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# Amyloid A Amyloidosis Secondary to Rheumatoid Arthritis

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## 1. Introduction

Amyloids are insoluble fibrous protein aggregates sharing specific structural traits. Abnormal accumulation of amyloid in organs may lead to amyloidosis, and may play a role in various diseases. The name *amyloid* comes from the early mistaken identification of the substance as starch (*amylum* in Latin), based on crude iodine-staining techniques. For a period, it was debated whether or not amyloid deposits were fatty or carbohydrate deposits until it was finally found that they were, in fact, deposits of proteinaceous mass. The underlying molecular abnormalities may be either acquired or hereditary and more than 20 different proteins can form clinically or pathologically significant amyloid fibrils *in vivo*. Current nomenclature lists of amyloid fibril protein have been provided from the nomenclature committee of the International Society of Amyloidosis.

Amyloidosis is a disorder of protein conformation and metabolism that results in the deposition of insoluble amyloid fibrils in tissues, which causes organ dysfunction; systemic amyloidosis is characterized by failure of various organs and the presence of amyloid precursor protein in the serum. Reactive amyloid A (AA) amyloidosis is one of the most severe complications of several chronic disorders, particularly rheumatoid arthritis (RA), and indeed, most patients with reactive AA amyloidosis have an underlying rheumatic disease. An extra-articular complication of RA, AA amyloidosis is a serious, potentially life-threatening disorder caused by deposition in organs of AA amyloid fibrils, which derive from the circulatory acute-phase reactant, serum amyloid A protein (SAA). AA amyloidosis secondary to RA is thus one of the intractable conditions found in patients with collagen vascular diseases and is an uncommon yet important complication of RA.

## 2. Reactive systemic amyloid A (AA) amyloidosis

### 2.1 Associated conditions

Several chronic inflammatory disorders induce reactive systemic AA amyloidosis as one of the serious complications. Organ and tissue damage results from the extracellular aggregation of proteolytic fragments from SAA as insoluble AA amyloid fibrils. AA amyloidosis occurs in association with chronic inflammatory disorders, chronic local or systemic microbial infections, and occasionally malignant neoplasias. In Western countries, the most frequent predisposing conditions are rheumatic diseases. AA

amyloidosis complicates about 6 % in patients with RA, although the reasons why the incidence is lower in the United States than in Europe and Japan are not clear. Tuberculosis and leprosy are important causes of AA amyloidosis where these infections are endemic. Chronic osteomyelitis, bronchiectasis, chronically infected burns, and decubitus ulcers as well as the chronic pyelonephritis of paraplegic patients are other well-recognized associations. Castleman's disease, Hodgkin's lymphoma and renal carcinoma, which often cause fever, other systemic symptoms, and a major acute phase response, are the malignancies most commonly associated with systemic AA amyloidosis.

<b>Rheumatic disorders</b>	Acne conglobata
Rheumatoid arthritis	Leprosy
Juvenile idiopathic arthritis	Chronic pyelonephritis in paraplegics
Ankylosing spondylitis	Whipple's disease
Psoriasis and psoriatic arthropathy	Decubitus ulcers
Reiter's syndrome	
Adult onset Still's disease	<b>Neoplasias</b>
Behçet's disease	Hepatocellular carcinoma
Crohn's disease	Renal carcinoma
Hereditary autoinflammatory syndrome	Lung adenocarcinoma
	Castleman's disease
<b>Chronic infections</b>	Hodgkin's lymphoma
Bronchiectasis	Basal cell carcinoma
Tuberculosis	Hairy cell leukemia
Osteomyelitis	Gut carcinoma

Table 1. Conditions associated with reactive systemic amyloid A amyloidosis.

Persistent inflammation supported by chronic diseases, such as rheumatic disorders, chronic infections, and neoplasias, is associated with persistently increased release of proinflammatory cytokines. [Modified from Pepys, M.B. & Hawkins, P.N. (2003). Amyloidosis, In: *Oxford Textbook of Medicine*, Warrell, D.A., Cox, T.M., Firth J.D. & Benz E.J., (Eds), pp. 162-173, Oxford University Press, ISBN-10 0192629220, London, UK.]

## 2.2 Clinical features

AA amyloid fibril involves the viscera but may be widely disturbed without causing clinical symptoms. The most common presentation is renal, with non-selective proteinuria due to glomerular deposition, and nephrotic syndrome may develop before progression to endstage renal failure. The second most common is with organ enlargement, such as hepatosplenomegaly or thyroid goiter, with or without overt renal abnormality, but in any case AA amyloid fibril deposits are almost always wide spread at the time of presentation. Involvement of the heart and gastrointestinal (GI) tract is frequent, but rarely causes functional impairment.

AA amyloidosis may become clinically evident early in the course of associated disease, but the incidence increases with duration of the primary condition. For most patients the prognosis is closely related to the degree of renal involvement and the efficacy of treatment of the underlying inflammatory condition. Availability of chronic haemodialysis (HD) and transplantation prevents early death from uremia *per se*, but AA amyloid fibril deposition in extrarenal tissues is responsible for a less favorable prognosis than other causes of endstage renal failure.

### 3. Pathophysiology of AA amyloidosis secondary to RA

RA is a representative of collagen vascular diseases, a group of systemic chronic progressive inflammatory disorders based on immunological disharmonies. Typically, AA amyloidosis will occur in those patients, who have sustained long-standing active disease. Therefore, AA amyloidosis may not be suspected during the early course of a potential disease. In rare case, however, it may occur within a year of a clinically apparent inflammatory disease. AA amyloidosis does not occur in the absence of an acute-phase response or without elevated serum SAA levels. Thus, a sustained high concentration of SAA is a prerequisite for AA amyloidogenesis (Fig. 1). AA amyloidosis seems to develop in only a minority of patients with active, long-standing inflammatory diseases, which indicate that significant disease-modifying factors may help modulate the occurrence of AA amyloidosis, the rate of AA amyloid fibril deposition in tissues, or induction of tissue damage in this form of amyloidosis. The persistent inflammation caused by RA is associated with increased release of the proinflammatory cytokines interleukin (IL)-1, IL-6, and tumor necrosis factor (TNF)  $\alpha$ . These cytokines induce a markedly increased synthesis of the acute-phase protein SAA by hepatocytes, the concentration of which can be 100 to 1000-fold higher than normal.

The progressive nature of AA amyloidosis largely reflects the persistent nature of the activity of the underlying conditions and, due to fluctuations of disease activity, not all patients show evidence of an acute-phase response at the very time of diagnosis. Although it is still unknown exactly how the pathophysiological functions of SAA are associated with the pathogenesis of AA amyloidosis, there appears a certain subset of patients, who are prone to process SAA into AA amyloid fibrils under different factors, such as proteases, proteoglycans, serum amyloid P component (SAP).

