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Chapter 1

Immunoregulatory Properties of Acute Phase Proteins — Specific Focus on α1-Antitrypsin

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Additional information is available at the end of the chapter

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1. Introduction

Activation of innate immune cells in response to various insults is a part of the host defence. However, if uncontrolled, this inflammatory response induces persistent hyper-expression of pro-inflammatory mediators and tissue damage. Tight control of pro-inflammatory pathways is therefore critical for immune homeostasis and host survival.

A complex network of activating and regulatory pathways controls innate immune responses; the hepatic acute-phase response is one of the crucial contributors to this regulation. For example, in response to infection or tissue injury within few hours the pattern of protein synthesis by the liver is drastically altered, i.e. increased expression of the so called positive acute phase proteins (APPs) like C-reactive protein (CRP), alpha1-antitrypsin (AAT) or alpha1-acid glycoprotein (AGP) and decreased expression of transthyretin, retinol binding protein, cortisol binding globulin, transferrin and albumin, which represent the group of negative APPs. This production of APPs in hepatocytes is controlled by a variety of cytokines released during inflammation whereas leading regulators are IL-1- and IL-6-type cytokines having additive, inhibitory, or synergistic effects. For instance, IL-1β is shown to almost completely abrogate IL-6-induced production of α2-macroglobulin and α1-antichymotrypsin but, in contrast, to enhance production of CRP and serum amyloid A. No doubt, this specific regulation of AAPs expression plays a critical role in the regulation of the host innate immune responses.

2. Alpha1-antitrypsin and the acute phase response

AAT, also referred to as alpha$_1$-proteinase inhibitor or SERPINA1, is the most abundant serine protease inhibitor in human blood. AAT consists of a single polypeptide chain of 394 amino

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acid residues containing one free cysteine residue and three asparagines-linked carbohydrate side-chains. AAT is mainly produced by liver cells but can also be synthesized by blood monocytes, macrophages, pulmonary alveolar cells, and by intestinal and corneal epithelium (Geboes et al., 1982; Perlmutter et al., 1985; Ray et al., 1982). In terms of tissue expression AAT has been demonstrated in the kidney, stomach, small intestine, pancreas, spleen, thymus, adrenal glands, ovaries and testes. De novo synthesis of AAT has also been demonstrated in human cancer cell lines. These observations indicate that AAT transcription is relatively widespread. In fact, tissue-specific promoter activity for AAT has been reported in the liver, the major source of AAT, and alternative promotors for other tissues that express the protein (Kalsheker et al., 2002; Tuder et al., 2010). Interestingly, AAT expression also shows some degree of substrate and/or auto-regulation: upon exposure to neutrophil and pancreatic elastases, either alone or as a complex of AAT, enhanced synthesis of AAT was observed (Perlmutter et al., 1988).

The normal daily rate of synthesis of AAT is approximately 34 mg/kg body weight and the protein is cleared with a half-life of 3 to 5 days. This results in high plasma concentrations ranging from 0.9 to 2 mg/ml when measured by nephelometry. In addition to high circulating levels in blood, AAT is also present in saliva, tears, milk, semen, urine and bile (Berman et al., 1973; Chowanadisai & Lonnerdal, 2002; Huang, 2004; Janciauskiene et al., 1996; Poortmans & Jeanloz, 1968). The distribution of the protein in the tissues is not uniform. For example, in the epithelial lining fluid of the lower respiratory tract its concentration is approximately 10% of plasma levels (Janciauskiene, 2001).

