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INSIGHTS

Friend turned foe: TREM2 agonist in battles against tau

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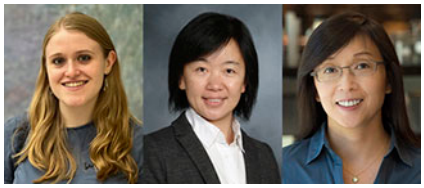
In this important study, Jain et al. (2022. *J. Exp. Med.* https://doi.org/10.1084/jem.20220654) find that chronic TREM2 activation by AL002a antibody exacerbates the seeding and spread of pathological tau, enhances the disease-associated microglial signature, and increases neurite dystrophy in 5xFAD mice seeded with Alzheimer's disease tau.

The microglial TREM2 receptor has been implicated in Alzheimer's disease (AD) by genetic studies showing that rare variants, including the R47H mutation, increase AD risk two- to fourfold (Guerreiro et al., 2013; Jonsson et al., 2013). As the risk variants are largely considered to induce partial loss of function, major efforts have been devoted to developing therapeutic strategies to enhance TREM2 function or its downstream actions. Several recent studies have presented beneficial effects of TREM2 agonist antibodies in animal models with amyloid plaque deposition (Price et al., 2020; Schlepckow et al., 2020; Wang et al., 2020; see figure). However, whether chronic activation of TREM2 remains protective in the presence of tau pathology, which correlates more closely with cognitive decline in AD than plaque load, had not been determined.

In this issue, Jain et al. (2022) investigated this critical question by chronic administration of murine TREM2 agonist antibody AL002a in 5xFAD mice seeded with AD tau, which models amyloid-enhanced spreading of pathogenic tau aggregates in brain (Jain et al., 2022). Strikingly, they found that chronic activation of TREM2 by AL002a, although increasing microglial number and responses around plaques as expected, exaggerated neurite dystrophy and enhanced peri-plaque synapse loss, without affecting amyloid burden. Moreover, chronic administration of AL002a exacerbated seeding and spread of phospho-tau aggregates. Considering that a humanized TREM2 agonist antibody is being tested in a Phase 2 human clinical trial, this study raises concerns about the potential detrimental effects of TREM2 agonist therapeutics, especially at the symptomatic stage of AD when tau pathology is prevalent.

In AD, amyloid deposition precedes cognitive decline by decades, followed by the accumulation and spread of tau pathology that is associated with the extent of cognitive impairment (see figure). To model amyloid-induced tau seeding and spreading in AD brains, Jain et al. (2022) injected sarkosyl-insoluble tau aggregates isolated from human AD brain (AD-tau) unilaterally into 6-mo-old 5XFAD brains with mature amyloid-β (Aβ) pathology. Studies have shown that TREM2 deficiency exacerbates tau spreading and neurodegeneration in the same model (Leyns et al., 2019), and worsens neurodegeneration in TauPS2APP mice with both amyloid and tau pathology (Lee et al., 2021). Thus, the authors hypothesized that chronic TREM2 activation would inhibit amyloid-induced tau seeding, spreading, and toxicity. Unexpectedly, they found quite the opposite: Chronic TREM2 activation significantly increased AT8-positive tau aggregates in hippocampus and cortex. This is accompanied by an increase in BACE1-positive neuritic dystrophy and a decrease in pre-synaptic marker synapsin surrounding the plaque area. While the study did not explore why both genetic TREM2 deficiency and TREM2 agonist AL002a exacerbate tau pathology and toxicity, one likely explanation lies at the timing of the two modes of TREM2 manipulation. In the genetic models, TREM2 is deficient from embryo long before amyloid deposition, profoundly altering amyloid morphology, resulting in barrier-less amyloid plaques driving tau seeding (Leyns et al., 2019) and toxicity (Lee et al., 2021). In contrast, in the current study, AL002a was administered at 6 mo of age, long after the onset of amyloid pathology. In this therapeutically relevant scenario, the lack of strong effects on amyloid load and morphology by AL002a argues against a direct role of amyloid in driving the detrimental effects on tau seeding and toxicity.