Human AA amyloid fibril deposits consist mostly of N-terminal fragments of SAA, which points to proteolytic cleavage of the precursor being a key event in pathogenesis. These AA amyloid fibril fragments almost exclusively derive from SAA1, which suggests that specific amino acid residues may contribute to a misfolding propensity or that differences in the catabolism exist. The fate of SAA depends largely on its interactions with cellular and extracellular tissue components. Mononuclear phagocytes are involved in SAA catabolism through endocytosis and trafficking to lysosomes, where SAA undergoes degradation.

A role of mononuclear phagocytes in initiating AA amyloid fibril formation was originally postulated because of the presence of AA amyloid fibrils in intracellular vesicles and close to cell membranes in amyloid-laden tissues. These phenomena were subsequently demonstrated in cell culture models. Studies of human monocyte cell lines showed the accumulation of newly formed AA amyloid fibrils in intracellular lysosomal compartments, which indicated that aberrant processing of SAA is relevant for the pathogenesis of AA amyloidosis. A role of monocytes in mediating prion-like transmissibility of AA amyloid fibrils acting as seeds was also suggested. Furthermore, SAA binds specifically to the heparan sulfate (HS)-

glycosaminoglycan complex, a common constituent of all kinds of amyloid deposits that was demonstrated to facilitate conformational conversion of a precursor to a  $\beta$ -plated sheet structure. Also, the SAA-HS interaction promotes AA fibrillogenesis by acting as a scaffold for fibril assembly. Both SAA and AA were reportedly biosynthesized by blood or tissue matrix metalloproteinases (MMPs) and cathepsin D, and this process may in part result in amyloidogenic peptide formation. AA amyloid fibrils would form within lysosomes in macrophages because of disturbed SAA processing. As another factor in amyloid metabolism, mannose-binding lectin (MBL) is a liver-derived protein involved in lectin-mediated complement activation, and lower serum MBL levels are thought to lead to reduced macrophage function. MBL-2 polymorphism determines the blood MBL level and is associated with the role of mononuclear phagocytes in amyloid metabolism. Susceptibility to AA amyloidosis has been linked to mononuclear phagocyte function, and SAA processing by monocytes under stimulation with IL-1 or interferon was reportedly disturbed in patients with AA amyloidosis, which suggests inflammation-induced abnormalities in monocyte function. Although synthesis of AA amyloid fibrils may be closely related to abnormal processing of SAA and AA in macrophages, the affinity of AA amyloid fibrils for different organs largely accounts for the heterogeneity of such AA amyloid deposits, which still requires explanation. In addition, MMPs contribute to proteolytic remodeling of SAA, with production of amyloidogenic species. Tissue glycosaminoglycans facilitate formation and local deposition of AA amyloid fibrils, along with other amyloidogenic substances, which may be protected from clearance by interaction with the pentraxin SAP. The main target organ of deposition is the kidney, with resulting significant proteinuria and progression toward renal failure. In cases of GI AA amyloidosis, decreased GI motility causes bacterial overgrowth, bile acid deconjugation, and consequently diarrhea, steatorrhea, and severe malabsorption.

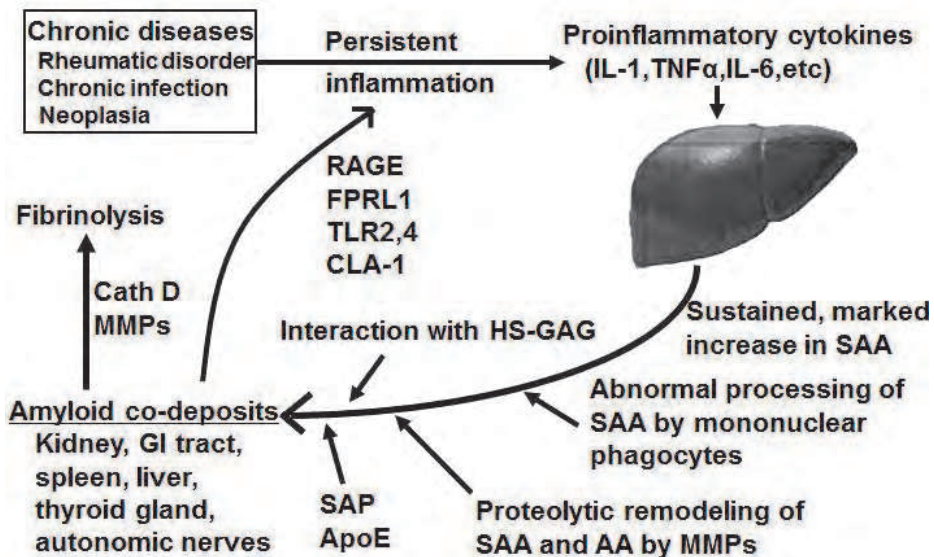


Fig. 1. Pathogenic events involved in amyloid A (AA) amyloidogenesis.

Persistent inflammation caused by chronic diseases is associated with a continuous increase in proinflammatory cytokines (IL-1: interleukin-1, TNF $\alpha$ : tumor necrosis factor  $\alpha$ , IL-6: interleukin-6). These cytokines induce markedly increased synthesis of the acute phase-phase protein serum amyloid A protein (SAA). Abnormal processing of SAA by mononuclear phagocytes is thought to initiate amyloidogenic peptide production and formation of amyloid A (AA) amyloid fibrils in lysosomes. Matrix metalloproteinases (MMPs) and cathepsin D (Cath D) contribute to proteolytic remodeling of SAA, with production of amyloidogenic species. AA fibrils, plus serum amyloid P component (SAP) and apolipoprotein E (ApoE), and after interaction with heparan sulfate-glycosaminoglycans (HS-GAG), deposit in multiple organs. SAA and AA participate in inflammation through receptors on inflammatory cells. RAGE: receptor for advanced glycation end products; FPR1: formyl peptide receptor-like 1; TLR2, 4: toll-like receptor 2 and 4; CLA-1: CD36 and LIMPII analogous-1, human orthologue of the scavenger receptor class B type I (SR-BI); GI: gastrointestinal. [From Nakamura, T. (2011). Amyloid A amyloidosis secondary to rheumatoid arthritis: pathophysiology and treatment. *Clinical and Experimental Rheumatology*, ISSN 0392-856X Accepted on March 8, 2011. (This article is now on process of publication.)]