As an acute-phase reactant, circulating AAT levels increase rapidly (3 to 4 fold) in response to inflammation or infection. The concentration of AAT in plasma also increases during oral contraceptive therapy and pregnancy. During an inflammatory response, tissue concentrations of AAT may increase as much as 11-fold as a result of local synthesis by resident or invading inflammatory cells (Boskovic & Twining, 1997). Blood monocytes and alveolar macrophages can contribute to tissue AAT levels in response to inflammatory cytokines (IL-6, IL-1 and TNFα) and endotoxins (Knoell et al., 1998; Perlmutter & Punsal, 1988). Recent data demonstrate that AAT expression by alpha and delta cells of human islets (Bosco et al., 2005) and intestinal epithelial cells (Faust et al., 2001) is also enhanced by pro-inflammatory cytokines. AAT synthesis by corneal epithelium, on the other hand, appears to be under the influence of retinol, IL-2, fibroblast growth factor-2, and insulin-like growth factor-I (Boskovic & Twining, 1997; Boskovic & Twining, 1998). Oncostatin M, a member of the IL-6 family was shown to induce AAT production by human bronchial epithelial cells. This effect of oncostatin M was in turn modulated by TGF-β and IFN-γ at both the protein and mRNA level. IFN-γ decreased oncostatin M-induced AAT production whilst TGF-β induced a significant and synergistic up-regulation of AAT that was not observed in a hepatocyte cell line (Boutten et al., 1998). Study by Shin and coworkers (Shin et al., 2011) have demonstrated that nasal lavage fluids from the patients with allergic rhinitis contains AAT and that the levels of nasal AAT markedly increase in response to allergenic stimulation. This response seems to be closely associated with the activation of eosinophils induced by allergen-specific IgA. In allergen-

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induced nasal inflammation, AAT might be a byproduct of the activated inflammatory cells, and is thus implicated in the allergic immune response (Shin et al., 2011).

According to recent studies, activated neutrophils and eosinophils can store and secrete AAT, which plays a role in protection of tissues at local inflammation sites (Johansson et al., 2001; Paakko et al., 1996). Furthermore, Clemmensen and coworkers found that the mRNA for AAT increases during maturity of the myeloid cell precursors and is even higher in blood neutrophils. This in itself is quite remarkable as blood neutrophils are generally considered transcriptionally inactive, but it is even more striking that the transcriptional activity of the AAT gene increases further when neutrophils migrate into tissues (Clemmensen et al., 2011). Moreover, circulating AAT produced by liver cells can enter granulocytes and is stored in the secretory vesicles (Borregaard et al., 1992).

3. Protective anti-inflammatory, immunomodulatory and antimicrobial effects of alpha1-antitrypsin

Findings from different experimental models provide clear evidence that AAT expresses broad anti-inflammatory and immunoregulatory activities (Figure 1). AAT has been reported to inhibit neutrophil superoxide production, adhesion, and chemotaxis, to enhance insulin-induced mitogenesis in cell lines and to induce IL-1 receptor antagonist, a negative regulator to IL-1 signalling, in blood monocytes and neutrophils (Tuder et al., 2010). Findings that AAT enhances the synthesis of transferrin receptor and ferritin revealed a role of AAT in iron metabolism (Graziadei et al., 1997). In murine models, exogenous human AAT protects islet cell allografts from rejection and increase survival in an allogeneic marrow transplantation models. In other models AAT therapy protects against TNF-α / endotoxin induced lethality, cigarette smoke induced emphysema and inflammation and even suppressed bacterial proliferation during infections ((Lewis, 2012), review). Furthermore, human AAT given to mice during renal ischemia–reperfusion (I/R) injury lessens tissue injury and attenuated organ dysfunction (Daemen et al., 2000).

These beneficial impacts of AAT are incompletely understood, although exscinding knowledge suggests that AAT promotes a switch from pro-inflammatory to anti-inflammatory pathways necessary for the resolution of inflammation.

AAT has long been thought of as a main inhibitor of neutrophil elastase, proteinase 3, and other serine proteases released from activated human neutrophils during an inflammatory response. In fact, the rate of formation of the AAT/neutrophil elastase inhibitory complex is one of the fastest known for serpins (6.5×10^7 M^{-1} s^{-1}) (Gettins, 2002). The structure of AAT consists of three β-sheets (A, B, C) and 9 α-helices (A-I). The inhibitory active conformation of AAT like for other serine protease inhibitors represents a metastable state, characterized by an exposed reactive center loop that acts as bait for the target enzyme (Stocks et al., 2012). Cleavage of the scissile bond in the loop results in a large conformational change in which the reactive site loop migrates and is inserted into the pre-existing β-sheet A forming a very stable complex

between the inhibitor and the protease. This reaction results in a rapid and irreversible inactivation of both AAT and its target protease.

