β-Amyloid pathogenesis: Chemical properties versus cellular levels

Although genetic Aβ variants cause early-onset Alzheimer's disease, literature reports on Aβ properties are heterogeneous, obscuring molecular mechanisms, as illustrated by recent failures of Aβ-level targeting trials. Thus, we combined available data on Aβ levels and ratios, aggregation propensities, toxicities, and patient data for Aβ variants and correlated these data to identify heterogeneity, significant relations, and basis for consensus. Despite heterogeneity, age of disease onset correlates to Aβ levels ($R^2 =0.38$, $P= .018$), but not to toxicities, Aβ42 levels, Aβ42/Aβ40 ratios, or aggregation propensities. Cytotoxicity correlates inversely with total Aβ42 ($R^2=0.65$, $P =.016$) and Aβ42/Aβ40 ratios ($R^2=0.76$, $P= .005$), i.e., chemical properties that increase Aβ42 also reduce toxicity. The complexity and heterogeneity of data reveal the need to understand these phenotypes better, e.g., by focusing on the chemical properties of the involved Aβ species.

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