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Maria M. Picken
Guillermo A. Herrera
Ahmet Dogan *Editors*

Amyloid and Related Disorders

Surgical Pathology and Clinical Correlations

Second Edition

Humana Press

CURRENT CLINICAL PATHOLOGY

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This book is dedicated to our patients, past and present, with the hope that it will make a difference in the lives of future amyloidosis patients.

MMP, GAH, AD

Preface (Second Edition)

Amyloidosis, although known since the nineteenth century, retained for a long time the aura of a rare and obscure disease that was untreatable and mainly of purely academic interest. This state of affairs has, however, changed dramatically in recent years. With the new therapies that are now available, patients with systemic light chain amyloidosis (AL) may achieve a durable response and live for more than a decade from the time of their first diagnosis. Treatments for other types of systemic amyloidosis are also improving. Thus, in addition to liver transplantation, patients diagnosed with hereditary amyloidosis derived from a mutant transthyretin (ATTR) are currently being offered pharmacologic therapies that are in clinical trials. However, treatment outcomes are most successful when they are applied early in the disease process. Thus, now more than ever, early diagnosis is of the utmost importance. Although there are a number of excellent amyloidosis treatment centers around the world, early diagnosis of affected patients is reliant upon widespread and effective screening, and, despite advances in laboratory medicine, this still hinges upon the detection of deposits in tissues. Thus, the role of the pathologist in this process is critical. This book therefore has, as its primary focus, the diagnosis of amyloidosis in surgical pathology. Although written primarily for pathologists, it is hoped that this volume will also be helpful to those who would wish to gain insight into recent diagnostic and treatment options.

This second edition of "Amyloid and related disorders" has been expanded to include seven new chapters, while the prior content has been updated. The volume begins with a history of amyloid investigations and the latest nomenclature. Separate chapters are devoted to the mechanism of amyloidogenesis and an overview of AL, AA, ALECT2, hereditary, dialysis, and localized amyloidoses; a brief overview of cerebral amyloidoses is also included. In Part II, diseases that mimic amyloid and related disorders are discussed. Part III is entirely devoted to pathologic diagnosis, including the generic diagnosis of amyloid, and issues pertaining to amyloid typing that involve both antibody-based and proteomic methods. Part IV provides an overview of laboratory support for the diagnosis of amyloidosis, including serum, urine, bone marrow, and genetic studies. Part V provides an overview of amyloid pathologies in the genitourinary tract, cardiac, gastrointestinal/liver, and peripheral nervous systems; new chapters on lymph nodes and spleen, pulmonary, dermal, breast, and iatrogenic amyloidoses have been added.

Part VI discusses clinicopathologic issues and the role of solid organ transplantation, as well as recent advances in therapies for AL, hereditary, and AA amyloidosis. Brief chapters on relevant legal issues, and the patient's perspective, conclude Part VI.

Those who are interested in the amyloidoses are also encouraged to review the contents of "Amyloid: The Journal of Protein Folding Disorders" and contact the International Society of Amyloidosis (www.amyloidosis.nl). Resources available to patients include the Amyloidosis Foundation (http://www.amyloidosis.org) and the Amyloidosis Support Group (http://www.amyloidosissupport.org).

It also behooves us to acknowledge that abnormal protein folding, the very essence of amyloid fibril formation, affects many more aspects of our lives than those covered by the chapters in this book. While amyloid formation represents a fundamental process in many diseases and aging, it also plays an important role in vertebrate and invertebrate biology, as functional amyloid; amyloid fibrils also have applications in the fields of nanotechnology and bioengineering. Therefore, understanding the driving forces behind both the regulated and unregulated formation of amyloid structures may help us to enlist that knowledge in the fight against disease and the aging process and may, unexpectedly, also lead to improvements in many other areas of our lives.