#### 4. SAA

SAA is produced primarily in the liver under proinflammatory cytokines stimulation; it is also a central acute-phase protein, like C-reactive protein (CRP). SAA complexes with a carrier protein, being transported into serum by high-density lipoprotein (HDL) in combination with apolipoprotein E, and plays an important role in enterohepatic cholesterol circulation. In obese individuals, the frequency of SAA mRNA expression and blood SAA level are both significantly high. Thus, the biologically versatile SAA has a significant relationship with lipid metabolism.

Human SAA composes 104 amino acids, and the four SAA-encoding genes are on chromosome 11p15.1. SAA contains three subtypes with different primary structures-SAA1, SAA2 and SAA4-which make up two groups. Those in the first group, SAA1 and SAA2, serve as acute-phase proteins. In the second group, SAA4 is expressed constitutively in plasma, is synthesized by different organs and tissues, and is not an acute-phase protein. Inflammation induces SAA1 and SAA2 genes and their expression but not expression of SAA3 (a pseudogene) and SAA4. SAA4 encodes a structural protein of HDL. Because of allele polymorphism, SAA1 has three isoforms (SAA1.1, SAA1.3, and SAA1.5) and SAA2 has two (SAA2.1 and SAA2.2), and the serum level of SAA is affected by SAA1 polymorphism. Expression of the SAA1.5 allele is associated with high blood SAA levels, and SAA1.5 has a high affinity for HDL. The primary structures of SAA1 and SAA2 have a 93% amino acid homology. SAA4 shows a 50% homology with the other SAA acute-phase proteins. Thus, acute-phase SAA has multiple patterns of protein polymorphism.

The normal functions of SAA are not known fully, although modulating effects on reverse cholesterol transport and on lipid functions in the microenvironment of inflammatory foci have been proposed. Other reports of potent cell regulatory functions of isolated denatured delipidated SAA have yet to be confirmed with physiological preparations of SAA-rich HDL. Regardless of its physiological role, the behaviour of SAA as an exquisitely sensitive acute phase protein with an enormous dynamic range

makes it an extremely valuable empirical clinical marker. It can be used to monitor objectively the biological disease responses. Furthermore, routine monitoring of SAA should be an integral part of the management of all patients with AA amyloidosis or disorders predisposing to it, as control of the primary inflammatory process in order to reduce SAA production is essential if AA amyloidosis is to be halted, enabled to regress, or prevented.

#### 4.1 SAA1.3 allele and genetic factors related to AA amyloidosis

Genetic factors seem to be involved in the prevalence and prognosis, and some factors would have an influence on the development and length of the latent period in AA amyloidosis secondary to RA. The frequency of SAA1 gene polymorphism and that of SAA1 alleles differ among races and regions worldwide. Three main SAA1 alleles-SAA1.1, SAA1.3, and SAA1.5-are defined by two single-nucleotide polymorphisms (SNPs) in exon 3, resulting in two amino acid differences at positions 52 and 57, respectively. In Japanese people, the three alleles occur at approximately the same rate. The association between AA amyloidosis and the SAA1 genotype was first observed in Japanese patients with RA, in whom homozygosity for the SAA1.3 allele proved to be a risk factor. The SAA1.3/1.3 genotype in Japanese patients with RA was associated with a shorter latency period before AA amyloidosis onset and more severe AA amyloidosis-related symptoms; it was also a univariate predictor of survival. Thus, the SAA1.3 allele was a risk factor for AA amyloidosis, had an association with clinical severity in this population, and served as an indicator of poor prognosis. Among Caucasians, AA amyloidosis was often observed in SAA1.1 homozygous individuals, and the SAA1.1 allele was thought to be a risk factor for AA amyloidosis.

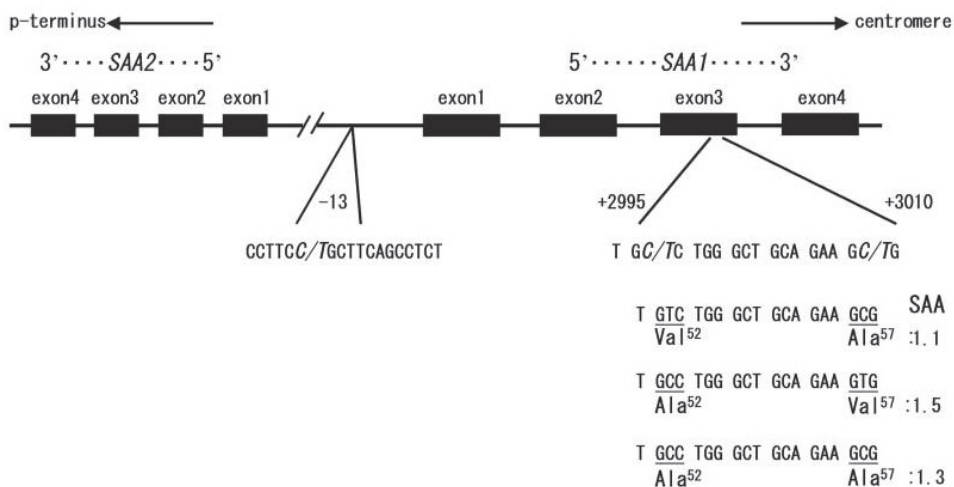


Fig. 2. Partial genomic structure and location of single nucleotide polymorphism (SNPs) in the SAA1 gene. [From Nakamura, T. (2007). Amyloid A amyloidosis secondary to rheumatoid arthritis: an uncommon yet important complication. *Current Rheumatology Reviews*, Vol. 3, No. 3, (August 2007), pp. 231-241, ISSN 1573-3971.]

With regard to SNPs of the *SAA1* gene promoter region, -13T is a high-risk factor for AA amyloidosis in Japanese patients with RA, with -13T/T and -13T/C being closely associated with AA amyloidosis than is -13C/C. Because *SAA1* gene polymorphism affects both blood SAA levels and SAA transcriptional activity in hepatocytes, differences in *SAA1* proteolysis by MMPs indicate a close association between *SAA1* gene polymorphism and onset of AA amyloidosis. However, the mechanism by which *SAA1* gene polymorphism is related to the onset of AA amyloidosis and the reason for ethnic differences in disease-susceptible SNPs are yet unknown.

The most extensively studied genetic marker in RA is *HLA-DRB1*. Several *HLA-DRB1* alleles share a common amino acid sequence, which is commonly called the shared epitope (SE), in the third hypervariable region of the molecule. Recently, it is reported that SE associates with not only the disease susceptibility of RA, but also the RA chronicity, severity, and extra-articular manifestations, in particular AA amyloidosis in RA patients. It is of particular importance that DRB1\*04SE has an increased risk of AA amyloidosis in RA and a higher prevalence of double \*04SE of *HLA-DR4* is demonstrated in patients with AA amyloidosis secondary to RA.

