vessel walls, and microvascular degenerative changes[19,24,25,64,65] that physiologically resulted in progressive functional and age-dependent deficit of the cerebrovascular reactivity[64,66]. Like in AD, TGF mice cerebral deficits includes the loss of specific neuronal populations in the hippocampus, the accumulation of proteic aggregates inside and outside neurons, and the activation of immune pathways in the brain[67,68]. By contrast, TGF mice did not develop memory impairment[63] suggesting that vascular pathology is not sufficient to induce memory impairment. Therefore, TGF-β1 appears as the key mediator of fibrosis in a variety of tissues and has been shown to induce expression of components of the extracellular matrix (ECM) and other genes that act to regulate the composition of the ECM[69,70]. The extensive deposition of collagen and other ECM components that are characteristic of fibrosis is thought to be the result of deregulation of fibrogenesis, a normal part of the wound healing response that occurs in almost all tissues after exposure to a destructive stimulus. TGF-β1 stimulates also the production of laminin and fibronectin and their incorporation into the ECM of primary culture of cerebellar astrocytes[71]. It promotes the appearance of actins stress fibers and increases the cell actins content. In vivo administration of TGF-β1 induces several neuronal and astrocytic cytoskeleton genes as Glial Fibrillary Acidic Protein (GFAP) and tubulin[72,73]. The result of such fibrosis in the brain is an inability of the cerebral blood vessel to maintain and autoregulate cerebral blood flow and therefore predisposes to ischemia[74] leading to localized ischemic areas of necrosis. Studies of fibrosis in a variety of tissue have established that collagen-secreting cells may also derive from resident epithelial cells by way of a mechanism termed epithelial-mesenchymal transition[75] which is involved in inducing the formation of fibroblasts after injury[76]. However, under the influence of combinations of cytokines, including TGF-β1, epithelial cells begin to secrete matrix metalloproteinase that degrades the extracellular matrix[77,78].

Conclusions

Data suggest well-established dysfunction of TGF-β1 signaling in AD. However, cerebrovascular pathology appears as the earlier marker of AD and likely a most important contributor to cerebrovascular and cognitive deterioration, even if TGF mice displayed unaffected memory. Indeed, TGF-β1 is associated with the release of pro-inflammatory cytokines IL-1β and TNF-α, and induces initiation and propagation of destructive inflammatory cycle in astroglial cells and neuronal apoptosis along with the development of vascular hypertrophy, fibrosis, and the accumulation of extracellular matrix components. Thus, targeting TGF-β1 to prevent cerebrovascular pathology or neuroinflammation may constitute an interesting avenue for AD therapeutic.

Conflict of interest

The authors declare no conflicts of interest.

References

1) Roberts AB, Lamb LC, Newton DL, Sporn MB, De Larco JE, Todaro GJ. Transforming growth factors: Isolation of polypeptides from virally and chemically transformed cells by acid/ethanol extraction. Proc Natl Acad Sci U S A 1980; 77: 3494-3498.

2) Moses HL, Branum EL, Proper JA, Robinson RA: Transforming growth factor production by chemically transformed cells. Cancer Res 1981; 41: 2842-2848.

3) Santibanez JF, Quintanilla M, Bernabeu C. TGF-beta/TGF-beta receptor system and its role in physiological and pathological conditions. Clin Sci (Lond) 2011; 121: 233-251.

4) Krstic J, Maslovaric I, Santibanez JF: Novel patents and cancer therapies for transforming growth factor-beta and urokinase type plasminogen activa-

tor: Potential use of their interplay in tumorigenesis. Recent Pat Anticancer Drug Discov 2014; 9: 354-371.

5) Attisano L, Wrana JL. Signal transduction by the TGF-β superfamily. Science 2002; 296: 1646-1647.

6) Abreu JG, Ketpura NI, Reversade B, De Robertis EM. Connective-tissue growth factor (CTGF) modulates cell signalling by BMP and TGF-beta. Nat Cell Biol 2002; 4: 599-604.

7) Bottner M, Krieglstein K, Unsicker K. The transforming growth factor-betas: Structure, signaling, and roles in nervous system development and functions. J Neurochem 2000; 75: 2227-2240.