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What then drives the detrimental effects of chronic TREM2 activation by AL002a in

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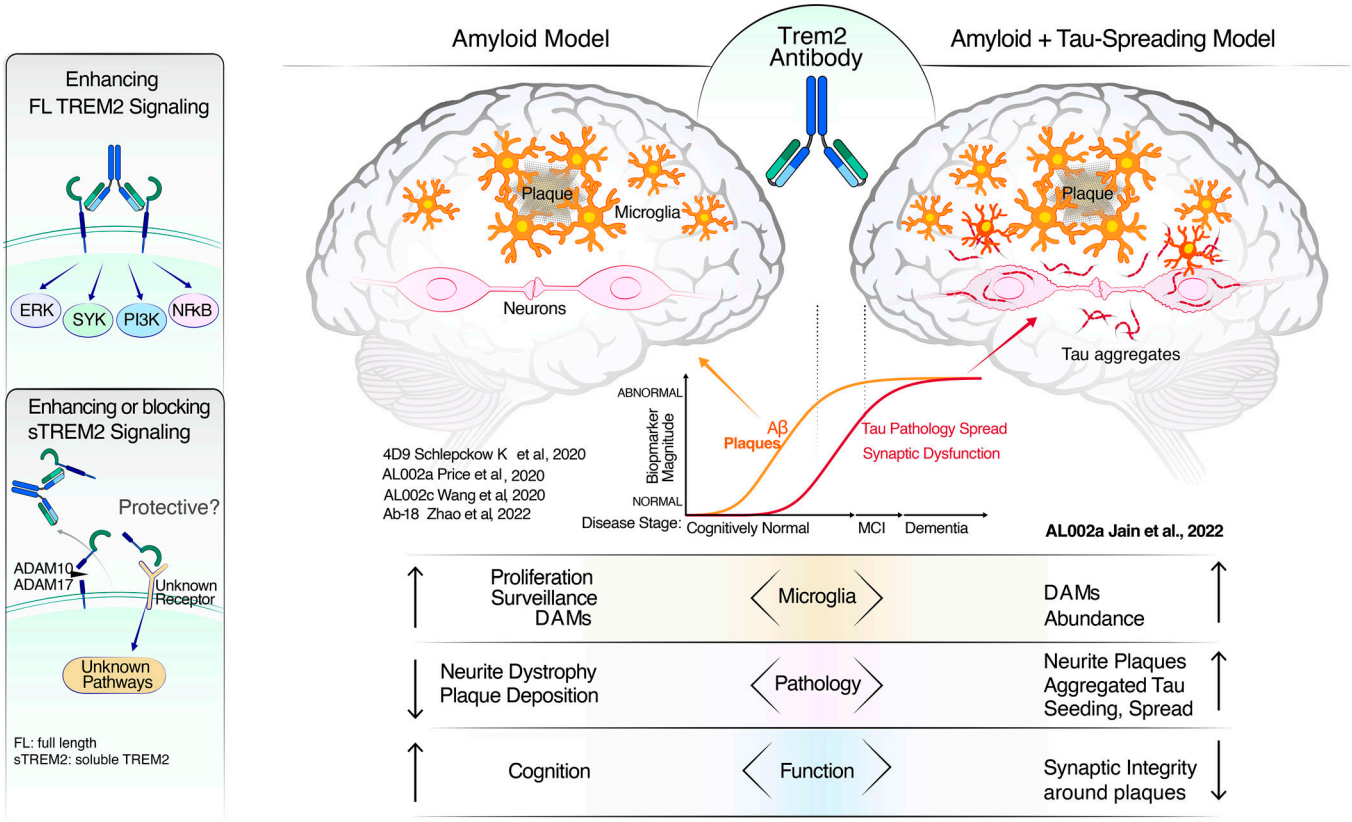

TREM2 agonist antibodies to treat AD: the importance of timing. In AD, amyloid plaque deposition precedes tau pathology and cognitive decline. TREM2 agonists could turn from friend to foe as disease progresses from predominantly amyloid pathology at early disease stage to more advanced stages with high tau burden. At the early amyloid-driven stage, activation of TREM2 is protective in promoting microglial barriers around toxic Aβ plaques, but could become damaging at the late tau-dominant stage by driving tau spreading and toxicity. It remains unclear how full-length TREM2 or sTREM2 mediates the protective or detrimental effects of TREM2 antibodies. ERK, extracellular signal-regulated kinase; Syk, spleen associated tyrosine kinase.

