If ineffective levels of transforming growth factors and their receptor account for old age being a risk factor for Alzheimer’s disease, then increasing TGFBR2 might be therapeutic

Jeffrey Fessel

Department of Medicine, University of California, San Francisco, California, USA

Correspondence
Jeffrey Fessel, Department of Medicine, University of California, 2069 Filbert Street, San Francisco, CA 94123, USA. E-mail: jeffreyfessel@gmail.com

Abstract
If it is correct that ineffective levels of transforming growth factors beta and their receptor account for old age being a risk factor for Alzheimer’s disease (AD), then increasing TGFBR2 might be therapeutic. Pacltaxel is a direct way to increase TGFBR2 levels. Indirect ways that will increase TGFBR2, include decreasing the levels of c-myc because that will lower the miRNA cluster 17-92, particularly its miR-17 and miR-20a components; and raising EGFR because that also will increase TGFBR2. Metformin and desferrioxamine are drugs that decrease c-myc; and statins increase levels of EGF. Clinical trials using those drugs, would demonstrate whether they decrease the progression from amnestic mild cognitive impairment to AD.

1 | INTRODUCTION

A recent article suggested that the strong connection between older age and late onset Alzheimer’s disease (AD) may be due to impaired neuronal efficacy of TGF\(\beta\)1 caused by a decreased level of its receptor, TGFBR2 (JF TRCI1). It also suggested that increasing the concentration of TGF\(\beta\)1, even though it is already higher in older persons with AD than in younger persons, might overcome the bottleneck created by the TGFBR2 deficiency. That might slowly work because bottlenecks only lower the rate of flow across the obstruction. However, another and perhaps more certain approach would be to increase the TGFBR2 level itself, to remove that obstruction and thus to improve the efficacy of an already high level of TGF\(\beta\)1. That may be accomplished by both direct and indirect means. The direct way is simple and uses paclitaxel, a drug used to treat breast cancer; the indirect way is more complex and aims to heighten some of the pathways that impinge TGFBR2. Those pathways include effects resulting from c-myc; the miRNA cluster 17-92, particularly its miR-17 and miR-20a components; and EGFR.

2 | THE TGF\(\beta\)1 SIGNALING PATHWAY

First discussed are TGF\(\beta\)1 and its receptors because they are our prime focus. We are here concerned with the effects of TGF\(\beta\) in the brain, although there are numerous other effects2 (see Morikawa et al.2). The TGF\(\beta\)1 signal transduction pathway determines transcription control.3 TGF\(\beta\)1 or TGF\(\beta\)2 initiate signaling by ligating a multicomponent receptor complex that includes a pair (TGFBR1 and TGFBR2) of serine/threonine kinases. The TGFBR2 phosphorylates and activates TGFBR1, which then phosphorylates and activates transcription factors Smad2 and Smad 3, which form a complex with Smad4; the complex translocates to the nucleus and activates various genes (see Massague and Xi3 for a more detailed review of this process).

2.1 | Effects of TGF\(\beta\)1 in the brain

A meta-analysis of five studies measuring plasma levels and five studies measuring cerebrospinal fluid (CSF) levels, showed significantly higher
levels in each source in patients with AD. An early study showed a high correlation \((r = 0.45)\) between the level of TGF\(\beta\) and severity of AD. In wild type mice, administration of TGF\(\beta\)1 converted early-phase long-term potentiation (LTP) into late-phase LTP; and in those mice, LTP and object recognition memory were impaired by an inhibitor of TGF\(\beta\)1 but rescued by administration of TGF\(\beta\)1. Electrophysiologic studies showed that TGF\(\beta\)2 facilitated postsynaptic currents, and TGF\(\beta\)1 prevented hippocampal dendritic spine loss and memory impairment in mice that had received an intracerebroventricular infusion of amyloid beta (A\(\beta\)) oligomers. TGF\(\beta\)1 knock down caused a 40% loss of laminin, which is implicated in neuronal survival, learning, and memory, whereas overexpression of TGF\(\beta\)1by astrocytes reduced the dendritic damage caused by kainate. While TGF\(\beta\)1 blocked generation of new neurons in mice, others showed that TGF\(\beta\)1 promotes stem cell quiescence but at the same time it improves neuronal survival. It was also shown that TGF\(\beta\)1 dramatically increased the potency of other neurotrophins such as GDNF and FGF2. Finally, TGF\(\beta\)1 promoted re-myelination and restored neurological function in an animal model of multiple sclerosis. Overall, the above plus abundant other data show that TGF\(\beta\)1 is critically important for brain integrity and function.