Maywood, IL, USA — Maria Mrozowicz Picken
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Part I

Introduction/General

Aspects of the History and Nomenclature of Amyloid and Amyloidosis

1

Per Westermark

A Short History of Amyloid

> The longer you can look back
> the further you can look forward
> Winston Churchill

This chapter deals with some aspects of the history of amyloid and its evolving nomenclature. The history is interesting and contains some of the characteristics of human behavior, including envy and rigidity. Those with a particular interest are referred to a number of earlier publications [1–5]. In addition, some very interesting aspects of the modern history can be found in the proceedings from the international symposia on amyloidosis, particularly the first ones [6, 7].

The designation "amyloid" is actually a misnomer. As a human affliction, the term was coined by Rudolf Virchow when he used iodine to search for a cellulose- (or starch-) related substance. He found that corpora amylacea of the brain had some tinctorial properties that were reminiscent of starch and named the stained substance amyloid [8]. Corpora amylacea are not an example of what is now called amyloid, but Virchow expanded his studies to include tissues that contained (what we now understand must have been) systemic amyloidosis of the AA type and found similar staining properties. It should be emphasized that the condition was well known among pathologists before Virchow, but under other names. Amyloid means "starch-like" (amylon or amylum is starch in Greek and Latin, respectively), but only 5 years after the term amyloid had been coined, it was found that the deposited substance was mainly proteinaceous [9].

Thus, after the mistake with corpora amylacea, Virchow and others studied "real amyloid," most likely AA amyloidosis, the most prevalent systemic amyloidosis at that time. Although there are variations, in comparison to some other systemic amyloidoses, particularly AL amyloidosis, AA has a fairly constant tissue distribution pattern. Patients with a diverse amyloid distribution and symptoms that were most probably due to AL amyloidosis were described at an early date [10]. The term "senile amyloidosis" was coined by Soyka, who described a condition that was most likely senile systemic amyloidosis [11], today known to be derived from wild-type transthyretin (TTR) and therefore now called "wild-type ATTR (ATTRwt) amyloidosis" according to recommendations by the Nomenclature Committee of the International Society of Amyloidosis [12]. The term "primary generalized amyloidosis" was well described by Lubarsch in 1929 [13] although single cases probably had been reported earlier [14]. Localized,

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tumor-like amyloid had already been described in the nineteenth century and, similar to a large number of other medical conditions, careful and exact descriptions can be found in German literature from this period (e.g., see [15]). Cases of hereditary amyloidosis, which today is known to be a very heterogeneous group of disorders with varying biochemical nature and genetic background, and spread throughout the world, were also described [16]. An account of the most common form of hereditary amyloidosis, that is derived from TTR, was published in 1952, almost 100 years after the term amyloid was first coined [17]. The exact nature of this amyloid as derived from TTR was elucidated in 1978 [18]. This form of ATTR amyloidosis is found in many parts of the world and had been demonstrated to be due to a missense mutation [19]. Since then, a great number of different mutations in the TTR gene have been found, most of them associated with systemic amyloidosis and with varying phenotypes [20–22]. Later, several additional hereditary amyloidoses of various biochemical types were described, almost exclusively dominant hereditary, and due to missense mutations. Surprisingly, as late as 2008, a form of systemic amyloidosis that is not extremely rare was characterized [23].

Biochemical Nature of Amyloid

Even before the seminal discovery that amyloid has a distinctive fine fibrillar structure [24] in which the protein has adopted a high degree of β-sheet structure with the molecules regularly arranged and bound to each other by hydrogen bonds [25], an organized substructure for the hyaline amyloid had been proposed [26, 27]. Most important of all were the studies by Benditt and Eriksen, who showed that the deposits present in secondary systemic amyloidosis are characterized by one specific protein, which they called "protein A" (now protein AA) while the proteins in other types of amyloidosis were preliminarily called "protein B" [28]. They remarked, wisely, that there may be several B proteins. The techniques used to extract amyloid fibrils, dissolve them in chaotropic agents, and purify the major proteins for characterization by Edman degradation revolutionized our comprehension of amyloid. Instead of being nonspecific degenerative materials, the amyloids were found to be polymers of highly specific proteins [29, 30]. At the end of the 1970s, four major amyloid fibril proteins had been described [18, 29–31]. Today, 31 different proteins have been accepted as major amyloid fibril proteins (Table 1.1).

