Abstract

Neurodegenerative diseases, such as Parkinson's and Alzheimer's disease, affect 50 million people worldwide, reducing the quality of life of patients and their families. Many neurodegenerative diseases are associated with amyloid proteins, which can form stable and insoluble fibrillar structures and are the main focus of research on these pathologies. The ongoing transformation of the age structure in developed countries will triple the population of patients with neurodegeneration by 2050. Despite the high importance and prevalence of neurodegeneration, no effective treatment is available, raising the need for novel ways to study these pathologies.

Finding novel drug targets and uncovering disease mechanisms is possible with protein-protein interaction networks (PPINs). PPINs may be interpreted as disease roadmaps, whose detailed analysis can provide new high-level information on the pathology. This work discusses the application of available PPINs in neurodegeneration, showing that current PPIN datasets are biased by our scientific interests, which harness their biological interpretation. The published research regarding Parkinson's and Alzheimer's disease discusses mostly amyloid proteins and their interactions, hindering the generalisation of protein-protein interactions in these disorders on a proteome-wide scale. Therefore, to better understand neurodegeneration, studies on the understudied groups of proteins are needed.

Microbial amyloids, including bacterial functional amyloids, are a great example of understudied topics in neurodegenerative diseases with the potential to shed light on the onset and progression of neurodegeneration. Such proteins are purposefully produced by an organism, e.g. to serve as biofilm scaffolding. Previous studies have shown that bacterial functional amyloid proteins may be present in the human microbiome and affect the rates of amyloid deposition in the brains of patients with neurodegeneration. In this thesis, bacterial functional amyloids are analysed in detail. Examination of sequences of these proteins reveals that their aggregation propensity might be regulated by characteristic sequence repeats. Structural analysis of bacterial functional amyloids is not yet possible, as AlphaFold is generally shown to struggle with amyloid proteins. This is the result of the low abundance of amyloid structures in the AlphaFold training dataset, which leads to frequent prediction of high-quality globular models instead of fibrillar structures for amyloid proteins. The presence of bacterial functional amyloids in the human microbiome is analyzed to give grounds for discussion about their potential clinical importance. Through a designed pipeline, 805 such proteins, potentially produced by a broad spectrum of bacterial species, are identified in the microbiome proteome. Predictions of interactions between human proteins and functional bacterial amyloids suggest that bacterial functional amyloids could affect multiple molecular pathways, including inflammatory response, cell transport and signalling, and even harness the functioning of cell junctions responsible for intestinal permeability.

This thesis demonstrates that current research on neurodegeneration is biased by scientific interests in this topic. Studying different protein groups, such as bacterial functional amyloids, can shed new light on the pathology and extend our biological knowledge. The

quality and quantity of the experimental data are always a limit for the computational analysis. Hence, future research on neurodegeneration may greatly benefit from general high-throughput experiments that provide information on a proteome-wide scale, enabling big data analysis approaches to uncover biological patterns in these disorders. Until such high-throughput experiments on amyloid proteins become a very common practice, reaching beyond the most studied group of proteins can make an impact.

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