### 2.2 TGFBR2 deficiency in AD neurons forms a bottleneck that limits the beneficial, functional effects of TGF\(\beta\)1

Rojas et al. used an agonist of TGFBR2 to show that with increasing levels of its receptor, TGF\(\beta\)1 had an increased functional effect. The reverse was demonstrated in a seminal study by Tesseur et al., who found that TGFBR2 levels in the prefrontal cortex of AD were only about half of those in non-demented controls and were already so in patients whose Mini-Mental State Examination (MMSE) scores were 21-25 but were not lower in those with MMSE scores 26-29 (presumably mild cognitive impairment [MCI]). That is, consistent with the fact that MCI may appear in the so-called young-old, only to progress to overt dementia a decade or more later when patients are now old-old. That was shown by Smith et al., who saw a gradual decline, starting 10 years before the AD diagnosis, in the Mayo Cognitive Factor Scale (derived from concurrent administration of Wechsler Adult Intelligence Scale-Revised [WAIS-R], Wechsler Memory Scale-Revised [WMS-R], and Auditory-Verbal Learning Test [AVLT]); Storandt et al. reported similar results, with decline starting up to almost 9 years before AD.

### 3 DIRECT WAY TO INCREASE LEVELS OF TGFBR2

An early study by Taxman et al. showed that paclitaxel increased levels of TGFBR2 by as much as four-fold; after that report, Iseri et al. saw an increase of approximately eight-fold from paclitaxel, and Bhola et al. an increase of approximately two-fold. Demonstrating the functional significance of the increased TGFBR2 levels, those authors also noted increases of genes downstream in the TGF\(\beta\)1signaling pathway: Smad 3 and Smad 4 genes, and the TSC-22 gene.

### RESEARCH IN CONTEXT

1. Systematic review: literature was reviewed by traditional means, to show ways of raising levels of TGFBR2, the receptor for TGF\(\beta\).
2. Interpretation: Those ways are direct, by using paclitaxel; and indirect, by using metformin, desferrioxamine, and statins.
3. Future directions: Clinical trials should demonstrate whether use of those drugs affect the progression of amnestic mild cognitive impairment to Alzheimer’s disease.

If it is correct that ineffective levels of transforming growth factors beta and their receptor account for old age being a risk factor for Alzheimer’s disease, then increasing TGFBR2 might be therapeutic. Pacltaxel is a direct way to increase TGFBR2 levels. Indirect ways that will increase TGFBR2, include decreasing the levels of c-myc because that will lower the miRNA cluster 17-92, particularly its miR-17 and miR-20a components; and raising EGF because that also will increase TGFBR2. Metformin and desferrioxamine are drugs that decrease c-myc; and statins increase levels of EGF.

3.1 Indirect approaches to increasing levels of TGFBR2

#### 3.1.1 Increase TGFBR2 by reducing c-myc

MiR-17 and miR-20 control the TGFR gene, and Dew et al. saw a reduction in the levels of TGFBR2 by miR-17 and miR20, respectively, by ≈40% and 30% when the cellular concentrations of those miRs were raised. Because c-myc activates the of miR-17-5p and miR-20, reducing the levels of c-myc will also reduce those of miR-17-5p and miR-20 as was shown by Thomas et al., who used siRNA to induce knock-down of c-myc mRNA levels by 65%-81%, and saw a reduction of 60%-70% in miR-17-92 (the cluster that contains miR-17 and miR-20).