Diagnosis of Amyloidosis

The introduction of the cotton dye Congo red was a great step forward in the identification of amyloid [32]. The dye was synthesized in 1883 for the textile industry, and there is evidence that its name has a firm connection with a political conference, held in Berlin in 1884–1885, where the colonial powers discussed Central Africa; thus, the name has nothing to do with the origin of the dye [33]. Congo red was introduced as an intravenous test for systemic amyloidosis in patients, since deposits in the tissues bound the dye, and enhanced plasma clearance was taken as a sign of disease [34]. A quite substantial amount of Congo red was injected, often more than 10 ml of a 1 % aqueous solution of the dye [35]. Although unreliable and potentially dangerous, this test seems to have continued in use until the 1970s [36, 37]. This can seem surprising to us now, when some laboratories hesitate to utilize Congo red in histopathology due to its potential to be carcinogenic [38]. As early as 1884, the dye was tested as a histological stain [39], but it was not until 1927 that its properties as an amyloid stain were described [26]. At that time, a very important property of amyloid stained with Congo red was identified: namely, the enhanced birefringence of amyloid in tissue sections viewed under polarized light [26]. In fact, this technique is still used in diagnostic work throughout the world. Diagnostic biopsies from organs showing symptoms had been used for some time (for examples and references, see [40]), but it was not until 1960 that the well-known rectal biopsy was introduced as a diagnostic tool for systemic amyloidosis [41]. This was a most important advance, since

Table 1.1 Amyloid fibril proteins and their precursors in human[a]

Fibril protein	Precursor protein	Systemic and/or localized	Acquired or hereditary	Target organs
AL	Immunoglobulin light chain	S, L	A, H[e]	All organs except CNS (Local AL amyloidosis may occur)
AH	Immunoglobulin heavy chain	S, L	A	All organs except CNS (Local AH amyloidosis may occur)
AA	(Apo) Serum amyloid A	S	A	All organs except CNS
ATTR	Transthyretin, wild type	S	A	Heart mainly in males, Ligaments, Tenosynovium
	Transthyretin, variants	S	H	PNS, ANS, heart, eye, leptomeninges
Aβ2M	β2-Microglobulin, wild type	L	A	Musculoskeletal system
	β2-Microglobulin, variant	S	H	ANS
AApoAI	Apolipoprotein A I, variants	S	H	Heart, liver, kidney, PNS, testis, larynx (C terminal variants), skin (C terminal variants)
AApoAII	Apolipoprotein A II, variants	S	H	Kidney
AApoAIV	Apolipoprotein A IV, wild type	S	A	Kidney medulla and systemic
AGel	Gelsolin, variants	S	H	PNS, cornea
ALys	Lysozyme, variants	S	H	Kidney
ALECT2	Leukocyte chemotactic factor-2	S	A	Kidney, primarily
AFib	Fibrinogen α, variants	S	H	Kidney, primarily
ACys	Cystatin C, variants	S	H	PNS, skin
ABri	ABriPP, variants	S	H	CNS
ADan[b]	ADanPP, variants	L	H	CNS
Aβ	Aβ protein precursor, wild type	L	A	CNS
	Aβ protein precursor, variant	L	H	CNS
APrP	Prion protein, wild type	L	A	CJD, Fatal insomnia
	Prion protein variants	L	H	CJD, GSS syndrome, Fatal insomnia
ACal	(Pro)calcitonin	L	A	C-cell thyroid tumors
AIAPP	Islet amyloid polypeptide[c]	L	A	Islets of langerhans, Insulinomas
AANF	Atrial natriuretic factor	L	A	Cardiac atria
APro	Prolactin	L	A	Pituitary prolactinomas, aging pituitary
AIns	Insulin	L	A	Iatrogenic, local injection
ASpc[d]	Lung surfactant protein	L	A	Lung
AGal7	Galectin 7	L	A	Skin
ACor	Corneodesmosin	L	A	Cornified epithelia, Hair follicles
AMed	Lactadherin	L	A	Senile aortic, Media