8) Dhandapani KM, Brann DW. Transforming growth factor-beta: a neuroprotective factor in cerebral ischemia. Cell Biochem Biophys 2003; 39: 13-22.

9) Qian L, Wei SJ, Zhang D, Hu X, Xu Z, Wilson B, El-Benna J, Hong JS, Flood PM. Potent anti-inflammatory and neuroprotective effects of TGF-beta1 are mediated through the inhibition of ERK and p47phox-Ser345 phosphorylation and translocation in microglia. J Immunol 2008; 181: 660-668.

10) Zhu Y, Ahlemeyer B, Bauerbach E, Krieglstein J. TGF-beta1 inhibits caspase-3 activation and neuronal apoptosis in rat hippocampal cultures. Neurochem Int 2001; 38: 227-235.

11) Prehn JH, Miller RJ. Opposite effects of TGF-beta 1 on rapidly- and slowly-triggered excitotoxic injury. Neuropharmacology 1996; 35: 249-256.

12) Vivien D, Ali C. Transforming growth factor-beta signalling in brain disorders. Cytokine Growth Factor Rev 2006; 17: 121-128.

13) Caraci F, Battaglia G, Busceti C, Biagioni F, Mastroiacovo F, Bosco P, Drago F, Nicoletti F, Sortino MA, Copani A. TGF-beta 1 protects against Abeta-neurotoxicity via the phosphatidylinositol-3-kinase pathway. Neurobiol Dis 2008; 30: 234-242.

14) Wyss-Coray T. Inflammation in Alzheimer disease: driving force, bystander or beneficial response? Nat Med 2006; 12: 1005-1015.

15) Querfurth HW, LaFerla FM. Alzheimer's disease. N Engl J Med 2010; 362: 329-344.

16) Guardia CM, Levison SW. Delayed ALK5 inhibition improves functional recovery in neonatal brain injury. J Cereb Blood Flow Metab 2016 Mar 16. pii: 0271678X16638669. [Epub ahead of print].

17) Haque R, Nazir A. SMAD transcription factor, sma-9, attunes TGF-beta signaling cascade towards modulating amyloid beta aggregation and associated outcome in transgenic C. Elegans. Mol Neurobiol 2016; 53: 109-119.

18) Koibuchi Y, Lee WS, Gibbons GH, Pratt RE. Role of transforming growth factor-beta 1 in the cellular growth response to angiotensin II. Hypertension 1993; 21: 1046-1050.

19) Kalaria RN, Pax AB. Increased collagen content of cerebral microvessels in Alzheimer's disease. Brain Res 1995; 705: 349-352.

20) Rosenkranz S. TGF-beta1 and angiotensin networking in cardiac remodeling. Cardiovasc Res 2004; 63: 423-432.

21) Yurovsky VV, Gerzanich V, Ivanova S, Dong Y, Tsymbalyuk O, Simard JM. Autocrine TGF-beta1 mediates angiotensin II-induced proliferative response of cerebral vessels in vivo. Am J Hypertens 2007; 20: 950-956.

22) Ruiz-Ortega M, Rodriguez-Vita J, Sanchez-Lopez E, Carvajal G, Egido J. TGF-beta signaling in vascular fibrosis. Cardiovasc Res 2007; 74: 196-206.

23) Akiyama H, Barger S, Barnum S, Bradt B, Bauer J, Cole GM, Cooper NR, Eikelenboom P, Emmerling M, Fiebich BL, Finch CE, Frautschy S, Griffin WS, Hampel H, Hull M, Landreth G, Lue L, Mrak R, Mackenzie IR, McGeer PL, O'Banion MK, Pachter J, Pasinetti G, Plata-Salaman C, Rogers J, Rydel R, Shen Y, Streit W, Strohmeyer R, Tooyoma I, Van Muiswinkel FL, Veerhuis R, Walker D, Webster S, Wegrzyniak B, Wenk G, Wyss-Coray T. Inflammation and Alzheimer's disease. Neurobiol Aging 2000; 21: 383-421.

24) Wyss-Coray T, Lin C, von Euw D, Masliah E, Mucke L, Lacombe P. Alzheimer's disease-like cerebrovascular pathology in transforming growth factor-beta 1 transgenic mice and functional metabolic correlates. Ann N Y Acad Sci 2000; 903: 317-323.