Desferrioxamine, which chelates iron from ferritin and hemosiderin, although less so from transferrin, and not from cytochromes or hemoglobin (with which it does not combine), is another drug that reduces c-myc. There are various ways by which desferrioxamine might
accomplish this. It may or may not be via reducing brain iron levels, because on one hand, a study by Ward and Mason using neutron activation analysis showed that the ranges of iron levels in hippocampus and cerebral cortex were quite similar in AD and controls: AD, 204.7-810.4 mcg/g dry weight; controls, 300.1-614.3 mcg/g.24; besides, the transferrin receptor was the fifth most downregulated gene in the AD total brain and is also downregulated in the AD frontal lobe.25 On the other hand, exposure of human synovial fibroblast cells to iron provoked an increase in the expression of c-myc;26 and c-myc itself was shown to both suppress expression of ferritin, which binds iron, and upregulate iron regulatory protein-2, the net effect being to increase the iron pool.27 Others have proposed a different mechanism, that desferrioxamine might alleviate the oxidative stress present in AD, because an important reaction of hydrogen peroxide with free or poorly liganded Fe(II) leads to the damaging hydroxyl radical (OH•): Fe^{++} + H2O2 → Fe^{+++} + OH• + H2O, and superoxide can also react with ferric iron to produce Fe^{+++} again, thereby effecting redox cycling: O2•- + Fe^{+++} → O2 + Fe^{++}.28 Because of that reaction, Liu et al. proposed that desferrioxamine might alleviate the oxidative stress present in AD.29 By whatever the mechanism, desferrioxamine reduces c-myc; mononuclear cells from thalassaemic patients receiving desferrioxamine had significantly lower levels of c-myc compared to cells from healthy volunteers or from thalassaemias receiving no desferrioxamine; and in vitro treatment of leukaemic cells with desferrioxamine also induced a rapid decrease in c-myc mRNA.30 In a clinical trial, McLachlan et al. randomly assigned 48 patients with probable AD to receive intramuscular desferrioxamine, oral placebo, or no treatment.31 The rate of decline in daily living skills as video-recorded at 6-, 12-, 18-, and 24-month intervals, was halved in the group that received desferrioxamine.

Metformin is the next drug that reduces levels of c-myc.32 Thomas et al.23 found that siRNA-induced 65%-81% knock-down of c-myc mRNA levels, caused a reduction of 60%-70% in miR-17-92 (the cluster that contains miR-17 and miR-20); as shown above, raising their levels reduced TGFB2, so reducing them by knock-down of c-myc would be expected to produce raised TGFRB2. Further evidence comes from studies of prostate cancer. In a population study of 1001 men with prostate cancer and 942 controls, Wright and Stanford showed that use of metformin was associated with 44% less risk of prostate cancer.33 Knowing that, and also that c-myc increases the risk of prostate cancer, Akinyeke et al. looked at whether metformin reduces levels of c-myc.34 Indeed, they were able to show that when c-myc containing prostate cancer cells were exposed to metformin, their number was reduced by about 50%.

Drugs used to treat various cancers—ibrutinib, milatinitin, dasatinib, and nilotinib—all reduce levels of myc family members (c-, L-, and n- myc) by several mechanisms35 and, coincidentally and beneficially, they also reduce miR-17 and miR-20a. Ibrutinib reduces c-myc by ∼five-fold;36 and imatinib reduces both c-myc by about 80% and miR20a by ≈60% (see fig 2A and 2B in Venturini et al.37). Notably, miR-17 was 77% reduced by imatinib, 87% by nilotinib, and 93% by dasatinib,38 and imatinib reduced miR20a by 20%;39