(continued)

Table 1.1 (continued)

Fibril protein	Precursor protein	Systemic and/or localized	Acquired or hereditary	Target organs
AKer	Kerato-epithelin	L	A	Cornea, hereditary
ALac	Lactoferrin	L	A	Cornea
AOAAP	Odontogenic ameloblast-associated protein	L	A	Odontogenic tumors
ASem1	Semenogelin 1	L	A	Vesicula seminalis
AEnf	Enfurvitide	L	A	Iatrogenic, local injection

From Sipe et al. [12]
[a]Proteins are listed, when possible, according to relationship. Thus, apolipoproteins are grouped together, as are polypeptide hormones
[b]ADan is the product of the same gene as ABri
[c]Also called amylin
[d]Not proven by amino acid sequence analysis
[e]Benson et al. [46]

before 1950, only 7 % of patients were diagnosed before death [42]. The technique most commonly used today, biopsy from subcutaneous fat tissue, was developed a decade later in the 1970s [43]. Since then, biopsy techniques have been further expanded to include determination of the biochemical nature of an amyloid deposit; today, this is considered to be a necessary step in the clinical handling of patients with systemic amyloidosis. Although a biopsy with microscopic demonstration of amyloid is still the only way to obtain a diagnosis, a method for visualizing amyloid in vivo based on the ubiquitously present serum amyloid P (SAP) component has been successfully developed [44].

Nomenclature

What Is Amyloid?

Most of us working with amyloid believe that we know what amyloid is. However, when reading the modern scientific literature, one can begin to hesitate since the word is now used in different ways. In clinical pathological practice, amyloid is a homogenous extracellular deposit that stains specifically with Congo red, shows clear yellow to green birefringence in polarized light, and has a characteristic fine-fibrillar ultrastructure. It should be stressed that the Congo red staining should be performed under strictly controlled conditions; otherwise other tissue components may also be stained. Other staining methods may be used but are generally not regarded as being as specific. In addition to this "classical" amyloid, fibrils made in vitro that possess some amyloid properties are often called amyloid in the biochemical literature. Even inclusion bodies, which may or may not stain with Congo red, are often referred to as amyloid. Examples of such inclusions are the intranuclear aggregates in Huntington's disease and Lewy bodies in Parkinson's disease. In clinical pathology, it is wise to stay within the classical definition.

Older Nomenclatures

Over the decades, there have been a number of different nomenclatures. The most prevalent prior classification stems from 1935 and divides the amyloidoses into four groups: primary, secondary, tumor-forming, and the amyloidosis associated with multiple myeloma. Unfortunately, it is sometimes still in use, which creates unnecessary confusion (Table 1.2). For a long time, it was widely discussed whether the localized, often small, but dispersed deposits with amyloid staining properties are indeed "true" amyloid or not, and the designation "para-amyloid" was sometimes used to describe them [16, 45]. This name should be avoided.

Table 1.2 Terminology often used in the older literature which should now be abandoned

Designation to avoid	Reason for avoidance
Familial amyloidotic cardiomyopathy (FAC)	It is a systemic amyloidosis with deposits in other tissues as well
Familial amyloidotic polyneuropathy (FAP)	It is a systemic amyloidosis with deposits in other tissues as well
Primary amyloidosis	An old, inexact term. It was used for AL amyloidosis but also for hereditary amyloid forms
Secondary amyloidosis	An old, inexact term. It was used for AA amyloidosis but often also for amyloidosis with multiple myeloma and sometimes for localized amyloid in tumors
Senile cardiac amyloidosis	This term was used for wild type ATTR (senile systemic) amyloidosis. Although cardiac symptoms often predominate, it is a systemic disease
Senile systemic amyloidosis	This term was coined when the nature of the amyloid protein was unknown. Since the disease sometimes affects persons in their 50s, wild-type TTR amyloidosis is to be preferred

