Understanding Alzheimer's Disease at the Molecular Level

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Alzheimer's disease (AD) is the most common type of dementia affecting 52 million people worldwide. It is a lethal neurodegenerative disorder that chronically affects memory and cognition. There are no curative or disease modifying agents available for the treatment of AD. A major hurdle in the discovery of such agents is the fact that the underlying mechanisms that cause AD are not understood and have not been elucidated. The time-honoured notion that AD is caused by misfolding and aggregation of a protein called β-amyloid (Aβ) has failed to deliver any useful small molecule therapeutics. AD is in need of new therapeutic directions. Based upon an extensive series of molecular modelling simulations (at the QM and MM levels), we have devised a new molecular-level mechanistic model of AD. In this model Aβ is reconceptualised as an antimicrobial immunopeptide which mistakes the molecular topography of neuronal membrane surfaces as bacterial membrane surfaces, subsequently mistakenly attacking host neurons rather than bacteria. This error in innate immunity processing culminates in neuronal death and the clinical presentation of AD. Exploiting this novel model for purposes of rational drug design and development via medicinal chemistry will be discussed.