As an inhibitor, AAT also shows true substrate-like behaviour and cleavage without complex formation. Novel studies show that AAT, without forming complexes, inhibits the activity of gelatinase B (MMP9) and caspases-1 and -3 that play an essential role in cell apoptosis. AAT also inactivates the catalytic domain of matriptase, a cell surface serine protease involved in the activation of epithelial sodium channels. In addition, recent evidence has emerged on the ability of AAT to inhibit the matrix metalloprotease, ADAM-17 (Bergin et al., 2010) and aspartic-cysteine protease, calpain I (Al-Omari et al., 2011). Calpain I activity has been implicated in neutrophil apoptosis (Chen et al., 2006), chemotaxis (Lokuta et al., 2003) and adhesion (Wiemer et al., 2010). In fact, AAT inhibits neutrophil adhesion, chemotaxis (Al-Omari et al., 2011; Bergin et al., 2010) and apoptosis (Zhang et al., 2007). The mechanism behind these latter effects of AAT might be directly linked to its ability to inhibit calpain I activity.

So far, it is assumed that anti-inflammatory and immunomodulatory functions of AAT are dependent on its metastable native conformation (with inhibitory activity); however, this has not been proven. Earlier studies by Churg and collaborators have demonstrated that oxidized AAT (without elastase inhibitory activity) is effective in preventing neutrophil influx and lung tissue damage in a silica-induced inflammation model in mice (Churg et al., 2001). We also

