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PERSPECTIVE

Caveolae, CD109, and endothelial cells as targets for treating Alzheimer's disease

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Abstract

Reduced functionality of transforming growth factor β (TGF-β) is a major pathogenetic component of Alzheimer's disease (AD). The reduction is caused by an ≈50% decrease in the AD brain of the TGF-β receptor, TGFBR, causing a bottleneck effect that reduces the downstream actions of TGF-β, which is highly disadvantageous for brain function. Degradation of TGFBR occurs in caveolae with participation by caveolin-1 (Cav-1) and CD109. Mechanisms for this are discussed. In the cerebral microcirculation, endothelial cells (which are rich in caveolae) carry CD109 as a surface marker that co-precipitates with Cav-1. Atorvastatin reduced Cav-1 by 75% and, because Cav-1 and CD109 co-immunoprecipitate reciprocally, atorvastatin would also reduce the level of CD109. Administration of atorvastatin as a component of combination therapy would diminish the degradation of TGFBR and thereby benefit patients with AD.

KEYWORDS
Alzheimer's disease, atorvastatin, caveolae, caveolin-1, CD109, TGFBR, TGF-β

Few have contemplated caveolae or CD109 in the context of Alzheimer's disease (AD), yet these two elements are relevant because, by enabling the degradation of its receptor TGFBR, together they reduce the neurotrophic efficacy, as well as other beneficial functions such as anti-inflammatory ones, of transforming growth factor β (TGF-β). Reports provide variable blood levels of TGF-β in AD—some show high and some show low levels, but for cerebrospinal fluid (CSF), which reflects the brain, almost all reports show increased levels of TGF-β1.[1,2] However, reports also show a low level of TGFBR in AD, which produces a bottleneck effect so that the activation of Smad proteins, which is a major downstream effect of TGF-β, is substantially reduced and is highly disadvantageous for brain function (see review in Ref 3). TGF-β dysfunction is shown by the aberrant response of the downstream Smad proteins in AD. Lee et al. found that in contrast to an expected nuclear localization, phosphorylated Smad2 in AD was predominantly, and ectopically, found in the neuronal cytoplasm, specifically colocalizing with neurofibrillary tangles and granulovacuolar degeneration.[4]

Given that a nuclear localization of Smad is required to regulate the transcription of TGF-β target genes that provide neuroprotection, the ectopic localization of phosphorylated Smad2 shows a defect in the signaling pathway of TGF-β in AD and consequent loss of its neuroprotective and other functions. Furthermore, inhibition of endogenous TGF-β signaling increases neuritic degeneration and Aβ production.[5] Wys-Coray's group reported that lack of TGF-β1 in neonatal brain reduced expression of synaptophysin and laminin, reduced survival of its neurons, and increased neuronal susceptibility to excitotoxic injury.[6] Wyss-Coray et al. also reported that even a modest increase in the TGF-β level gave a strikingly lessened deposition of amyloid in AD-model mice, with a 3-fold reduction in the number of amyloid plaques and a 50% reduction in amyloid beta (Aβ) load in the hippocampus.[7]

Later, the Wys-Coray group demonstrated that in the AD brain, the level of the TGF-β2 receptor, TGFBR, is decreased to about 50% of normal, and that in patients with mild cognitive impairment (MCI) with Mini-Mental State Examination (MMSE) score 21 to 25, it was already

substantially decreased.[5] It is unknown what causes that severe decrement. Lotz-Jenne et al. identified 19 compounds that blocked epithelial to mesenchyme transition and three of them did so via TGFBR, demonstrating yet another of its functions.[8] It is possible that unidentified/unknown molecules besides caveolin-1 (Cav-1) and CD109, also block the TGFBR. Because of its neurotrophism, raising the concentration of TGF-β to overcome the bottleneck caused by the low level of TGFBR, might be beneficial for AD, and there are several ways to accomplish this,[3] but an approach discussed here that differs from those previously suggested, and that is arguably the most rational because TGF-β levels may already be elevated, would be to interrupt the reason why TGFBR is low. To accomplish that fully requires knowing whether the mechanism is decreased production, increased loss, or both. Although little is known about its production, some data exist that provide insight into the mechanism of TGFBR's increased loss. These data are explored here together with ways to interrupt that mechanism so as to raise the level of TGFBR. The likely elements that are involved include caveolae, Cav-1, and CD109.

