

Self-Assembly of the Alzheimer's Amyloid-Beta Protein and the Immune Response

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A signature feature of Alzheimer's disease (AD) is the accumulation of aggregated amyloid- β peptide ($A\beta$) as dense core plaques in the brains of affected patients. Significant inflammation is observed in AD as $A\beta$ plaques are surrounded by activated microglia, some of which are believed to be derived from infiltrating peripheral blood monocytes. Our *in vitro* studies in human monocytes demonstrated that $A\beta$ effectively induced monocyte adhesion and monocyte activation with clear differences observed in the $A\beta$ aggregation state driving the two immune cell activities. For monocyte adhesion, we noted an inverse correlation between $A\beta(1-42)$ -induced adhesion and aggregation. Freshly reconstituted $A\beta(1-42)$ solutions in sterile water were the most effective, yet continued aggregation abolished this ability. $A\beta(1-40)$, lower $A\beta(1-42)$ aggregation concentrations, and an aggregation-restricted $A\beta(1-42)$ L34P mutant had little effect on monocyte adhesion under the same conditions. These findings implicated oligomeric, but not monomeric or fibrillar, $A\beta(1-42)$ in the adhesion process. Monocyte activation was more complex in that freshly-reconstituted $A\beta(1-42)$ did not effectively stimulate tumor necrosis factor α (TNF α) production. However, continued aging of the peptide greatly increased TNF α production which surprisingly declined upon further aging. Microscopy images revealed that TNF α production coincided with the appearance of thin flexible fiber structures although faster-aggregating $A\beta(1-42)$ solutions were unable to stimulate the cells. $A\beta(1-42)$ aggregation buffered at pH 7.1 showed a meshwork of loosely-defined fibrillar structures which failed to evoke a proinflammatory response compared with incubation in water (pH 3.6). Toll-like receptors 2 and 4 were found to mediate $A\beta(1-42)$ -induced TNF α production using antibody neutralization assays. Monocyte adhesion induced by oligomeric $A\beta(1-42)$ was mediated by formyl peptide receptor-like 1 based on almost complete inhibition by an antagonist peptide. The observations that immune cells respond differently to different aggregation $A\beta$ states may help to explain the complex inflammatory response in the AD brain.

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