### 3.1.2 | Upregulating epidermal growth factor

The final indirect approach is upregulation of epidermal growth factor (EGF) because EGF increased TGFB2 by eight-fold.40 Yamane et al. showed that in human dermal fibroblasts, upregulation of TGFB2 by EGF was inhibited by both a phosphoinositide 3-kinase (PI3K) inhibitor and an AKT inhibitor, so the authors inferred that the upregulation was via activation of the PI3K/AKT pathway.41 Activation of the PI3K/AKT pathway may be achieved by statins.42 Another mechanism by which statins indirectly raise EGF levels is via an increase of tissue transglutaminase (tTg), which upregulates EGF.43 and,Sohelnlein et al. showed that atorvastatin induced a two- to three-fold increase of tTg.44 Although EGF has substantial potential for oncogenesis, there is no good evidence that statins are oncogenic. A comparison of 24,439 older statin users having a mean age of 76.4, with 7384 controls having a mean age of 80.1, showed no significant difference in the prevalence of breast, lung, or colorectal cancers, even when separate comparisons were made for simvastatin, lovastatin, fluvastatin, atorvastatin, and pravastatin.45 Bonovas et al. made a meta-analysis of 35 randomized clinical trials of statins used for cardiovascular outcomes, involving 109,143 patients and controls, with an average follow-up of 4.5 years, and found no evidence of an increased risk of cancers.46 Finally, although interferon-gamma and androgens both raise EGF, their potential side effects militate against using them for that purpose.

### 4 | CONCLUSIONS

If it is correct that an inadequate level of TGFBRS in the brain is the reason why old age is the major risk factor for AD, then raising the level of TGFB2 might be therapeutic. The level of TGFB2 may be raised by both direct and indirect means.

The direct way would use paclitaxel, perhaps in a dose that is 25% of that used to treat breast cancer. Several drugs may indirectly raise the level of TGFB2; of those, metformin and statins, in their usual doses, would be preferable. A clinical trial would randomize patients with amnestic, mild cognitive impairment to either active treatment with the chosen drug or matching placebo, and assess the rates of subsequent progression to AD.

### ACKNOWLEDGMENTS

This study received no specific grants from funding agencies in the public, community, or not-for-profit sectors.

### REFERENCES

1. Fessel J. Ineffective levels of transforming growth factors and their receptor account for old age being a risk factor for Alzheimer’s disease. Alzheimers & Dement: Trans Res & Clin Interven. 2019;5:899-905.
2. Morikawa M, Derynck R, Miyazono K. TGF-β and the TGF-β family: context-dependent roles in cell and tissue physiology. Cold Spring Harb Perspect Biol. 2016;8:a021873.
3. Massagué J, Xi Q. TGF-β control of stem cell differentiation genes. FEBS Lett. 2012;586:1953-1958.
4. Swardfager W, Lanctôt K, Rothenburg L, Wong A, Cappell J, Herrmann N. A meta-analysis of cytokines in Alzheimer’s disease. Biol Psychiatry. 2010;68:930-941.

5. Chao C, Ala T, Hu S, et al. Serum cytokine levels in patients with Alzheimer’s disease. Clin Diagn Lab Immunol. 1994;1:433-436.

6. Caraci F, Guisano W, Guida C, et al. A key role for TGF-β1 in hippocampal synaptic plasticity and memory. Sci Rep. 2015;5:11252.

7. Fujikawa T, Liu Y, Byrne JH. Transforming growth factor-β1 modulates synaptic efficacy and plasticity and induces phosphorylation of CREB in hippocampal neurons. Hippocampus. 2007;17:5-9.

8. Diniz LP, Tortelli V, Matias I, et al. Astrocyte transforming growth factor beta 1 protects synapses against Aβ oligomers in Alzheimer’s disease model. J Neurosci. 2013;37:6797-6809.

9. Brionne TC, Tesseract I, Masilah E, Wyss-Coray T. Loss of TGF-β1 leads to increased neuronal cell death and microgliosis in mouse brain. Neuron. 2003;40:1133-1145.

10. Buckwalter MS, Yamane M, Coleman BS, et al. Chronically increased transforming growth factor-β1 strongly inhibits hippocampal neurogenesis in aged mice. Am J Pathol. 2006;169:154-164.