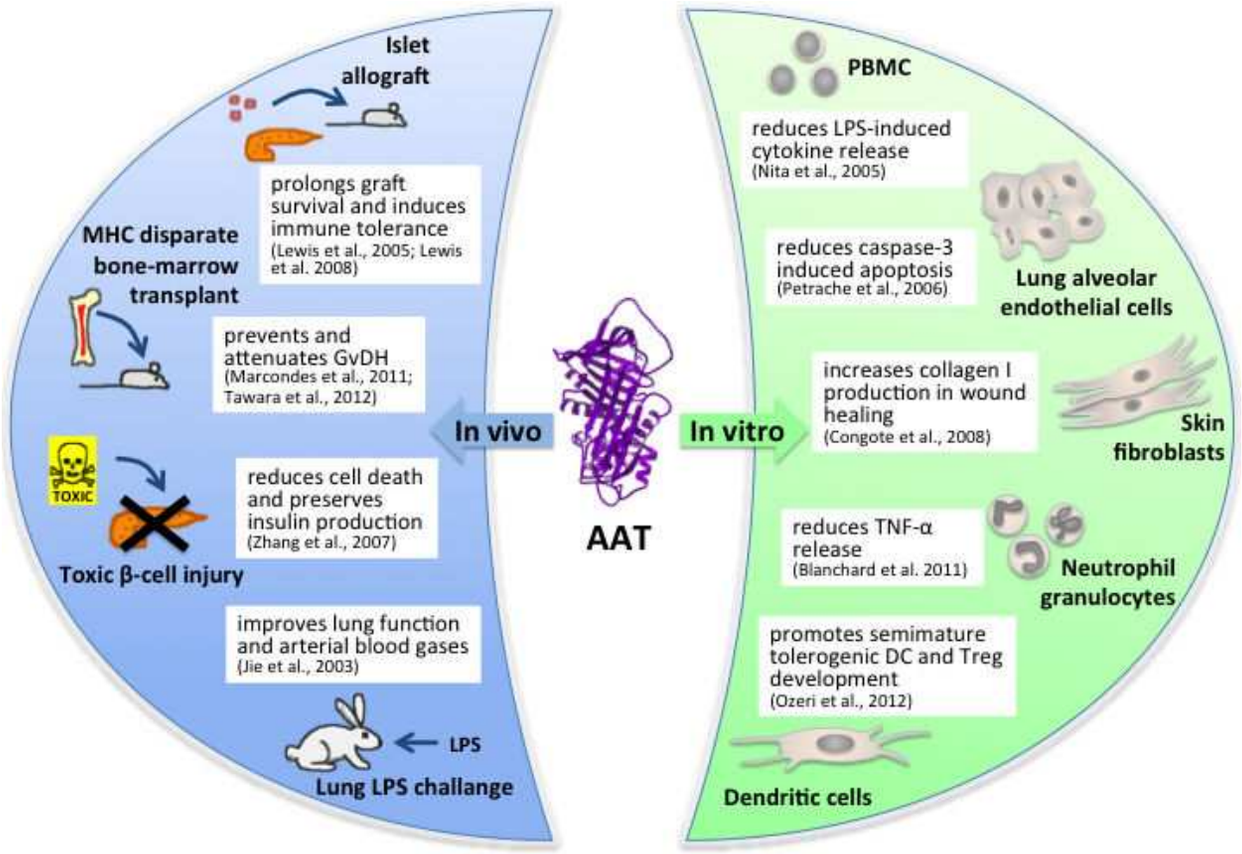


Figure 1. Selected anti-inflammatory and immunoregulatory activities of AAT.

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reported that oxidized AAT (again without elastase inhibitory activity) reduces endotoxin-induced TNF-α, IL-8, MCP-1, and IL-1 release in human monocytes *in vitro* (Janciauskiene et al., 2004). We also found that the pattern of gene expression regulated in human primary lung endothelial cells by native and oxidized AAT was similar with neither inducing pro-inflammatory gene expression (Subramaniyam et al., 2008).

Moreover, a specific short carboxyl terminal peptide of AAT which doesn´t inhibit elastase is a more potent inhibitor of LPS-induced TNF-α and IL-8 production than native AAT (Amelinckx et al., 2011; Subramaniyam et al., 2006)

Recently, we examined the effects of plasma purified AAT in LPS-induced acute lung injury in wild-type (WT) and neutrophil elastase-deficient mice as well as in neutrophils isolated from the bone marrow of WT and elastase-deficient mice. Analyses of lung lavage fluids and tissues revealed that, regardless from the mouse strain, AAT induced a 50% decrease in LPS-induced neutrophil counts as well as a reduction in the lavage fluid levels of IL-8 and TNF-α. Furthermore, AAT inhibited the ability of LPS to increase TNF-α, DNA damage-inducible transcript 3 and X-box binding protein 1 gene expression in the lung parenchyma (Jonigk et al., PNAS, in press).

These findings provide clear evidence that inhibition of elastase is not the sole mechanism behind the anti-inflammatory and immunoregulatory activities of AAT. The responsible molecular mechanisms remain to be elucidated.

4. Interaction with other macromolecules and cell surface 'receptors' and signalling mechanisms

AAT shows the property to interact with other proteins. For example, in sera from patients with myeloma and Bence-Jones proteinemia complexes between AAT and the kappa light chain of immunoglobulins were detected (Laurell & Thulin, 1975). In plasma from diabetic subjects, complexes between AAT and factor Xia, AAT and heat shock protein-70 as well as AAT and glucose were detected (Murakami et al., 1993; Finotti & Pagetta, 2004; Hall et al., 1986). Moreover, complexes between AAT and immunoglobulin A have been detected in the sera and synovial fluid of patients with rheumatoid arthritis, systemic lupus erythematosus and ankylosing spondylitis (Adam & Bieth, 1996). Localization of AAT-low-density-lipoprotein (LDL) complexes in atherosclerotic lesions and enhanced degradation of AAT-LDL by macrophages suggested the involvement of the complex in atherogenesis (Mashiba et al., 2001).

Earlier studies have shown that cellular internalization and degradation of AAT-elastase-, or AAT-trypsin-complexes, but not of the native form of AAT, is mediated by serpin-enzyme complex (SEC) receptor (Perlmutter et al., 1990), low-density lipoprotein receptor related protein (Poller et al., 1995) and very-low-density lipoprotein receptor which require intact raft lipid environment (Wu & Gonias, 2005; Yoon et al., 2007).

Recent studies provide new evidence that clathrin-mediated endocytosis (Sohrab et al., 2009) and the caveolar pathway (Aldonyte et al., 2008) and Fc receptor(s) (Bergin et al., 2010) might

be responsible for the interaction and entry of native AAT into the cell. Experimental studies have shown that various APPs, like C-reactive protein (CRP), interact with lipid rafts (Ji et al., 2009) and therefore, gave support for the hypothesis that APPs-lipid raft interaction may be a putative mechanism responsible for the diverse activities of APPs during inflammation.