Modern Amyloid Nomenclature

At the international symposium on amyloidosis in 1974 in Helsinki, Finland, a committee was organized to oversee the nomenclature of the amyloid fibril proteins. Although only two amyloid proteins were known at the time (AA and AL), this decision proved prescient given the situation that pertains today, when at least 31 amyloid fibril proteins have been identified. The committee is now part of the International Society of Amyloidosis (ISA) and meets at each ISA symposium. On those occasions, the nomenclature committee updates the accepted amyloid fibril protein table and the updated nomenclature is published in the journal Amyloid. The latest nomenclature [12] is given in Table 1.1.

All amyloid proteins are designated as A plus a suffix, identifying the nature of the precursor. Thus, immunoglobulin light chain amyloid protein is called AL (A + immunoglobulin light chain), transthyretin amyloid is ATTR, and so on. Any substitutions are indicated by a suffix, identifying the position in the mature protein flanked by the normal amino acid residue to the left and the variant to the right. If deemed important, the position based on the transcript may be given in parenthesis. Consequently, the most common transthyretin variant protein is designated ATTRVal30Met where valine is the normal residue and this is substituted by methionine and the translated gene product (p.TTRVal50Met) [12]. Amyloid deposits, and diseases, should be named after their main fibrillar protein and should also be identified as localized or systemic and whether they are sporadic or hereditary. Old designations, such as primary or secondary, typical or atypical, should be abandoned (Table 1.2). Familial amyloidotic polyneuropathy (FAP), which is very often used for hereditary ATTR amyloidosis, particularly with the Val30Met mutation, is also a designation that should be avoided although the name may be too well established to be replaced.

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2 Amyloid Diseases at the Molecular Level: General Overview and Focus on AL Amyloidosis

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General Overview

In the vast and heterogeneous group of disorders collectively termed "amyloidoses", a protein or peptide loses, or fails to acquire, its physiologic, functional folding and, in its misfolded state, undergoes fibrillization and extracellular accumulation in the form of amyloid deposits [1]. These deposits display distinctive chemical, ultrastructural and tinctorial properties, which allow for their correct identification and help to distinguish amyloidoses from other pathologic conditions similarly characterized by abnormalities in protein conformation or metabolism [2, 3]. The process of amyloid formation and deposition ultimately results in tissue damage and organ dysfunction and is the pathological substrate of numerous clinical conditions, local or systemic, acquired or hereditary, extremely rare or rather frequent, which may represent a diagnostic challenge for pathologists and clinicians [1].

What Makes a Protein Amyloidogenic?

Based on extensive experimental evidence, any protein, either folded or natively unstructured, is predicted to form amyloid fibrils in vitro under appropriate circumstances [4]. However, only a limited number of proteins do so in vivo. The reason for this discrepancy is not fully understood, but it is assumed that the mild physico-chemical conditions of living systems and the existence of the orchestrated network of protein homeostasis (or proteostasis) contribute to preserve the folding state and function of the proteome [5, 6]. Nonetheless, there are situations where such constraints are no longer effective and, as a result, a protein or peptide aggregates and becomes toxic [1].