11. Kandasamy M, Lehner B, Kraus S, et al. TGF-beta signalling in the adult neurogenic niche promotes stem cell quiescence as well as generation of new neurons. J Cell Mol Med. 2014;18:1444-1459.

12. Kriegstein K, Streit K, Schober A, Sullivan A, Unsicker K. TGF-β and the regulation of neuron survival and death. J Physiol-Paris. 2002;96:25-30.

13. Hamaguchi M, Muramatsu R, Fujimura H, Mochizuki H, Kataoka H, Yamashita T. Circulating transforming growth factor-β1 facilitates remyelination in the adult central nervous system. Elife. 2019;8:e41869.

14. Rojas A, Padidam M, Cress D, Grady WM. TGF-β receptor levels regulate the specificity of signaling pathway activation and biological effects of TGF-β. Biochim Biophys Acta. 2009;1793:1165-1173.

15. Tesser I, Zou K, Esposito L, et al. Deficiency in neuronal TGF-β signaling promotes neurodegeneration and Alzheimer’s pathology. J Clin Invest. 2006;116:3060-3069.

16. Smith G, Pankratz V, Negash S, et al. A plateau in pre-Alzheimer memory decline: evidence for compensatory mechanisms? Neurology. 2007;69:133-139.

17. Storandt M, Grant EA, Miller JP, Morris JC. Longitudinal course and neuropathologic outcomes in original vs revised MCI and in pre-MCI. Neurology. 2006;67:467-473.

18. Taxman DJ, Mackeigan JP, Clements C, Bergstralh DT, Ting JP. Transcriptional profiling of targets for combination therapy of lung cancer with paclitaxel and mitogen-activated protein/extracellular signal-regulated kinase inhibitor. Cancer Res. 2003;63:5095-5104.

19. OD İçişer, MD Kars, Arpacı F, A latino C, Pak I, Güdüz U. Drug resistant MCF-7 cells exhibit epithelial-mesenchymal transition gene expression pattern. Biomed Pharmacother. 2011;65:40-45.

20. Bhola NE, Baloo JM, Dugger TC, et al. TGF-β1 inhibition enhances chemotherapy action against triple-negative breast cancer. J Clin Invest. 2013;123:1348-1358.

21. Dews M, Fox JL, Hultine S, et al. The myc-mir-17-92 axis blunts TGFβ signaling and production of multiple TGFβ-dependent antiangiogenic factors. Cancer Res. 2010;70:8233-8246.

22. O’Donnell KA, Wentzel EA, Zeller KI, Dang CV, Mendell JT. c-Myc-regulated microRNAs modulate E2F1 expression. Nature. 2005;435:839.

23. Thomas M, Lange-Grüneweller K, Hartmann D, et al. Analysis of transcriptional regulation of the human miR-17-92 cluster; evidence for involvement of Pim-1. Int J Mol Sci. 2013;14:12273-12296.

24. Ward N, Mason J. Neuron activation analysis techniques for identifying elemental status in Alzheimer’s disease. J Radioanalytical and Nuclear Chemistry. 1987;113:515-526.

25. Twine NA, Janitz K, Wilkins MR, Janitz M. Whole transcriptome sequencing reveals gene expression and splicing differences in brain regions affected by Alzheimer’s disease. PLoS One. 2011;6:e16266.

26. Wen F-Q, Jabbbar AA, Chen Y-X, Kazarian T, Patel DA, Valentino LA. C-myc proto-oncogene expression in hemophilic synovitis: in vitro studies of the effects of iron and ceramide. Blood. 2002;100:912-916.

27. Wu K-J, Polack A, Dalla-Favera R. Coordinated regulation of iron-controlling genes, H-ferritin and IRP2, by c-MYC. Science. 1999;283:676-679.

28. Kell DB. Iron behaving badly: inappropriate iron chelation as a major contributor to the aetiology of vascular and other progressive inflammatory and degenerative diseases. BMC Med Genomics. 2009;2:2.

29. Liu G, Men P, Perry G, Smith MA. Development of iron chelator--nanoparticle conjugates as potential therapeutic agents for Alzheimer disease. Prog Brain Res. Elsevier; 2009:97-108.