Jain et al. (2022)? Consistent with previous studies, Jain et al. (2022) showed that AL002a increased microglial abundance around the plaques and induced higher expression of disease-associated microglia (DAM) markers, including Clec7a, Cd68, and Apoe. It is thus possible that the elevated TREM2 downstream signaling could exacerbate tau seeding, spread, and toxicity in an amyloid-independent manner. Indeed, TREM2 deficiency protected against tau-mediated neurodegeneration in tauopathy models (Leyns et al., 2017), while enhancing TREM2 downstream signaling, including NF-κB signaling and exacerbated tau seeding, spread, and/or toxicity (Wang et al., 2022). Thus, the effects of TREM2 agonism are dependent on disease stage. While TREM2 activation could be protective by promoting microglial barriers around toxic Aβ plaques, continued activation could become detrimental at later disease stage once tau pathology is prominent and cognitive decline takes place (see figure). Understanding the consequences of TREM2 agonism at different disease stages is critical for targeting the right patient population for TREM2 agonists clinical trials.

There are intriguing differences in TREM2 agonistic antibodies that are worth further investigation. Some antibodies have exhibited stronger plaque-lowering effects than AL002a in the current study (Price et al., 2020; Schlepckow et al., 2020; Wang et al., 2020; Zhao et al., 2022), which could conceivably ameliorate amyloid-dependent tau seeding and toxicity. Another potential important difference lies in their effects on the shedding of soluble TREM2 (sTREM2), whose role is currently not well understood (see figure). Differing from the two TREM2 agonist antibodies 4D9 and AL002c that reduce sTREM2 (Schlepckow et al., 2020; Wang et al., 2020), Jain et al. (2022) found that chronic AL002a administration significantly increased both surface and soluble Trem2, likely due to antibody-aided stabilization. It is not known if the antibody-bound form of sTREM2 interferes in the potential biological activity of sTREM2. Interestingly, AD patients with higher levels of cerebrospinal fluid sTREM2 have slower AD progression, suggesting sTREM2 is protective against disease (Morenas-Rodriguez et al., 2022). Supporting this theory, sTREM2 protects against amyloid pathology and dampens inflammation after injection into amyloid mouse brains (Zhong et al., 2019). A recent study showed that sustained activation of TREM2 via introducing a mutation that blocks TREM2 shedding by ADAM10 upregulates inflammatory genes, aggravates inflammation, increases early plaque deposition and neuritic dystrophy, and accelerates microglial response to Aβ (Dhandapani et al., 2022). Further investigation of the effects of sTREM2 on amyloid, tau, and inflammation is critical to understanding the effects of TREM2 activation and to designing effective TREM2-targeted therapeutics against both amyloid and tau toxicity.

In summary, Jain et al. (2022) demonstrate that TREM2 agonists could turn from friend to foe as disease progresses from predominantly amyloid pathology at early

disease stage to more advanced stages with high tau burden (see figure). The protective effects of TREM2 activation by promoting microglial barriers around toxic Aβ plaques could reverse into damaging effects as enhanced inflammatory pathways in microglia become drivers of tau spread and toxicity (Wang et al., 2022). The R47H variant of TREM2 may augment the detrimental aspects of the receptor by reducing microglial ability to surround and compact Aβ plaques (Yuan et al., 2016), as well as enhancing inflammatory responses to pathogenic tau (Sayed et al., 2021). Intriguingly, acute AL002c treatment led to a significantly higher increase in the proportion of microglia transitioning to the DAM state in 5XFAD mice carrying R47H mutation compared to common variant (Wang et al., 2020). It is possible that TREM2 agonism has differing effects on common variant and R47H TREM2 due to different baseline levels of sTREM2, which should be further investigated in the future. Dissecting the pathways underpinning these phenotypes will help identify strategies to enhance the protective effects of TREM2 and minimize the detrimental outcome. Until these pathways are better understood, TREM2 agonist treatments should be viewed with caution, as they may heighten unwanted effects of the receptor, and the potential injurious effects of TREM2 agonism in the presence of tau pathology cannot be ignored.

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