

Can SARS-Co-V2 Proteins Catalyze Abeta42-Induced Toxicity In Vivo?

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Previous studies found that SARS-Co-V2 proteins or RNAs can persist in different tissues, including the brain, for several months after infection, but the pathological implications of this finding are largely unknown. Given observed structural brain changes in SARS-CoV-2 infected individuals, particularly in learning and memory regions, a concern exists regarding increased Alzheimer's disease (AD) risk. Our study aimed to determine if SARS-CoV-2 proteins accelerate the onset, duration, and severity of A β 42 toxicity in *Drosophila*. We individually manipulated all 29 SARS-CoV-2 proteins (16 non-structural, 9 accessory, 4 structural) in transgenic flies using conditional expression systems to assess their pathogenic potential *in vivo* across multiple tissues. We evaluated their contribution to A β 42-dependent phenotypes in AD fly models via pathological and behavioral analyses. Remarkably, one non-structural protein exhibited an extraordinary capacity to induce an aggressive phenotype when expressed in the *Drosophila* eye and caused loss of axonal projections in memory-related neurons. Crucially, this protein also triggered A β 42-induced neurodegeneration in the fly brain, accelerated the formation of thioflavin-positive A β 42 structures, and led to early death in A β 42-expressing flies. These findings suggest varying neurotoxicity among SARS-CoV-2 proteins *in vivo*, with at least one non-structural protein accelerating A β 42-induced pathology. This has significant implications for understanding long-term neurological sequelae of SARS-CoV-2 infection. We are currently testing the effect on TDP-43 pathology and preliminary results will be presented.

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