The *SAA2* gene is located in p-terminus side from the *SAA1* gene. Positions of nucleotides in the sequence of *SAA1* are numbered relative to transcription start site of exon 1. The site of SNPs at both 2995 and 3010 underlined, leading to the *SAA1* protein polymorphism.

#### 4.2 SAA receptors

Several SAA receptors have been described, including CD36 and LIMPII analogous-1 (CLA-1); lipoxin A1 receptor/formyl peptide receptor-like 1 (FPRL1); tanis, a hepatic receptor activated by glucose; and toll-like receptor (TLR) 4 and TLR2. SAA reportedly activated rheumatoid synovial fibroblasts by binding to receptors for advanced glycation end products (RAGE). Also, an HDL receptor, the scavenger receptor class B type I (SR-BI), is expressed in RA synovial tissue and is apparently involved in SAA-induced inflammation in arthritis, including production of SAA-induced reactive oxygen species (ROS) and proliferation of fibroblasts. Although RAGE is a receptor for signal transduction with biological stimuli, neither SAA nor AA is incorporated into cells via this receptor. SAA serves as a chemoattractant for neutrophils, T cells, and monocytes via FPRL1 and induces production of CCL2, which is a prototype of the CC chemokine subfamily that has the highest chemotactic activity for monocytes. Because cytotoxic drugs and cytokine inhibitors affect AA amyloid deposits via their ability to suppress SAA production, anticytokine therapies, by inhibiting expression of RAGE, have been proposed to reduce interactions between AA amyloid fibrils and RAGE and thereby prevent AA-mediated cell toxicity.

SAA reportedly exerts cytokine-like actions, stimulates fibroblast differentiation, and elevates ROS production in neutrophils and fibroblasts. Furthermore, not only does SAA induce synthesis of MMP-1 and MMP-3 in synoviocytes and chondrocytes and increase production of MMP-9, but it is also involved in innate immunity via TLR4. Additional studies must identify specific receptor(s) involved in SAA-induced biological phenomena in health and disease.



## 5. Clinical features and diagnosis of AA amyloidosis secondary to RA

Clinical features of overt AA amyloidosis include long-term psychological distress of RA, markedly high disease activity, and significant inflammatory states. Although a high level of blood SAA is an important factor associated with AA amyloidosis onset, this factor does not always lead to AA amyloidosis in all patients. Several important factors, including the genetic one, are believed to modify the onset of AA amyloidosis. The actual incidence of AA amyloidosis in RA is still undefined and probably underestimated, in that distinguishing clinical and subclinical phase is quite difficult. A cohort study of patients with RA showed that fat AA amyloid deposits were not uncommon-16.3%-so subclinical AA amyloidosis may indeed be common in RA. Prevalent values of AA amyloidosis in RA patients in recent series ranged from 7% to 26%. The prevalence of clinical amyloidosis is likely to be lower, however, as it probably reflects differences in RA treatments and in genetic backgrounds.

AA amyloid deposits primarily target the kidneys, liver, and spleen, and AA amyloidosis becomes clinically overt mainly when renal damage occurs, manifesting as proteinuria, nephrotic syndrome, or impaired renal function. Proteinuria is the clinical sign that most often leads to diagnosis of AA amyloidosis in RA patients. Diagnosis must be based on histological examination of tissue specimen, such as from upper GI or rectal biopsy. Although mucosal biopsy of the upper GI tract to screen for AA amyloid fibril deposition is an easy, simple diagnostic method, antiulcer drugs may mask amyloidotic signs and symptoms in the GI tract, which may delay diagnosis of AA amyloidosis in RA patients. Positive Congo-red staining, susceptibility to oxidation with potassium permanganate, and green birefringence by polarization microscopy after Congo-red staining can confirm the presence of AA amyloid fibrils, however.

### 5.1 Predictive and prognostic factor of SAA1.3 allele genotype

Whereas there is startling variation in the frequency of AA amyloidosis worldwide, differences also exist for AA amyloidosis complicating RA. The reasons, however, for the marked geographic differences are still unclear. A closer relationship between SAA1.3 allele and AA amyloidosis secondary to RA is known, that is considered to be one of the factors responsible for the lower incidence of AA amyloidosis among Western patients with RA.

Though AA amyloidosis usually develops more than 10 years after the onset of RA, one RA patient complicated by severe AA amyloidosis was encountered just one year after the onset of RA, who was proven to be an SAA1.3 homozygote. Subsequent statistical analysis of a large number of RA patients with AA amyloidosis carrying SAA1.3 allele revealed that the risk for association of AA amyloidosis was about 8 times higher for SAA1.3 homozygotes than for the control group, and that homozygotes can develop AA amyloidosis very early after the onset of RA. It was thus shown that SAA1.3 allele serves not only as a risk factor for the association with AA amyloidosis, but also as a poor prognostic factor in Japanese patients with AA amyloidosis secondary to RA (Fig.3). The generalization of the importance of SAA1.3 allele as both risk and poor prognostic factor may be limited for some reasons; the lack of wide-range control studies, the ethnic differences in SAA gene polymorphism, the relative small number of patients with AA amyloidosis, and the heterogeneity in RA and healthy controls. Although a crude agreement of the significance of SAA1.3 allele in AA amyloidosis in Japanese RA patients is recognized, careful and discreet attitude should be required when judging the utility in between SAA1.3 allele and AA amyloidosis.

