

Preface

The folding of proteins into unique three dimensional structures is integral to their specific biological functions within the body. Of the tens of thousands of proteins encoded within the human genome, fewer than thirty are known to share the feature of being susceptible to increased folding of the polypeptide backbone into the beta sheet conformation and assembly into amyloid fibrils. In each case, the increased beta sheet folding is associated with a clinically distinct disease or disorder, one of the amyloidoses. The pathological consequences of amyloid fibril formation are implicated in a wide range of both common and rare diseases, including Alzheimer's disease and other brain disorders, adult onset (type II) diabetes mellitus, plasma B-cell dyscrasias, long term hemodialysis, hereditary polyneuropathies and hereditary periodic fever syndromes.

During the latter half of the twentieth century, chemical and physical studies of amyloid fibrils that had been isolated and purified from amyloid laden tissues and organs led to the recognition that there is a unique association between the chemical identity of the fibril forming protein and the pattern of localized or systemic clinical symptoms. However, despite their biochemical and clinical differences, each of the amyloidoses shares the common pathophysiological features of an amyloidogenic protein precursor, permissive host genetic background, abnormalities in proteolysis that permit accumulation of precursor protein and fibril intermediates, and alteration in the chemistry of the extracellular matrix. Each of the more than 20 chemically distinct types of amyloid deposits contains a common set of extracellular matrix constituents, glycosaminoglycans and non-fibril forming proteins, serum amyloid P component and apolipoprotein E.

Until now, to some extent, clinical studies and basic studies have proceeded in parallel. Now, we are poised to integrate and utilize our knowledge of protein structure, physiology and pathology to forestall or ameliorate the clinical consequences of the tendency of amyloid fibril forming proteins to undergo increased folding into the beta sheet conformation. Outside the body, using conditions that alter protein folding, amyloid fibrils have been created from many more than 30 proteins; this is an indication of the key role of the local tissue environment in triggering amyloid fibril formation within the body.

These volumes bring together preeminent amyloid clinicians and basic scientists to consider our present knowledge in terms of those structural and thermodynamic features which, over time, lead to amyloid fibril formation, deposition and disease. The authors present an overview of amyloidosis and amyloid proteins today, including the history of amyloid investigation, the internationally accepted nomenclature and the anatomic and clinical clues as to why amyloid fibrils form within the body. Protein folding, unfolding and refolding are considered in terms of thermodynamics, posttranslational modification and lipid association, and the influence of the extracellular matrix, serum amyloid P component and apolipoprotein E. Pathways to amyloid fibril formation are considered in terms of folding of natively unfolded proteins and unfolding of natively folded, globular proteins. The use of computational approaches to derive potential structures of amyloid fibril intermediates is presented. How the process of amyloid fibril formation causes damage to organs and tissues of the body is considered in terms of oligomeric fibril forming intermediates and cellular toxicity and brain dysfunction. Most of the amyloid proteins are considered individually in terms of current knowledge of structure, function and metabolism. Some of the more recently identified forms of amyloid, including medin, lactoferrin, apoA-IV or keratoepithelin (Table 1.1) have not been considered in detail here. It is anticipated they will be the subject of greater study in the future and that additional chemical forms of amyloid, particularly localized, will be identified in future studies. There is also within this volume the call for development of molecular diagnostics and targeted therapeutics in the amyloidoses. It is to that end that this volume is dedicated, to the acceleration of progress in understanding the contribution of the beta sheet conformation to the etiology and pathophysiology of disease, in order to enable prevention and better informed treatment of the amyloidoses.

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