Role of the plasma membrane in amyloid formation and toxicity

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A number of neurodegenerative diseases are caused by the aggregation and deposition of amyloid in the nervous system. For example, the deposition of β-amyloid peptide (Aβ) is considered to be a key event in the pathogenesis of the Alzheimer's disease (AD), which is the prototypic amyloidosis. Another example is Transthyretin (TTR), a plasma protein produced in the liver and the choroid plexus that can form amyloid. TTR is the predominant component of the amyloid fibrils in familial amyloidotic polyneuropathy (FAP), a hereditary disorder characterized by systemic extracellular deposition of amyloid fibrils, mainly in the peripheral nervous system. Native TTR consists of four identical subunits that form an extensive β-sheet structure, which is prone to misfolding. So far nearly eighty mutations have been identified in TTR, most of which are amyloidogenic. It is believed that structural modifications by these mutations destabilize the native tetrameric conformation and favour its dissociation into monomeric structure, which is the building block of TTR amyloid fibrils. While the mechanism by which amyloidogenic proteins cause neurotoxicity is unclear, it is now emerging that the cytotoxicity of amyloids is a direct consequence of binding to the plasma membrane. We have therefore used surface plasmon resonance (SPR) for the study of Aβ- and TTR-membrane interactions to determine whether this binding could explain the toxic effects of Aβ and TTR seen in cell culture.

Our results show that Aβ and TTR bind to the lipids of the plasma membrane through electrostatic interactions and that the amount of binding is increased upon aggregation. We also show that the amount of Aβ and TTR binding to the plasma membrane correlates with the degree of cytotoxicity observed in cell culture. Finally, we demonstrate that binding of Aβ and TTR amyloid to the plasma membrane alters membrane fluidity, providing a possible explanation for the cytotoxic effect. Overall, the results strongly support the view that both Aβ and TTR toxicity is a direct consequence of binding to lipids in the membrane. However, there are specific differences in the factors that affect this interaction. In particular, binding of Aβ was strongly influenced by the concentration of cholesterol in the membrane but did not affect TTR binding. This presentation demonstrates the application of SPR to the study of the molecular interactions associated with AD and FAP and how this information enhances our molecular understanding of neurodegenerative diseases