Lipid rafts are dynamic assemblies of proteins and lipids that play a central role in various cellular processes, including membrane sorting and trafficking, cell polarization, and signal transduction (Baird et al., 1999; Janes et al., 2000; Zhu et al., 2006). Biochemical and cell-biological studies have identified cholesterol as a key factor determining raft and related structure (e.g., caveolae) stability and organization in mammalian cell membranes, and have shown that the equilibrium between free and raft cholesterol plays a critical role in lipid raft function and cell signalling (Golub et al., 2004; Gombos et al., 2006). Many proteins involved in signal transduction, such as Src family kinases, G proteins, growth factor receptors, mitogen-activated protein kinase and protein kinase C are predominantly found in lipid rafts, which act as signaling platforms by bringing together (i.e., colocalizing) various signaling components (Simons & Toomre, 2000).

Our studies on the putative role of lipid rafts and lipid raft cholesterol for AAT entry into monocytes revealed that exogenously added AAT becomes translocated into lipid rafts in the same fraction as the lipid raft marker flotillin (Slaughter et al., 2003; Subramaniyam et al., 2010). It is well documented that plasma membranes of mammalian cells contain a 30–50% molar fraction of cholesterol (Warnock et al., 1993), which is the dynamic glue for the lipid raft assembly (Simons & Toomre, 2000). Taken with the finding that exogenous AAT localizes in the lipid raft prompted us to examine whether altering the integrity of the lipid raft cholesterol would affect AAT-monocyte association. In fact, AAT association with monocytes was remarkably inhibited by various cholesterol depleting/efflux-stimulating agents such as nystatin, filipin, methyl-betacyclodextrin, oxidized low-density lipoprotein and high density lipoproteins, and conversely, enhanced by free cholesterol. We had previously identified that AAT can directly interact with free cholesterol in vitro (Janciauskiene & Eriksson, 1993). In support, we confirmed that AAT /monocyte association *per se* depletes lipid raft cholesterol as characterized by the activation of extracellular signal-regulated kinase 2, increased HMG-CoA reductase expression, formation of cytosolic lipid droplets, and a complete inhibition of oxidized low-density lipoprotein and oxidized phopspholipid uptake by monocytes (Subramaniyam et al., 2010).

Lipid rafts act as platforms, bringing together molecules essential for the activation of immune cells, but also separating such molecules when the conditions for activation are not appropriate (Ehrenstein et al., 2005). We hypothesize that AAT/ lipid raft interaction and cholesterol depletion contributes to re-organize membrane domains and facilitate the formation of compartment-specific signalling platforms. As a consequence, several events can occur intracellularly like transient release of calcium and Na^+/K^+-ATPase-EGFR-Src-caveolin-1 complex formation leading to an increased tyrosine phosphorylation of caveolin-1 and the activation of the Rac1-Cdc42-ERK cascade, and transient activation of hemoxygenase-1. It has been previously reported that exogenous AAT is rapidly internalized into the cells and is localized in the plasma membranes and in the cytoplasm (Sohrab et al., 2009). Whether internalized AAT is further trafficking to the interstitium or remains within the cells is

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unknown. As a matter of fact, AAT is shown to interact with the transferrin receptor (Graziadei et al., 1994) which is constantly internalized via endocytic vesicles that fuse with early endosomes and returns to the plasma membrane through recycling endosomes (Harding et al., 1983). Thus it cannot be excluded that excess of internalized AAT trafficking occurs via transferrin receptor pathway.

Nevertheless, incorporation of AAT into membranes and transient depletion of cholesterol can affect recruitment of TLRs into lipid rafts subsequently desensitizing signalling by bacterial endotoxins and resulting in consequent reduction of the pro-inflammatory response. In support, human innate immune cells stimulated with bacterial lipopolysaccharide (LPS) in the presence of AAT show suppressed TNFα, IL-8, IL-12 and IL-1β, but enhanced IL-10 production (Figure 2) (Janciauskiene et al., 2004; Nita et al., 2005).