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1.1 | Caveolae

Caveolae are 50- to 100-nm cell-surface plasma membrane invaginations present in in most of the body's terminally differentiated cells. Their plasma membrane incorporates a protein called caveolin-1 (or Cav-1).[9] Caveolae internalize molecules and send them for transcytosis and degradation, which is a process that differs from yet relates to autophagy because a deficiency of Cav-1 promotes autophagy.[10] Cav-1 is essential for the formation and stability of caveolae: In its absence no caveolae are seen.[11] In addition to formation of caveolae, Cav-1 modulates the activity of several signaling proteins through the so-called caveolin-scaffolding domain. Mice engineered to have no caveolae, had impaired nitric oxide (NO) and calcium signaling in the cardiovascular system, causing aberrations in endothelium-dependent relaxation and contractility; and their lungs had thickening of alveolar septa caused by uncontrolled endothelial cell proliferation and fibrosis, resulting in severe physical limitations.[12] Others saw a depletion of several mitochondrial genes in caveolin-null mice.[13] In sum, caveolae and Cav-1 have a fundamental role in organizing multiple signaling pathways.

1.2 | Drugs inhibiting formation of caveolae include atorvastatin and rosuvastatin

Cav-1 may be efficiently down-regulated by some but not all statins. It is notable that atorvastatin reduced Cav-1 by 75% while it simultaneously potentiated endothelial nitric oxide (NO) synthase , which is beneficial[14]; similar results for rosuvastatin were seen by Pelat et al.[15] It is noteworthy, however, that certain other statins have the opposite effect: Indeed, both lovastatin and pravastatin increased Cav-1.[16]

The precise mechanism by which atorvastatin benefits the cerebral microvasculature is unknown but there are some clues. Dimmeler et al. showed that statins induce endothelial progenitor cell (EPC) differentiation via the PI 3-kinase/Akt (PI3K/Akt) pathway, as demonstrated by the inhibitory effect of either pharmacological PI3K blockers or the overexpression of a dominant negative Akt construct.[17] Brouet et al. showed that statins' effects on endothelial function are through an increase in NO production via phosphorylation of eNOS on Ser1177, and that this is directly dependent on the ability of heat shock protein 90 (HSP90) to recruit Akt, which further potentiates the NO-dependent angiogenic processes.[18] By targeting HSP90, statins are dually beneficial, potentiating both the activation of ndothelial nitric oxide (NO) synthase (eNOS) and the differentiation of EPCs to endothelial cells (ECs). Important points are that the extent of this interaction may vary dramatically according to the cell types in the endothelial bed, and that different statins may variably affect ECs. Notably, the promotion of angiogenesis by statins was independent of lipid levels.[19]

Although some reports suggest that statins might increase the risk of dementia, indication bias affects interpretation of those reports because hyperlipidemia causes vascular dementia, and lipid-lowering was the reason for the use of statins. Both the Rotterdam[20] and Cache County[21] reports involved subjects for whom the prescription of statins was for hyperlipidemia, and the liraglutide with or without oral antidiabetes drugs (LEAD) study subjects had a high, mean LDL cholesterol of 143 mg/dL.[22]

Besides their common effect on lipids, different statins have diverse other effects that differ according to the particular statin. Thus Ohkita et al. showed that cerivastatin but not pitavastatin, pravastatin, or atorvastatin markedly suppresses endothelin-1 production,[23] although with regard to ECs most published work has used atorvastatin. Another example of differing effects is the increased risk of diabetes that is associated with some but not all statins. Among 8749 non-diabetic patients followed for 5.9 years, there was a 45% increased risk of diabetes.[24] However, simvastatin and atorvastatin accounted for most of the increase in diabetes, whereas neither pravastatin nor lovastatin increased that risk. In addition, not all statins are alike in affecting insulin sensitivity. In 16 studies involving 1146 patients receiving pravastatin, atorvastatin, or rosuvastatin, results showed that pravastatin significantly improved insulin sensitivity while simvastatin significantly worsened it.[25] The mechanisms for these differing effects are unknown.