Decades of research and clinical observations have identified a few elements associated with the ability of a protein to form amyloid in vivo and give rise to disease (Fig. 2.1), and these include: (1) a pathologic and sustained increase in the concentration of a protein with increased propensity to

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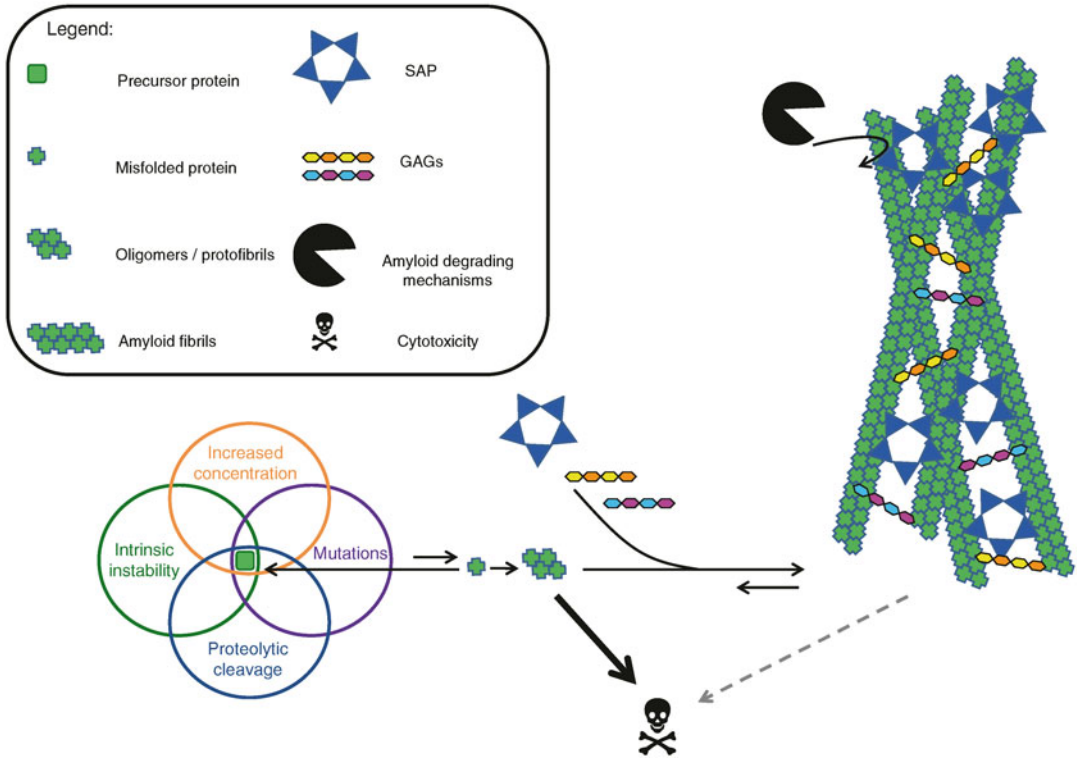

Fig. 2.1 Mechanisms of amyloid formation and toxicity. Intrinsic instability, increased concentration, mutations, proteolytic cleavage or a combination thereof can favour the conversion of the amyloidogenic precursor into its misfolded conformation. This process results in the formation of prefibrillar species and ultimately amyloid fibrils. Oligomers in equilibrium with amyloid fibrils are believed to exert a direct cytotoxic effect. Interactions with tissue factors, including glycosaminoglycans (*GAGs*) and serum amyloid P component (*SAP*), contribute to the formation and persistence of amyloid deposits, which contribute to the functional impairment of affected organs

aggregate; (2) an inherited modification of a protein primary sequence; (3) a proteolytic remodelling of a protein; (4) an intrinsic propensity to acquire a pathologic conformation [1].

More often, a combination of these factors actually determines the amyloidogenicity of an individual protein:

1. Increased concentration

   Some proteins can form amyloid only at persistently increased concentrations, as is the case for the acute phase reactant serum amyloid A (SAA) in chronic inflammations [7] and for wild-type β_2-microglobulin in patients with end-stage renal failure, where kidney-mediated clearance of this protein from the circulation is not efficiently replaced by dialysis [8].

