Vascular-associated neuroinflammation in Alzheimer's disease: differential effects on disease progression modulated by underlying amyloid burden

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Of the modifiable factors that collectively account for over half of Alzheimer's disease (AD) cases, the majority are vascular risk factors (VRFs). Given that the number of AD patients is expected to double by 2040, this situation presents an important opportunity to reduce negative impacts on public health. Clearer understanding of the precise temporal and mechanistic alterations linking VRFs to AD may enable development of therapeutic approaches to sever that link. The overall goal of this proposal is therefore to elucidate potentially targetable mechanisms underlying the connection between early vascular damage and subsequent AD pathology. Vascular inflammation is one unifying feature of many VRFs, and this can induce or propagate neuroinflammatory changes in the brain. Considering the established role of neuroinflammation in AD pathogenesis, it may be clinically useful to target neuroinflammatory alterations secondary to vascular insult. This proposal will therefore test the hypothesis that vascular risk factors contribute to AD primarily by increasing neuroinflammatory responses and altering subsequent amyloid pathology. For these studies, I will use a well-characterized amyloid beta (A) overexpression mouse model of AD (APPswe/PS1dE9) along with a dietary hyperhomocysteinemia (HHcy) model to induce vascular damage and inflammation. In Aim 1, I will induce HHcy in AD mice within a period corresponding to prodromal AD, and in Aim 2 within a period corresponding to early AD. In both aims I will acutely treat the vascular-associated neuroinflammation in half of the animals. I will characterize how vascular damage and associated neuroinflammation interact with underlying A pathology to produce additive cognitive deficits at different stages of AD progression. In addition, both aims will include clinically relevant neuroimaging measures to connect pathological alterations with detectable alterations in cerebral blood flow (arterial spin labeling) and metabolic changes (magnetic resonance spectroscopy). Successful completion of this project will provide clinically-relevant insight into the links between VRFs and AD. Further, it will provide proof-of-concept of the utility of targeting neuroinflammation secondary to vascular damage as a means of preventing or delaying future cognitive decline. Ideally, such an approach will someday be incorporated into a comprehensive strategy of managing AD risk.