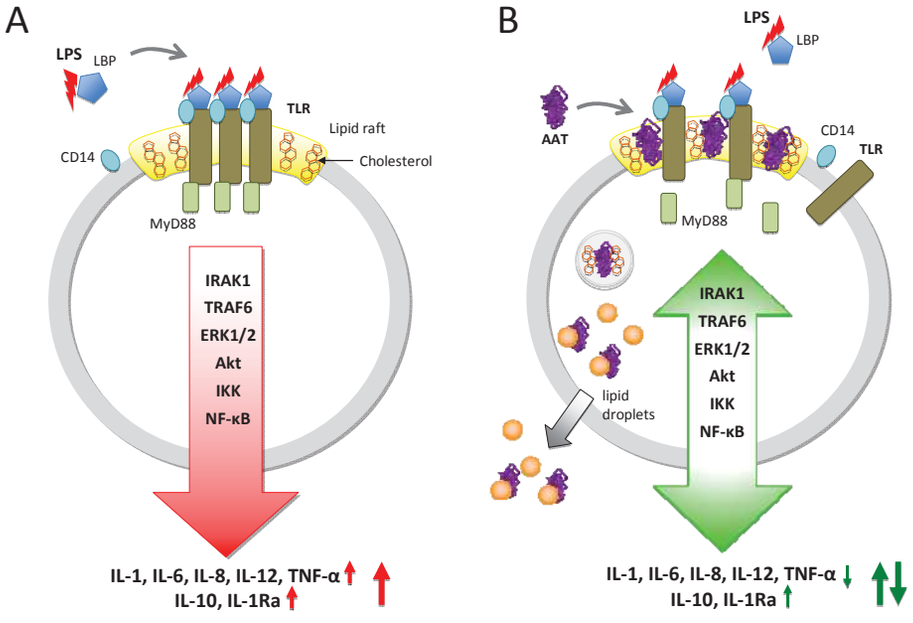


Figure 2. Hypothesis of the immune modulator effect of AAT. A: LPS signalling and cell activation; B: effects of AAT on LPS signalling and cell activation.

In general, this hypothesis provides the basis for future studies linking bioactivities of acute phase proteins to signalling pathways associated with lipid rafts. Lipid rafts are therapeutic targets for various diseases and studies on physiological significance of interaction between acute phase proteins and lipid rafts of great importance.

5. Diseases associated with AAT deficiency

The clinical relevance of AAT is highlighted in individuals with inherited deficiency in circulating AAT who have an increased susceptibility to early onset pulmonary emphysema, and liver as well as pancreatic diseases. The most interesting AAT variants associated with deficiency are the S and Z genes commonly found in Europeans. Both S and Z AAT result from

single amino acid substitutions. In the S variant there is a substitution of a valine residue for glutamate at position 264 (Val264Glu) (Curiel et al., 1989). The Z mutation (Glu342Lys) results from the substitution of a positively charged lysine for a negatively charged glutamine at the base of the reactive centre. Severe ZZ deficiency of AAT is characterized by a decrease in serum AAT levels below a protective threshold of 11 mmol/L (Fregonese et al., 2008; Hubbard & Crystal, 1988) and is associated with increased but variable risk for the development of lung emphysema (Janciauskiene et al., 2010).

From retrospective studies we also know that up to 25% of those with severe AAT deficiency will suffer from liver cirrhosis and for liver cancer in late adulthood (Propst et al., 1994). Also heterozygous AAT deficiency is a cofactor in the development of chronic liver diseases (Kok et al., 2007). Adults with AAT deficiency–associated genotypes develop liver disease less frequently than pulmonary manifestations. However, AAT is a relevant cause for liver cirrhosis, after viral hepatitis, alcohol abuse, and chronic cholangitis. Other factors that can also predispose AAT-deficient individuals to liver disease are male sex and obesity (Bowlus et al., 2005).The underlying cause may be the intrahepatic accumulation of polymerized AAT molecules. The polymers of Z-mutant AAT can be identified in endoplasmic reticulum by the electron microscopy as diastase resistant inclusion bodies reacting positively with PAS-staining (Periodic acid-Schiff). Intracellular inclusion bodies in the liver have also been observed with other polymer-forming phenotypes of AAT deficiency (M_{malton} (52Phe del), and S_{iiyama} (Ser53Phe) (Tuder et al., 2010).