1.3 | CD109: It enhances entry of TGFBR into caveolae, and is expressed in the ECs of the microcirculation

There are two TGFBRs: TGFBR1 and TGFBR2. TGF-β preferentially ligates TGFBR2, causing activation of TGFBR1 by phosphorylation. Activated TGFBR1 is necessary and sufficient for propagation of transcriptional responses.[26] CD109 associates with Cav-1 and also is a co-receptor for TGF-β, so it amplifies attachment of TGF-β1 to TGFBR2; and it associates with Cav-1 and thus causes the complex to enter caveolae.[27] From the caveolae both TGFBR and TGF-β are trafficked

by the ubiquitin/proteasome system to lysosomes, where they are degraded.[28] Decreasing the expression of CD109 would, therefore, diminish degradation of TGFBR as well as TGF-β1 and raise their levels.

CD109 is a cell-surface glycoprotein that is expressed on ECs. Chow et al. found that, unlike other segments of ECs in the central nervous system (CNS), arteriolar ECs (aECs) contain abundant caveolae.[29] That has significance for AD because as Chow et al. found, the caveolae-mediated pathway in these aECs is a major contributor to neurovascular coupling, a consequence of which is that any alteration in the function of aECs such as decrement in Cav-1 or CD109 will occur in intimate proximity to neurons and therefore be likely to affect them.[30] The importance for AD of cerebral microvessels and their ECs had been demonstrated by Grammas et al., who found that either direct co-culture of AD cerebral microvessels with neurons or incubation of cultured neurons with conditioned medium from those microvessels, results in neuronal cell death; vessels from elderly nondemented donors were significantly ($P < .001$) less lethal.[31] One possible explanation comes from other studies from the same laboratory, showing that in AD, brain ECs produce neurotoxic thrombin.[32]

CD109 has a two-fold importance for AD. First, it is an accessory receptor for TGF-β, binds TGF-β1 with high affinity, and inhibits TGF-β signaling; second, it is intimately linked to Cav-1, as shown by Bizet et al., who found that an anti-Cav-1 antibody co-precipitates CD109 and, reciprocally, an anti-CD109 antibody co-precipitates Cav-1.[27] For this reason, a drug that inhibits Cav-1, for example, atorvastatin (see above) will by necessity also inhibit CD109. Confirming the specificity of the association, Bizet et al. found that, as the level of Cav-1 becomes too low, CD109 is no longer co-precipitated.

CD109 promotes transport of both TGF-β and TFGBR into the caveolae from where they are sent for degradation in the lysosomal pathway. It seems likely that this mechanism contributes to the 50% reduction of TGFBR in AD, although it is certainly possible that there may be additional participants. Interrupting the degradation of TGFBR would be one way to raise its level and, with that, increase the efficacy of TGF-β. There are two ways to interrupt the mechanism: One involves inhibiting the formation of caveolae themselves, and the other requires reducing the level of CD109.

2 | CONCLUSION

Caveolae, CD109, and ECs are dysfunctional in AD, and they participate in the decreased level of TGFBR that creates a bottleneck, causing a functional decrement in the downstream action of TGF-β. Atorvastatin should be beneficial for treating AD by increasing the level of TGFBR and, thereby, the functional efficacy of TGF-β1. In a prior report, I suggested that a combination of three or four drugs, chosen from a total of eight, has the potential to prevent progression from MCI to AD.[33] Atorvastatin should be added to that list of eight drugs.

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CONFLICTS OF INTEREST

The author has no conflicts of interest to disclose.

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