25) Wyss-Coray T, Lin C, Sanan DA, Mucke L, Masliah E. Chronic overproduction of transforming growth factor-beta1 by astrocytes promotes Alzheimer's disease-like microvascular degeneration in transgenic mice. Am J Pathol 2000; 156: 139-150.

26) Zetterberg E, Lundberg LG, Palmblad J. Characterization of blood vessels in bone marrow from patients with chronic myeloid leukemia and polycythemia vera. Scand J Clin Lab Invest 2004; 64: 641-647.

27) Zetterberg H, Andreasen N, Blennow K. Increased cerebrospinal fluid levels of transforming growth factor-beta1 in Alzheimer's disease. Neurosci Lett 2004; 367: 194-196.

28) Mittaud P, Labourdette G, Zingg H, Guenot-Di Scala D. Neurons modulate oxytocin receptor expression in rat cultured astrocytes: involvement of TGF-beta and membrane components. Glia 2002; 37: 169-177.

29) Gomes FC, Sousa Vde O, Romao L. Emerging roles for TGF-beta1 in nervous system development. Int J Dev Neurosci 2005: 23: 413-424.

30) Sousa Vde O, Almeida JC, Eller CM, Gomes FC. Characterization of TGF-beta1 type II receptor expression in cultured cortical astrocytes. In Vitro Cell Dev Biol Anim 2006; 42: 171-175.

31) Farkas LM, Dunker N, Roussa E, Unsicker K, Krieglstein K. Transforming growth factor-beta(s) are essential for the development of midbrain dopaminergic neurons in vitro and in vivo. J Neurosci 2003; 23: 5178-5186.

32) Roussa E, Farkas LM, Krieglstein K. TGF-beta promotes survival on mesencephalic dopaminergic neurons in cooperation with Shh and FGF-8. Neurobiol Dis 2004; 16: 300-310.

33) Poulsen KT, Armanini MP, Klein RD, Hynes MA, Phillips HS, Rosenthal A. TGF beta 2 and TGF beta 3 are potent survival factors for midbrain dopaminergic neurons. Neuron 1994; 13: 1245-1252.

34) Stipursky J, Romao L, Tortelli V, Neto VM, Gomes FC. Neuron-glia signaling: Implications for astrocyte differentiation and synapse formation. Life Sci 2011; 89: 524-531.

35) Pelton RW, Saxena B, Jones M, Moses HL, Gold LI. Immunohistochemical localization of TGF beta 1, TGF beta 2, and TGF beta 3 in the mouse embryo: expression patterns suggest multiple roles during embryonic development. J Cell Biol 1991; 115: 1091-1105.

36) Unsicker K, Strelau J. Functions of transforming growth factor-beta isoforms in the nervous system. Cues based on localization and experimental in vitro and in vivo evidence. Eur J Biochem 2000; 267: 6972-6975.

37) Bottner M, Krieglstein K, Unsicker K. The transforming growth factor-betas: structure, signaling, and roles in nervous system development and functions. J Neurochem 2000; 75: 2227-2240.

38) Flanders KC, Ren RF, Lippa CF. Transforming growth factor-betas in neurodegenerative disease. Prog Neurobiol 1998; 54: 71-85.

39) Gomes FC, Sousa VO, Romao L. Emerging roles for TGF-beta1 in nervous system development. Int J Dev Neurosci 2005; 23: 413-424.

40) Gagelin C, Pierre M, Gavaret JM, Toru-Delbauffe D. Rapid TGF beta 1 effects on actin cytoskeleton of astrocytes: comparison with other factors and implications for cell motility. Glia 1995; 13: 283-293.

41) Brionne TC, Tesseur I, Masliah E, Wyss-Coray T. Loss of TGF-beta 1 leads to increased neuronal cell death and microgliosis in mouse brain. Neuron 2003; 40: 1133-1145.

42) Annes JP, Munger JS, Rifkin DB: Making sense of latent TGFbeta activation. J Cell Sci 2003; 116: 217-224.

43) Hyytiainen M, Penttinen C, Keski-Oja J. Latent TGF-beta binding proteins: Extracellular matrix association and roles in TGF-beta activation. Crit Rev Clin Lab Sci 2004; 41: 233-264.

44) Derynck R, Zhang YE. Smad-dependent and Smad-independent pathways in TGF-beta family signalling. Nature 2003; 425: 577-584.