2. Mutations

   Mutations, although frequently consisting of only a single amino acid substitution, can dramatically destabilize a protein and favour its aggregation and subsequent amyloid deposition—as demonstrated for cystatin C [9], transthyretin [10], lysozyme [11], gelsolin [12], apolipoprotein A-I [13] and β_2-microglobulin [14]. Such mutations (reported in a dedicated online registry [15], at www.amyloidosismutations.com) are the molecular substrate for a group of conditions that are collectively termed hereditary amyloidoses [16].

3. Proteolytic cleavage

   In the majority of cases, only a limited portion of the amyloidogenic precursor is actually found in amyloid deposits. The enzymes responsible for the proteolytic

remodelling of the precursor are largely unknown. They are postulated to be extracellular and whether proteolysis occurs before or after the monomer has been incorporated within the amyloid fibrils is currently a matter of speculation [1]. There have been only a few cases where such enzymes have been unambiguously identified and the proteolysis has been shown to take place before amyloidogenesis: the enzyme furin, residing in the Golgi apparatus, cleaves ABri [17] and gelsolin [18] and the membrane proteases β- and γ-secretases release amyloid-β (Aβ) peptides from the amyloid precursor protein (APP) in Alzheimer's disease [19]. Remarkably, several mutations in genes encoding APP or presenilins, members of the γ-secretases, can strongly favour the amyloidogenic proteolytic cleavage of APP and are hence associated with familial forms of the disease [20].

4. Intrinsic instability

There are a few proteins that are believed to display an intrinsic propensity to adopt more than one conformation, a feature strongly influenced by hydrophobicity, electric charge and secondary structure [5] and which might—in the long term—lead to amyloid formation. Typical examples of this class of amyloidogenic proteins are transthyretin and apolipoprotein A-I, both associated, in their wild-type conformation, with ageing-related amyloid deposition [21–24]. The intrinsic instability of both proteins is further increased by pathogenic mutations associated with hereditary forms of the disease [25, 26]. Intriguingly, the propensity of wild-type transthyretin to form amyloid is also enhanced by exposure to a mutant disease-related form of the protein. In individuals heterozygous for one of the pathogenic mutation, both the mutated and the wild-type transthyretin are found in deposits [27–30], and this phenomenon explains why cardiac amyloid deposits can further progress in patients for whom liver transplantation has minimized the production of the mutant protein [27–29].

The inherent amyloidogenicity of a specific protein, per se, is not sufficient to explain the likelihood that amyloid deposition finally occurs in vivo. For example, only a minority of patients with long-lasting inflammation and subsequent elevation of SAA levels develop AA amyloidosis [31, 32]. Similarly, the disease-associated Val30Met mutation of transthyretin shows significant differences in penetrance and clinical presentation among different ethnic groups and geographic areas [33]. Other factors, both environmental and genetic, are probably involved and understanding their roles will certainly improve our current knowledge of amyloidogenesis and, hopefully, pave the way to the discovery of novel therapeutic approaches.

Common Constituents of Amyloid Deposits

Amyloid deposits are classified and named based on the chemical nature of the most abundant fibril protein, according to internationally adopted nomenclature guidelines [34]. However, additional components are regularly found in the deposits (Fig. 2.1), including proteoglycans [35], glycosaminoglycans [36], and the pentraxin family member, serum amyloid P component (SAP) [37]. Proteoglycans and glycosaminoglycans can contribute to the formation and stabilization of amyloid fibrils and, through their interaction with extracellular matrix elements, influence the localization of amyloid deposits [1]. The SAP component binds avidly and reversibly to all types of amyloid [38], a property which allows for the clinical use of a radiolabeled version of this protein for scintigraphic imaging of amyloid deposits [39, 40], and which renders amyloid resistant to degradation [41]. This latter feature, and the observation that mice genetically devoid of SAP show a delayed deposition of experimentally-induced amyloid [42], is the rationale for the development of therapeutic approaches aimed at reducing circulating and amyloid-associated SAP through small palindromic drugs and antibodies [43, 44], which have already started to enter into the clinical phase of testing [44].