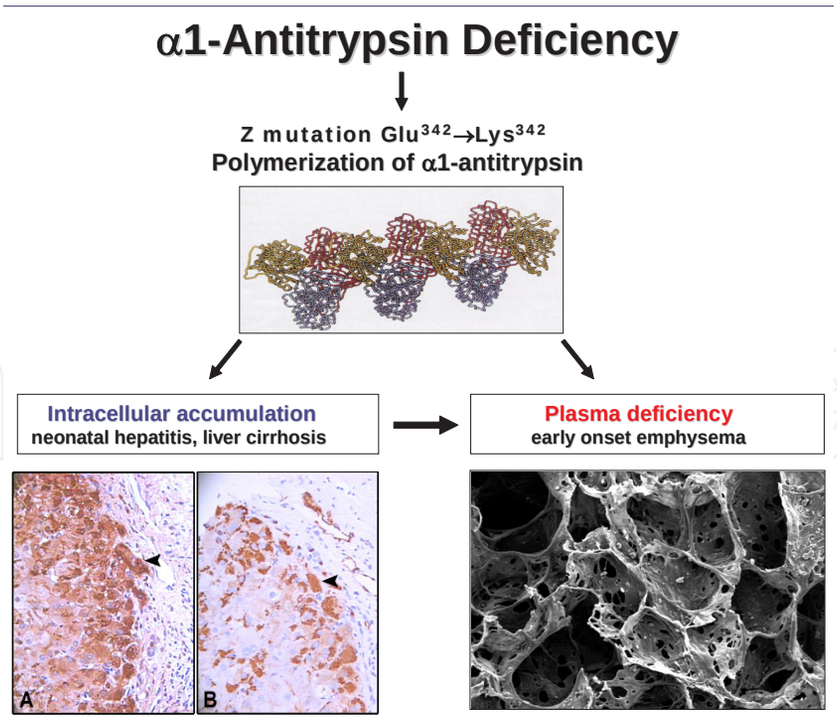


Figure 3. Schematic diagram depicting the role of polymers of α1-Antitrypsin (AAT) in the development of liver and lung diseases. A) AAT polymers stained with rabbit polyclonal antibody against human AAT, B) AAT polymers stained with mouse monoclonal ATZ11 antibody against human Z polymers.

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Inherited AAT deficiency is occasionally associated with antiproteinase-3-associated vasculitis (Wegener's granulomatosis), necrotizing panniculitis and aneurysms of the abdominal aorta and brain arteries. AATD has also been associated with a number of other inflammatory diseases, although the association is only moderate or weak. These include bronchial asthma, bronchiectasis, rheumatoid arthritis, psoriasis, chronic urticaria, glomerulonephritis, pancreatitis and pancreatic tumors, multiple sclerosis, fibromyalgia and other conditions reported occasionally (Janciauskiene et al., 2011)

Remarkably, associations have been found between reduced plasma AAT levels and HIV-1 infection, hepatitis, diabetes mellitus, systemic vasculitis and necrotizing panniculitis (Lewis, 2012; Tuder et al., 2010).

5.1. AAT augmentation therapy

Given the concept of the protease/antiprotease imbalance role in causing emphysema, augmentation of circulating AAT was introduced 30 years ago to treat emphysema patients with severe ZZ deficiency of AAT. Augmentation therapy with human AAT has been performed for over a decade in the United States and in a number of European countries. Worldwide, more than 4,000 patients are currently receiving regular AAT substitution. Most patients receive weekly intravenous application of 3–5 g AAT (60 mg/kg body weight), which is derived from pooled human plasma. Patients with emphysema may be considered for augmentation if their serum concentration is below 0.8 g/L (≤ 11 μmol/L), if their post-bronchodilator FEV_1 is between 35% and 60% of predicted, or if their annual decline of FEV_1 is more than 100 mL (for review see (Mohanka et al., 2012))

Substitution therapy has been studied in a few clinical trials, and the evidence for its efficacy is limited. A last double-blind, placebo-controlled trial EXACTLE (the EXAcerbations and computed tomography (CT) scan as Lung Endpoints), was designed to explore the use of CT densitometry as an outcome measure for the assessment of the effect of AAT augmentation therapy on the progression of emphysema in individuals with inherited AAT deficiency (Stockley et al., 2010). This study showed that the rate of lung density decline was reduced by the intravenous augmentation therapy, and although the exacerbation frequency was unaltered by this treatment, a reduction in severity of exacerbations was observed.