45) Ten DP, Hill CS. New insights into TGF-beta-Smad signalling. Trends Biochem Sci 2004; 29: 265-273.

46) Briones-Orta MA, Tecalco-Cruz AC, Sosa-Garrocho M, Caligaris C, Macias-Silva M. Inhibitory Smad7: emerging roles in health and disease. Curr Mol Pharmacol 2011; 4: 141-153.

47) Konig HG, Kogel D, Rami A, Prehn JH. TGF-{beta}1 activates two distinct type I receptors in neurons: implications for neuronal NF-{kappa}B signaling. J Cell Biol 2005; 168: 1077-1086.

48) Chalmers KA, Love S. Phosphorylated Smad 2/3 colocalizes with phospho-tau inclusions in Pick disease, progressive supranuclear palsy, and corticobasal degeneration but not with alpha-synuclein inclusions in multiple system atrophy or dementia with Lewy bodies. J Neuropathol Exp Neurol 2007; 66: 1019-1026.

49) Tesseur I, Zou K, Esposito L, Bard F, Berber E, Can JV, Lin AH, Crews L, Tremblay P, Mathews P, Mucke L, Masliah E, Wyss-Coray T. Deficiency in neuronal TGF-beta signaling promotes neurodegeneration and Alzheimer's pathology. J Clin Invest 2006; 116: 3060-3069.

50) Wang H, Liu J, Zong Y, Xu Y, Deng W, Zhu H, Liu Y, Ma C, Huang L, Zhang L, Qin C. miR-106b aberrantly expressed in a double transgenic mouse model for Alzheimer's disease targets TGF-beta type II receptor. Brain Res 2010; 1357: 166-174.

51) Caricasole A, Copani A, Caraci F, Aronica E, Rozemuller AJ, Caruso A, Storto M, Gaviraghi G, Terstappen GC, Nicoletti F. Induction of Dickkopf-1, a negative modulator of the Wnt pathway, is associated with neuronal degeneration in Alzheimer's brain. J Neurosci 2004; 24: 6021-6027.

52) Schober A, Peterziel H, von Bartheld CS, Simon H, Krieglstein K, Unsicker K. GDNF applied to the MPTP-lesioned nigrostriatal system requires TGF-beta for its neuroprotective action. Neurobiol Dis 2007; 25: 378-391.

53) Unsicker K, Krieglstein K. TGF-betas and their roles in the regulation of neuron survival. Adv Exp Med Biol 2002; 513: 353-374.

54) Huang WC, Yen FC, Shie FS, Pan CM, Shiao YJ, Yang CN, Huang FL, Sung YJ, Tsay HJ. TGF-beta1 blockade of microglial chemotaxis toward Abeta aggregates involves SMAD signaling and down-regulation of CCL5. J Neuroinflammation 2010; 7: 28.

55) Zhang Y, Qiu L, Li MY. [Effects of radix astragali on expression of transforming growth factor beta 1 and Smad 3 signal pathway in hypertrophic scar of rabbit]. Zhonghua Shao Shang Za Zhi 2010; 26: 366-370.

56) Wyss-Coray T, Masliah E, Mallory M, McConlogue L, Johnson-Wood K, Lin C, Mucke L. Amyloidogenic role of cytokine TGF-beta1 in transgenic mice and in Alzheimer's disease. Nature 1997; 389: 603-606.

57) Blobe GC, Schiemann WP, Lodish HF. Role of transforming growth factor beta in human disease. N Engl J Med 2000; 342: 1350-1358.

58) Javelaud D, Mauviel A: Mammalian transforming growth factor-betas: Smad signaling and physio-pathological roles. Int J Biochem Cell Biol 2004; 36: 1161-1165.

59) Wyss-Coray T, Lin C, Sanan DA, Mucke L, Masliah E. Chronic overproduction of transforming growth factor-beta1 by astrocytes promotes Alzheimer's disease-like microvascular degeneration in transgenic mice. Am J Pathol 2000;156:139-150.

60) Ridet JL, Malhotra SK, Privat A, Gage FH. Reactive astrocytes: cellular and molecular cues to biological function. Trends Neurosci 1997; 20: 570-577.