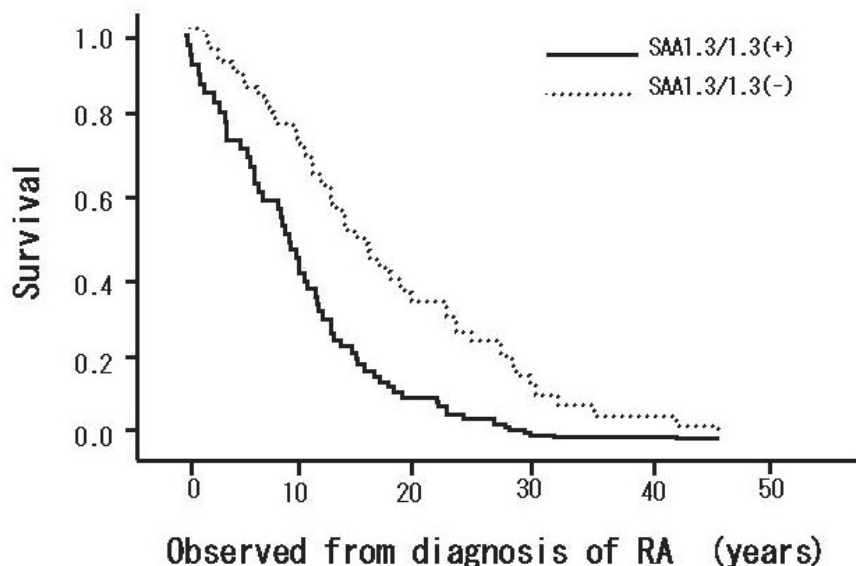


Fig. 3. Kaplan-Meier survival curve in RA disease course for RA patients with (continuous line) and without (dotted line) SAA1.3/1.3 ( $p=0.015$ , log-rank test). [From Nakamura, T., Higashi, S., Tomoda, K., Tsukano, M., Baba, S. & Shono, M. (2006). Significance of SAA1.3 allele genotype in Japanese patients with amyloidosis secondary to rheumatoid arthritis. *Rheumatology (Oxford)*, Vol. 45, No. 1, (January 2006), pp. 43-49, ISSN 1462-0324.]

## 5.2 Clinical diversity and severity

It is suggested that SAA1.3 allele genotype could be related with the symptomatic diversity and severity in patients with AA amyloidosis secondary to RA. Amyloidotic involvement of the urinary bladder is very rare but severe, which is often revealed massive macroscopic hematuria. Once massive hematuria occurs it would trend to be fatal. Secondary bladder AA amyloidosis should be considered as a possible cause of hematuria in patients with long-standing RA, especially carrying SAA1.3 allele, and as an important prognostic factor of RA.

## 5.3 Prevalence

Though subclinical phase of AA amyloidosis is defined by the formation of AA amyloid deposits in tissue without any clinical manifestation, it is very hard to distinguish clinical from subclinical phase. Obviously, it is difficult to evaluate the natural history of AA amyloid deposition and to know the length of this phase and its final outcome. The prevalence of clinical amyloidosis is likely to be lower. Taking the discordance between prevalence rates of clinical and subclinical AA amyloidosis into consideration, the wide variation in the prevalence of AA amyloidosis secondary to RA is due, in part, to the frequency for the marked geographic differences worldwide, possibly including genetic factors, and due to the lack of unified statistical studies for AA amyloidosis between races and districts. That seems to reach the notion AA amyloidosis would be complicated with RA more than so far estimated.

#### 5.4 Outcome

The survival time after the diagnosis of AA amyloidosis secondary to RA seems to be 4-5 year. These are, of course, dependent on the time at which AA amyloidosis is verified, which may differ considerably among patients. This partly explains the great individual variation in survival time observed, that leads us the notion that an active diagnostic attitude towards AA amyloidosis in patients with RA is advisable. Although the relationship among the production of AA precursor protein, the turnover of AA amyloid fibrils, and amyloidotic organ function is complex, it has been proved that outcome is favorable in AA amyloidosis when SAA concentration is maintained below 10 $\mu$ g/ml. The clinical risk factors associated with a poor survival included female, older age, a reduced serum albumin, and an increased serum creatinine concentration upon diagnosis of AA amyloidosis (Fig. 4). Renal involvement has been considered to be the most critical problem in patients with AA amyloidosis, and dominates the clinical picture in AA amyloidosis

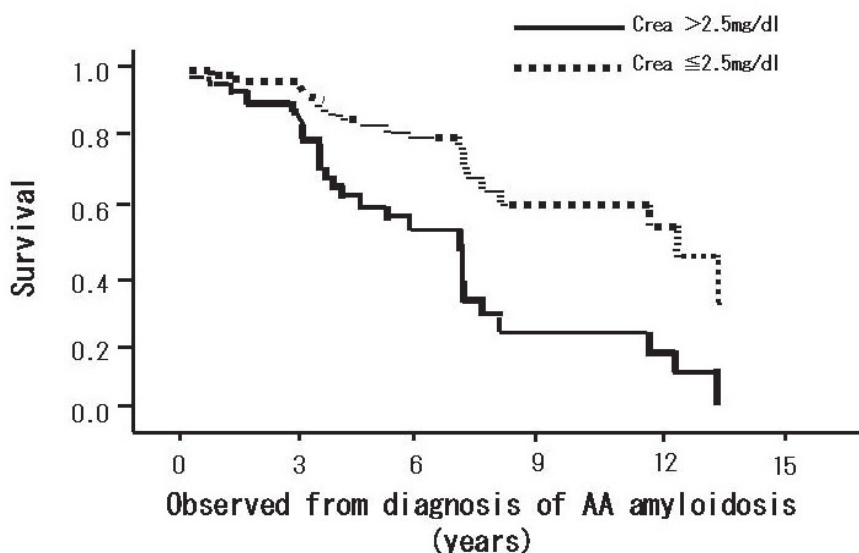


Fig. 4. Kaplan-Meier survival curve after diagnosis of AA amyloidosis for patients with serum creatinine >2.5 mg/dl (continuous line) and serum creatinine  $\leq$ 2.5 mg/dl (dotted line) ( $p=0.013$ , log-rank test). [From Nakamura, T., Higashi, S., Tomoda, K., Tsukano, M., Baba, S. & Shono, M. (2006). Significance of SAA1.3 allele genotype in Japanese patients with amyloidosis secondary to rheumatoid arthritis. *Rheumatology (Oxford)*, Vol. 45, No. 1, (January 2006), pp. 43-49, ISSN 1462-0324.]

Amyloidotic cardiac involvement has been revealed to trend to be a poor prognostic factor. Heart failure is likely to be directly responsible for death in only a minority of patients, however, patients with heart failure may be complicated by multiple organ failures in later phase of the RA disease course. It seems to be suggested that dysautonomia plays an important role in etiology of heart failure to some extent in patients with AA amyloidosis in addition to direct AA amyloid fibril deposits *in situ*. Although the number of reports

published to date concerning AA amyloidosis and autonomic nerve dysfunction in patients with RA is extremely rare, taking an importance of cardiovascular symptoms into account of dysautonomia, which could induce sudden death in AA amyloidosis secondary to RA, autonomic nerve dysfunctions may serve as one of the clinical predictors of poor prognosis in RA. Dysautonomia like abnormal gustatory sweating or orthostatic hypotension seems to be one of the typical symptoms in endstage of the disease course in RA patients with AA amyloidosis.