30. Kryiakou D, Eliopoulos A, Papadakis A, Alexandrakis M, Eliopoulos G. Decreased expression of c-myc oncoprotein by peripheral blood mononuclear cells in thalassaemia patients receiving desferrioxamine. Eur J Haematol. 1998;60:21-27.

31. McLaclachan DC, Kruck T, Kalow W, et al. Intramuscular desferrioxamine in patients with Alzheimer’s disease. Lancet. 1991;337:1304-1308.

32. Blandino G, Valerio M, Cicco M, et al. Metformin elicits anticancer effects through the sequential modulation of DICER and c-MYC. Nat Commun. 2012;3:865.

33. Wright JL, Stanford JL. Metformin use and prostate cancer in Cau- casian men: results from a population-based case-control study. Cancer Causes Control. 2009;20:1617.

34. Akinyeke T, Matsumura S, Wang X, et al. Metformin targets c-MYC oncogene to prevent prostate cancer. Carcinogenesis. 2013;34:2823-2832.

35. Whitfield JR, Beaulieux M-E, Soucek L. Strategies to inhibit Myc and their clinical applicability. Front Cell Dev Biol. 2017;5:10.

36. Secchiero P, Voltan R, Rimondi E, et al. The γ-secretase inhibitors enhance the anti-amyloidic activity of ibritinib in B-CLL cells. Oncotar. 2017;8:59235.

37. Venturini L, Batteker K, Castoldi M, et al. Expression of the miR-17-92 polycistrion in chronic myeloid leukemia (CML) CD34+ cells. Blood. 2007;109:4399-4405.

38. Fratigil B, Ç BirayAvcı, Baran Y. miR-17 in imatinib resistance and response to tyrosine kinase inhibitors in chronic myeloid leukemia cells. JBUON. 2013;18:437-441.

39. Flament S, Ritchie W, Guilhot J, et al. Micro-RNA response to imatinib mesylate in patients with chronic myeloid leukemia. Haematologica. 2010;95:1325-1333.

40. Shu DY, Hutcheon AE, Zieske JD, Guo X. Epidermal growth factor stimulates transforming growth factor-beta receptor type II expression in corneal epithelial cells. Sci Rep. 2019;9:8079.

41. Yamane K, Asano Y, Tamaki K, Ikon H. Epidermal growth factor upregulates transforming growth factor-β receptor type II in human dermal fibroblasts via p38 mitogen-activated protein kinase pathway. Biochem Biophys Res Commun. 2007;352:69-77.

42. van der Most PJ, Dolga AM, Nijholt IM, Luiten PG, Eisel UL. Statins: mechanisms of neuroprotection. Prog Neurobiol. 2009;88:64-75.

43. Zhang J, Antonyak MA, Singh G, Cerione RA. A mechanism for the upregulation of EGF receptor levels in glioblastomas. Cell Rep. 2013;3:2008-2020.

44. Soehnlein O, Eskafi S, Schmeisser A, Kloos H, Daniel WG, Gar- lichs CD. Atorvastatin induces tissue transglutaminase in human endothelial cells. Biochem Biophys Res Commun. 2004;322:105-109.
45. Setoguchi S, Glynn RJ, Avorn J, Mogun H, Schneeweiss S. Statins and the risk of lung, breast, and colorectal cancer in the elderly. *Circulation*. 2007;115:27.
46. Bonovas S, Filioussi K, Tsavaris N, Sitaras NM. Statins and cancer risk: a literature-based meta-analysis and meta-regression analysis of 35 randomized controlled trials. *J Clin Oncol*. 2006;24:4808-4817.

**How to cite this article:** Fessel J. If ineffective levels of transforming growth factors and their receptor account for old age being a risk factor for Alzheimer’s disease, then increasing TGFBR2 might be therapeutic. *Alzheimer’s Dement*. 2020;6:e12019. [https://doi.org/10.1002/trc2.12019](https://doi.org/10.1002/trc2.12019)