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PERSPECTIVE

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

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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. Paclitaxel 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 TGFβ1 caused by a decreased level of its receptor, TGFBR2 (JF TRCI[1]). It also suggested that increasing the concentration of TGFβ1, 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 TGFβ1. 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 TGFB1 SIGNALING PATHWAY

First discussed are TGFβ1 and its receptors because they are our prime focus. We are here concerned with the effects of TGFβ in the brain, although there are numerous other effects[2] (see Morikawa et al.[2]). The TGFβ1 signal transduction pathway determines transcription control.[3] TGFβ-1 or TGFβ-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 Xi[3] for a more detailed review of this process).

2.1 | Effects of TGFβ1 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.[4] An early study showed a high correlation (r = 0.45) between the level of TGFβ and severity of AD.[5] In wild type mice, administration of TGFβ1 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 TGFβ1 but rescued by administration of TGFβ1.[6] Electrophysiologic studies showed that TGFβ2 facilitated postsynaptic currents,[7] and TGFβ1 prevented hippocampal dendritic spine loss and memory impairment in mice that had received an intracerebroventricular infusion of amyloid beta (Aβ) oligomers.[8] TGFβ1 knock down caused a 40% loss of laminin, which is implicated in neuronal survival, learning, and memory, whereas overexpression of TGFβ1by astrocytes reduced the dendritic damage caused by kainate.[9] While TGFβ1 blocked generation of new neurons in mice,[10] others showed that TGFβ1 promotes stem cell quiescence but at the same time it improves neuronal survival.[11] It was also shown that TGFβ1 dramatically increased the potency of other neurotrophins such as GDNF and FGF2.[12] Finally, TGFβ1 promoted re-myelination and restored neurological function in an animal model of multiple sclerosis.[13] Overall, the above plus abundant other data show that TGFβ1 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 TGFβ1

Rojas et al. used an agonist of TGFBR2 to show that with increasing levels of its receptor, TGFβ1 had an increased functional effect.[14] 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]).[15] 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., [16] 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]);[16] Storandt et al. reported similar results, with decline starting up to almost 9 years before AD.[17]

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;[18] after that report, Işeri et al. saw an increase of approximately eight-fold from paclitaxel,[19] and Bhola et al. an increase of approximately two-fold.[20] Demonstrating the functional significance of the increased TGFBR2 levels, those authors also noted increases of genes downstream in the TGFβ1signaling 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 TGFβ.
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 EGFR 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 Dews 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.[21] Because c-myc activates the of miR-17-5p and miR-20,[22] 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).[23]

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- + OH •, 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 thalassaemics 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 TGFRB2, 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, milatinib, dasatinib, and nilotinib—all reduce levels of myc family members (c-, L-, and n- myc) by several mechanisms[35] 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 TGFBR2 by eight-fold.[40] Yamane et al. showed that in human dermal fibroblasts, upregulation of TGFBR2 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 Soehnlein 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 TGFBR2 might be therapeutic. The level of TGFBR2 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 TGFBR2; 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.

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