### **5.5 Causes of death**

Infection and renal failure are generally the commonest causes of death in RA patients with AA amyloidosis, and they comprised 42.3% and 19.2% of deaths, respectively. A higher risk of severe infections is a substantial problem in management of RA with AA amyloidosis. Also, the higher causal proportion of renal failure and GI diseases than RA patients without AA amyloidosis can be attributable to more AA amyloid fibril deposition in these organs.

## **6. Treatment of AA amyloidosis secondary to RA**

The principal aim in treating RA patients with AA amyloidosis is to switch off SAA production, by controlling the RA inflammatory process. Anti-inflammatory treatment must be empirical but, as in all patients with AA amyloidosis, should be guided by frequent assessment of SAA concentrations in view of reported correlations between survival and this measure. Estimated survival at 10 years was 90% in AA amyloidosis patients whose median SAA concentration was below 10  $\mu\text{g}/\text{ml}$  and was 40% among those whose median SAA exceeded this value, which were statistically significant results. Treatment of AA amyloidosis secondary to RA may involve the following strategies.

### **6.1 Suppression of SAA production**

The efficacy of corticosteroid treatment on AA amyloidosis secondary to RA is still controversial. Corticosteroids are capable of reducing the magnitude of acute phase reaction including synthesis of CRP and SAA. In human hepatocyte cultures a stimulating effect of corticosteroids was seen on SAA but not on CRP production. Although corticosteroid suppresses both CRP and SAA levels in longitudinal studies of patients with RA, the effect is somewhat more pronounced for CRP than for SAA. Monitoring of SAA instead of CRP levels would be advisable particularly if corticosteroids are being used. It seems reasonable to treat patients with AA amyloidosis secondary to RA using cytostatic drugs either alone or in combination with prednisolone. As the effect of cytostatics may take weeks or months to appear, it is recommended to give steroids in addition in order to ensure an immediate reduction of the acute phase response and in particular the synthesis of SAA.

Traditional management of AA amyloidosis has been to target RA disease process behind the inflammation. Although there is no evidence that disease-modifying anti-rheumatic drugs (DMARDs) have a specific effect on amyloidogenesis and AA amyloidosis in RA, there have been encouraging reports evaluating alkylating agents as beneficial in clinical trials in RA patients with AA amyloidosis. It is suggested that the use of immunosuppressive agents can improve prognosis, and cyclophosphamide (CYC) has been proved to be superior to methotrexate (MTX) in treatment with RA patients with AA amyloidosis (Fig.5). The possibility that CYC would be more effective predominantly in

patients with SAA1.3/1.3 homozygosity than heterozygosity, suggesting SAA1.3/1.3 homozygosity as a CYC treatment-susceptible factor.

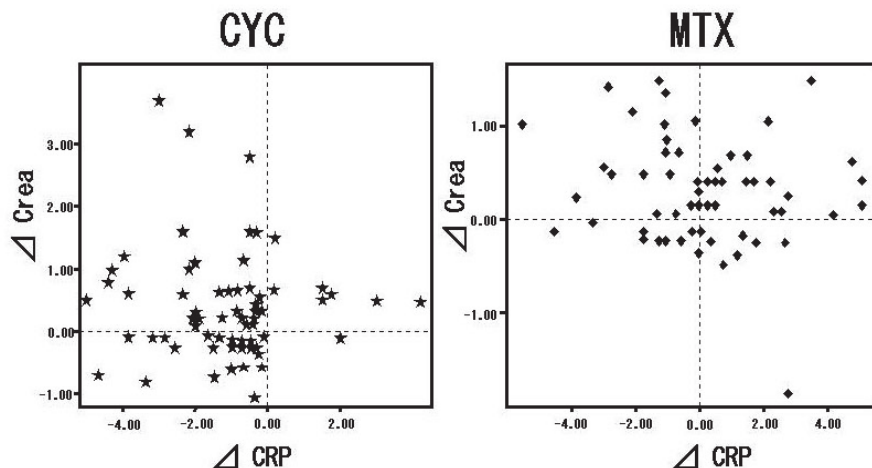


Fig. 5. Differences between CYC and MTX treatments for RA patients with AA amyloidosis. The deducted value (placed in figures) was calculated by subtracting the starting value of CRP and/or serum creatinine from the endpoint value in each treatment. [From Nakamura, T., Higashi, S., Tomoda, K., Tsukano, M., Baba, S. & Shono, M. (2006). Significance of SAA1.3 allele genotype in Japanese patients with amyloidosis secondary to rheumatoid arthritis. *Rheumatology (Oxford)*, Vol. 45, No. 1, (January 2006), pp. 43-49, ISSN 1462-0324.]

For AA amyloidosis in patients with RA, treatment has centered on using cytotoxic agents and biologics. Although case reports and studies of small series of patients showed that these agents can reverse nephrotic syndrome and even lead to complete resolution of proteinuria, anticytokine agents have recently been proposed as therapeutic options (Table 2). Anti-proinflammatory cytokine therapy is expected to show efficacy against systemic inflammation and against local inflammation mediated by macrophage differentiation or activation in glomeruli, such as in renal AA amyloidosis secondary to RA. The strategy of these treatments focuses on tight control of underlying RA disease activity. Requirements include diagnosis of RA as early as possible and treatment with DMARDs, including MTX as the anchor drug. Achieving low disease activity via DMARDs early in the disease course has a strong positive outcome on disease progression. However, although MTX is the most common and effective drug for RA, management of patients with AA amyloidosis secondary to RA and renal involvement is too complex to limit the discussion to MTX.

In RA treatment, tight control of RA is emphasized to obtain clinical remission or lower disease activity; this control is possible through periodic evaluations of RA disease activity and aggressive pursuit of other more effective treatments. Together with this strategy, the genetic predisposition allele SAA1.3, which is a known risk factor for AA amyloidosis in Japanese RA patients, should be evaluated when treating both RA and AA amyloidosis.

