Title: The Ultrastructural Mechanisms of Microglial Amyloid-β Endocytosis

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Abstract:
Amyloid beta's (Aβ) role in triggering Alzheimer's disease (AD) is accepted, but not understood. New treatments which simply reduce Aβ plaques have not significantly improved cognitive outcomes in AD patients. This indicates that another factor is at play. Recent genetic studies have indicated that microglia are also central to the progression of AD. Microglia are the primary immune cells and phagocytes of the brain. In AD, microglia isolate and phagocytose Aβ. This work hypothesizes that a subset of microglia, increased by the activation of the integrated stress response (ISR), become overwhelmed by Aβ uptake, accumulating indigestible Aβ aggregates in their lysosomes. I propose that this phagocytic failure further activates the ISR, compounding dyshomeostasis. Live cell imaging and western blotting results characterize the bidirectional relationship between Aβ phagocytosis and digestion, and the ISR in support of this hypothesis. To elucidate the structural underpinnings of this effect work is underway to employ advanced cryogenic electron microscopy techniques to map structural changes in microglial lysosomes during aberrant Aβ phagocytosis. Together, these studies will elucidate molecular mechanisms of neurodegeneration and may inform potential new avenues of treatment.

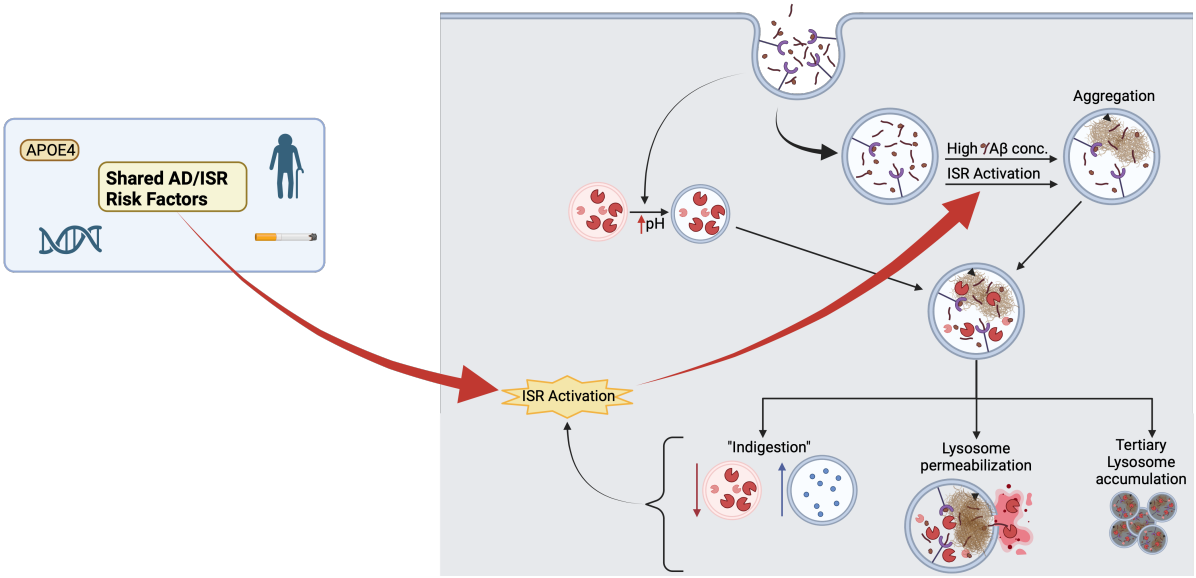

Figure 1. Proposed mechanism of interaction between Aβ accumulation and ISR within microglia.