61) Medeiros R, LaFerla FM. Astrocytes: conductors of the Alzheimer disease neuroinflammatory symphony. Exp Neurol. 2013: 239: 133-138.

62) Pratt BM, McPherson JM. TGF-beta in the central nervous system: Potential roles in ischemic injury and neurodegenerative diseases. Cytokine Growth Factor Rev 1997; 8: 267-292.

63) Nicolakakis N, Aboulkassim T, Aliaga A, Tong XK, Rosa-Neto P, Hamel E. Intact memory in TGF-beta1 transgenic mice featuring chronic cerebrovascular deficit: Recovery with pioglitazone. J Cereb Blood Flow Metab 2011; 31: 200-211.

64) Tong XK, Nicolakakis N, Kocharyan A, Hamel E. Vascular remodeling versus amyloid beta-induced oxidative stress in the cerebrovascular dysfunctions associated with Alzheimer's disease. J Neurosci 2005; 25: 11165-11174.

65) Wang PQ, Wang AP, Cao ZH, Wang P, Wang S, Zhang GB. The study of the distribution character of cerebral arterial stenosis in patients with ischemic cerebrovascular disease by means of 64 slices CT. Eur Rev Med Pharmacol Sci 2015; 19: 2287-2292.

66) Wyss-Coray T, Feng L, Masliah E, Ruppe MD, Lee HS, Toggas SM, Rockenstein EM, Mucke L. Increased central nervous system production of extracellular matrix components and development of hydrocephalus in transgenic mice overexpressing transforming growth factor-beta 1. Am J Pathol 1995; 147: 53-67.

67) Tesseur I, Wyss-Coray T. A role for TGF-beta signaling in neurodegeneration: evidence from genetically engineered models. Curr Alzheimer Res. 2006: 3: 505-513.

68) Buckwalter MS, Yamane M, Coleman BS, Ormerod BK, Chin JT, Palmer T, Wyss-Coray T. Chronically increased transforming growth factor-beta1 strongly inhibits hippocampal neurogenesis in aged mice. Am J Pathol 2006; 169: 154-164.

69) Ihn H. Pathogenesis of fibrosis: Role of TGF-beta and CTGF. Curr Opin Rheumatol 2002; 14: 681-685.

70) Chen Y, Zheng YL, Qiu DB, Sun YP, Kuang SJ, Xu Y, He F, Gong YH, Zhang ZG. An extracellular matrix culture system for induced pluripotent stem cells derived from human dental pulp cells. Eur Rev Med Pharmacol Sci 2015; 19: 4035-4046.

71) Baghdassarian D, Toru-Delbauffe D, Gavaret JM, Pierre M. Effects of transforming growth factor-beta 1 on the extracellular matrix and cytoskeleton of cultured astrocytes. Glia. 1993; 7: 193-202.

72) Laping NJ, Teter B, Nichols NR, Rozovsky I, Finch CE. Glial fibrillary acidic protein: regulation by hormones, cytokines, and growth factors. Brain Pathol 1994; 4: 259-275.

73) Laping NJ, Morgan TE, Nichols NR, Rozovsky I, Young-Chan CS, Zarow C, Finch CE. Transforming growth factor-beta 1 induces neuronal and astrocyte genes: Tubulin alpha 1, glial fibrillary acidic protein and clusterin. Neuroscience 1994; 58: 563-572.

74) Lammie GA. Hypertensive cerebral small vessel disease and stroke. Brain Pathol. 2002: 12: 358-370.

75) Iwano M, Plieth D, Danoff TM, Xue C, Okada H, Neilson EG. Evidence that fibroblasts derive from epithelium during tissue fibrosis. J Clin Invest 2002; 110: 341-350.

76) Kalluri R, Neilson EG. Epithelial-mesenchymal transition and its implications for fibrosis. J Clin Invest 2003; 112: 1776-1784.

77) Yang J, Liu Y. Dissection of key events in tubular epithelial to myofibroblast transition and its implications in renal interstitial fibrosis. Am J Pathol 2001; 159: 1465-1475.

78) Zeisberg M, Maeshima Y, Mosterman B, Kalluri R. Renal fibrosis. Extracellular matrix microenvironment regulates migratory behavior of activated tubular epithelial cells. Am J Pathol 2002; 160: 2001-2008.