## For TNF $\alpha$ antagonists

	E: etanercept/ I: infliximab
Elkayam O, <i>et al</i> : <i>Arthritis Rheum</i> 2002; 46: 2571-3	I
Gottenberg J-E, <i>et al</i> : <i>Arthritis Rheum</i> 2003; 48: 2019-24	E/I
Ortiz-Santamaria V, <i>et al</i> : <i>Rheumatology</i> 2003; 42: 1425-6	E/I
Smith GR, <i>et al</i> : <i>Intern Med J</i> 2004; 34: 570-2	E
Ravindran J, <i>et al</i> : <i>Rheumatology</i> 2004; 43: 669-72	E/I
Fernandes-Nebro A, <i>et al</i> : <i>Am J Med</i> 2005; 118: 552-6	E/I
Nakamura T, <i>et al</i> : <i>Clin Exp Rheumatol</i> 2007; 25: 518-22	E
Kuroda T, <i>et al</i> : <i>Rheumatol Int</i> 2008; 28: 1155-9	I
Kuroda T, <i>et al</i> : <i>J Rheumatol</i> 2009; 36: 2409-15	E/I
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Nobre CA, <i>et al</i> : <i>Rev Bras Reumatol</i> 2010; 50: 205-10	E
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## For the IL-6 receptor antagonist

Okuda Y, <i>et al</i> : <i>Arthritis Rheum</i> 2006; 54: 2997-3000
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Table 2. Selected references to biologics for treatment of AA amyloidosis secondary to RA. [Modified from Nakamura, T. (2011). Amyloid A amyloidosis secondary to rheumatoid arthritis: pathophysiology and treatment. *Clinical and Experimental Rheumatology*, ISSN 0392-856X Accepted on March 8, 2011 (This article is now on process of publication). ]

Etanercept and infliximab, both TNF $\alpha$  antagonists, can reduce serum SAA levels in RA patients with AA amyloidosis, which improves rheumatoid inflammation, reduces swollen and tender joint counts, lowers or normalizes proteinuria, and ameliorates renal function. Despite the small number of series of patients with AA amyloidosis secondary to RA who had etanercept treatment, this drug did benefit both RA inflammation and AA amyloidosis, as measured via the surrogate markers DAS28-ESR, CRP, SAA, and proteinuria, in SAA1.3 allele-carrying RA patients. Also, serum creatinine levels significantly improved in patients with mild RA disease and renal dysfunction. This result suggests that the earlier the intervention with biologics, the better the outcome for patients. Etanercept alone may therefore be efficacious, without MTX.

Tocilizumab, an IL-6 receptor antagonist, also demonstrates excellent suppression of SAA levels and may have potential as a therapeutic agent for AA amyloidosis. Circulating SAA normally reflects changes in CRP, and levels of both acute-phase reactants usually increase simultaneously, but some differences can occur. SAA and CRP seem to be partly influenced by different cytokines. IL-6-blocking therapy has shown promise in normalizing serum SAA levels in RA patients. Moreover, blocking IL-6 alone, but not IL-1 or TNF $\alpha$ , completely prevented SAA mRNA expression in human hepatocytes during triple cytokine stimulation. For signal transduction, IL-6 binds to membrane-bound IL-6 receptor gp80, and then the IL-6-gp80 dimer interacts with gp130. Formation of gp130-

containing complexes leads to activation of Janus kinases (JAKs), which stimulates signal transducers and activators of transcription (STATs). Certain evidence suggests that STAT3 is the key transcription factor responsible for IL-6 activation of SAA gene transcription. Therefore, the function of JAK inhibition in the IL-6 signaling pathway will be one target of RA treatments. Suppressing IL-6-mediated proinflammatory signaling pathways via JAK inhibitors may be a novel anti-inflammatory therapeutic strategy for RA and AA amyloidosis. Another agent, tacrolimus, may inhibit T-cell function in pathogenesis of AA amyloidosis.

### **6.2 Inhibition of AA amyloid fibril deposits**

Eprodisate, a small sulfonated molecule with structural similarity to heparan sulfate, which can cause regression of amyloidosis by destabilizing the glycoasaminoglycan backbone of amyloid deposits, delayed progression of renal disease associated with AA amyloidosis. In a trial for AA amyloidosis, eprodisate had a beneficial effect on the rate of deterioration of renal function but no effect on urinary protein excretion. That eprodisate did not affect SAA levels and preserved kidney function but had no effect on proteinuria raises the interesting possibility that it is the precursors of mature amyloid fibrils are responsible for proteinuria in amyloidosis.

### **6.3 Removal of deposited AA amyloid fibrils**

The normal plasma protein SAP binds to all types of amyloid fibrils and contributes to amyloidosis pathogenesis. A pyrrolidine carboxylic acid derivative, which is a competitive inhibitor of SAP binding to amyloid fibrils, can intervene in this process and affect SAP levels. This compound cross-linked and dimerized SAP molecules, which led to extremely rapid clearance by the liver, and thus produced marked depletion of circulating human SAP. This drug action thus removed SAP from human amyloid deposits in tissues and may have a favorable effect on amyloidosis.

Another compound, dimethyl sulfoxide (DMSO), is a hydrogen-bond disrupter, cell-differentiating agent, hydroxyl radical scavenger, cryoprotectant, and solubilizing agent that is used as a compound for preparation of samples for electron microscopy, as an intracellular low-density lipoprotein-derived cholesterol-mobilizing antidote to extravasation of vesicant anticancer agents, and as a topical analgesic. A notable DMSO side effect is garlic-like breath odor and taste in the mouth because of pulmonary excretion of a small amount of DMSO as dimethyl sulfide. Oral DMSO was effective against AA amyloidosis, especially GI involvement and early renal dysfunction, but using it would not likely be feasible in current clinical practice.

### **6.4 Treatment of organ failure**

The predominant feature of AA amyloidosis is proteinuria with or without renal failure. If conservative treatment of renal failure is not sufficient, renal replacement therapy including renal transplantation, continuous ambulatory peritoneal dialysis, or HD should be considered. Even in RA patients with AA amyloidosis who undergo HD, anti-TNF $\alpha$  blockers can demonstrate efficacy. HD reportedly had no effect on plasma etanercept concentration, and etanercept pharmacokinetics in patients undergoing HD for chronic renal failure were similar to those with normal renal function. Administration of etanercept to HD patients would therefore appear reasonable.



For RA patients complaining severe diarrhea due to AA amyloidosis, corticosteroid, codeine phosphate, and lactate bacteriae are useful. In remarkable protein losing enteropathy with intractable diarrhea due to AA amyloidosis, a successful treatment combined with somatostatin analogue octreotide and corticosteroid has been reported.

## 7. Biological diversity and significance of SAA

The life expectancy of patients with RA has been estimated to be 1.2 to 1.7 times worse than that of the general population. Complications involving AA amyloidosis may further reduce life expectancy in such patients. Treatment-related clinical remission in RA may lead to structural and functional remissions, which will result in a better quality of life. SAA has biologically diverse and significant roles in health and disease (Fig. 6). Thus, SAA may modify progression of disease-either AA amyloidosis (high-grade inflammation) or metabolic syndrome (low-grade inflammation)-via its biological actions. Alleviated inflammation and improved nutritional metabolism would lead to suppression of cardiovascular events and would reduce the incidence of AA amyloidosis in RA. Elucidation of the biological diversity and significance of SAA should enhance understanding of the pathophysiology of AA amyloidosis secondary to RA.

