The damage signals hypothesis of Alzheimer's disease pathogenesis

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Virtually none of the hypotheses on Alzheimer's disease (AD) pathogenesis address the earliest events that trigger the molecular alterations that precede cerebral degeneration and account for the diversity of risk factors that converge on a well-defined disease phenotype. We propose that long-term activation of the innate immune system by an individual array of risk factors constitutes a unifying mechanism leading to the triggering of an inflammatory cascade that converges in cytoskeletal alterations (tau aggregation, paired helical filament formation) as a previously hypothesized final common pathway in AD. The key pathogenic phenomena consist in the long-term, maladaptive activation of innate immunity-triggering receptors - such as the toll-like and advanced glycation end-products receptors, and others located in the microglial membrane - by seemingly heterogeneous risk factors such as hyperlipidemia, hyperglycemia, oxidative stress, head injury, amyloid oligomers, etc. Our hypothesi