Compatibility rules for glycosaminoglycan-amyloid interactions

https://neurodegenerationresearch.eu/survey/compatibility-rules-for-glycosaminoglycan-amyloid-interactions-2/

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United Kingdom

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Compatibility rules for glycosaminoglycan-amyloid interactions

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Research Abstract
Over 30 polypeptides self-assemble into insoluble amyloid fibrils associated with amyloid disease. As early as the 1850’s it was found that amyloid deposits are associated with carbohydrates, later identified and classified as proteoglycans and glycosaminoglycan (GAG) polysaccharides. GAGs are now known to co-localise widely with amyloid assembled from a variety of protein precursors, and to influence fibril growth rate, fibril morphology, fibril stability and the pathogenic properties of the soluble pre-fibrillar intermediates. How the chemical composition of GAGs or their amyloid protein partners influence their molecular compatibility, however, remains unknown.

Capitalising on our exciting recent developments which have revealed the first atomic resolution structures of a fibril-GAG interaction, we propose here to determine the molecular determinants of fibril-GAG interactions using both natural and model GAGs and fibrils of Abeta1-40 and Abeta1-42 (associated with Alzheimer’s disease), and amylin, the pancreatic islet amyloid polypeptide associated with type II diabetes. Using a combination of solid-state NMR and biochemical and biophysical techniques, we will determine how GAG-amyloid interactions are modulated by protein sequence, fibril architecture, and saccharide substitution patterns. We will establish the relative importance of different GAG family members as potential partners for interacting with amyloid fibrils and elucidate the structural consequences of binding at the detailed level of protein structure. Furthermore, the first details on how GAGs direct the early stages of amyloid assembly will be provided from structural measurements on assembly intermediates in the presence/absence of GAGs. A comprehensive atomistic dissection of these long-overlooked interactions will thus emerge, providing holistic insights into the amyloid assembly process and guidance for the design of therapeutic or diagnostic agents against amyloid assembly and disease.

Further information available at:

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