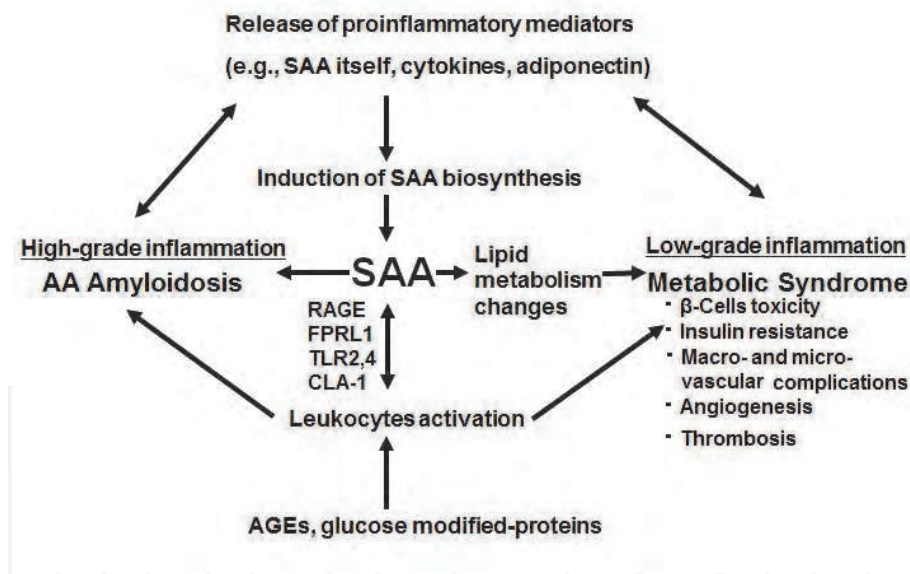


Fig. 6. Biological versatility of serum amyloid A protein (SAA).

SAA plays important roles in both high-grade inflammation and low-grade inflammation. It acts, as cytokines do, via autocrine, endocrine, and paracrine mechanisms. As a precursor protein of amyloid A (AA) fibrils, SAA induces AA amyloidosis. SAA also affects metabolic syndrome via various modes of action. These humoral and cellular inflammatory events interact, with SAA being a key player. RAGE: receptor for advanced glycation end products; FPRL1: formyl peptide receptor-like 1; TLR2, 4: toll-like receptor 2 and 4; CLA-1: CD36 and



LIMPII analogous-1, human orthologue of the scavenger receptor class B type I (SR-BI); AGEs: advanced glycation end products. [From Nakamura, T. (2011). Amyloid A amyloidosis secondary to rheumatoid arthritis: pathophysiology and treatment. *Clinical and Experimental Rheumatology*, ISSN 0392-856X Accepted on March 8, 2011 (This article is now on process of publication.).]

## 8. Issues that require further perspective

Important issues of future interest that are related to AA amyloidosis secondary to RA include the following: i) tight control of inflammation occurring with underlying RA; ii) factors associated with the risk of AA amyloidosis, such as SAA1.3 allele, which indicates a genetic predisposition to the disease; and iii) screening tools for AA amyloidosis for use even during the subclinical phase. The mechanisms of AA amyloid fibril formation are complicated pathways involving multiple factors, as Figure 1 shows, and elucidation of mechanisms on both deposition and turnover of AA amyloid fibrils should allow development of novel therapeutic options. Reducing the supply of amyloidogenic precursors is usually associated with reabsorption of AA amyloid deposits and perhaps recovery of target organ function. Because AA amyloid fibril shows heterogeneity in organ deposition, clarification of the affinity of AA amyloid fibrils to various organs is needed. Addressing the involvement of various organs and systems- renal, GI, cardiac, thyroid, and autonomic nervous-may permit development of therapeutic countermeasures against complications.

## 9. Conclusion

Although significant advances have been made in understanding of the pathology, pathogenesis, and clinical treatment of AA amyloidosis secondary to RA, the disease is still an important complication that warrants investigation. The SAA1.3 allele serves not only as a risk factor for AA amyloidosis but also as a factor related to poor prognosis and shortened survival of Japanese patients with RA, and understanding both disorders would benefit from investigation of the SAA1.3 allele. AA amyloidosis secondary to RA is now clearly influenced by many variables, and clinical pictures differ among patients. The pathological process in RA patients with AA amyloidosis seems to be more complicated and subtle than previously realized. Clarification of the formation and degeneration or turnover of AA amyloid fibrils and elucidation of the biological contributions of SAA in health and disease are indispensable prerequisites to the management of AA amyloidosis secondary to RA. The introduction of biological therapies targeting specific inflammatory mediators revolutionized the treatment of RA. Targeting key components of the immune system allows efficient suppression of the pathologic inflammatory cascade that gives rise to RA symptoms and subsequent joint destruction. Reactive AA amyloidosis is one of the most severe complications of RA, and is a serious, potentially life-threatening disorder caused by deposition in multiple organs of AA amyloid fibrils. The AA amyloid fibrils are derived from the circulatory acute-phase reactant, SAA, and likely subject to control. With newly developed biologics, AA amyloidosis secondary to RA seems to become a treatable and even controllable disorder. The pathophysiological understanding and clinical factors including the genetic predisposition require that rheumatologists need to take these into account when diagnosing and treating patients with AA amyloidosis secondary to RA. Based on previous works as to AA amyloidosis secondary to RA, the critical overview in

terms of AA amyloidosis is discussed with special reference to therapeutic importance of biologic agents.

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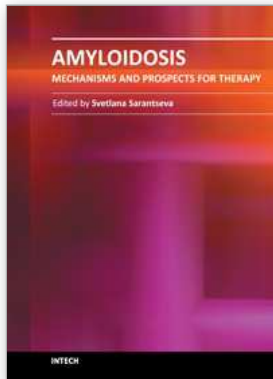
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## **Amyloidosis - Mechanisms and Prospects for Therapy**

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Amyloidoses are a heterogeneous group of diverse etiology diseases. They are characterized by an endogenous production of abnormal proteins called amyloid proteins, which are not hydrosoluble, form depots in various organs and tissue of animals and humans and cause dysfunctions. Despite many decades of research, the origin of the pathogenesis and the molecular determinants involved in amyloid diseases has remained elusive. At present, there is not an effective treatment to prevent protein misfolding in these amyloid diseases. The aim of this book is to present an overview of different aspects of amyloidoses from basic mechanisms and diagnosis to latest advancements in treatment.

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