To date fewer than 50 cases of panniculitis associated with various phenotypes of AAT deficiency have been reported (Piliang & Stoller, 2008). The clinical features that distinguish the AAT deficiency-associated panniculitis include higher frequency of ulceration, a vigorous neutrophilic response and histological evidence of both necrosis and elastin breakdown (Smith et al., 1989). In support of AAT deficiency as a contributor to the inflammatory pathogenesis of panniculitis, a few case reports provide evidence that the infusion of purified pooled human AAT induces a rapid clinical resolution of panniculitis (Gross et al., 2009; O'Riordan et al., 1997; Furey et al., 1996).

The putative association between AAT deficiency and vasculitis (Wegener's granulomatosis) is based on the fact that AAT deficiency variants occur more frequently among individuals with multisystem vascultitis (anti-neutrophilic cytoplasmic antibodies (C-ANCA) or anti-

protease-3 (PR-3) and glomerulonephritis (Esnault et al., 1993; O'Donoghue et al., 1993; Montanelli et al., 2002). Moreover, since AAT plays an important role in inhibiting PR3, it has been suggested that AAT deficiency could trigger an autoimmune response due to increased extracellular exposure to PR3 (Esnault et al., 1997). Alternatively, although unproven, it is conceivable that circulating Z AAT polymers could prompt a vascular response.

5.2. New perspectives for use of the AAT augmentation therapy

Administration of exogenous human plasma-derived AAT is used in various animal models to test the value of AAT augmentation. Several studies report that administration of AAT results in a change from the pro-inflammatory to the anti-inflammatory pathways that is necessary for the resolution of inflammation. Cystic Fibrosis (CF) is a condition caused by a known gene defect which predisposes individuals to chronic lung inflammation and infection. To date work has demonstrated that CF neutrophils secrete abnormally high levels of the pro-inflammatory cytokines, such as IL-8 and TNFα, and proteolytic enzymes specifically elastase which not only causes lung parenchymal damage, but can also perpetuate a vicious cycle of inflammation by inducing expression of the neutrophil chemoattractant, IL-8, from bronchial epithelial cells. Therefore, the interest in the application of treatment with inhaled AAT in CF lung disease is discussed (Siekmeier, 2010)

Based on preclinical and clinical studies, it is suggested that AAT therapy can be successfully used for non-deficient individuals with Type-1 and Type-2 diabetes, acute myocardial infarction, rheumatoid arthritis, inflammatory bowel disease, cystic fibrosis, transplant rejection, graft-versus-host-disease and multiple sclerosis. AAT also appears to be antibacterial and an inhibitor of viral infections, such as influenza and HIV, and is currently evaluated in clinical trials for Type-1 diabetes, cystic fibrosis and graft-versus-host-disease (Blanco et al., 2011; Lewis, 2012). New experimental approaches show that AAT therapy might be an option for arthritis treatment in a combination with doxycycline (Grimstein et al., 2010)

Thus, AAT can be used as potential treatment for a broad spectrum of inflammatory and immune-mediated diseases. Future treatment developments include gene therapy (via injections of viral or non-viral vector systems carrying the SERPINA1-cDNA), strategies to inhibit intra-hepatic AAT polymerization by small chemicals and chaperons, and inhibition of neutrophil elastase by using small molecules. Inhaled application of AAT is currently under development by several companies.

6. Immunoregulatory properties of other APPs

The change in the concentrations of APPs is universally used to monitor the course of the disease, independently of its nature (Parra et al., 2006). However, specific APPs can also modify inflammatory responses. The spectrum of action of various APPs extends to regulation of leukocyte migration, adhesion and production of inflammatory mediators, control of ion channels and mucus secretion, and modulation of other host defence mechanisms (table 1).

Acute-phase protein	Main biological function
Proteins whose plasma concentration increase	
C-reactive protein (CRP)	Binding of phosphocholine (opsonin); immunoregulation
Alpha1-Acid Glycoprotein (AGP)	Carry lipophilic compounds; immunoregulation
Serum amyloid A (SAA)	Recruitment of immune cells; activation enzymes that degrade extracellular matrix
Fibronectin	Wound healing
Ferritin	Iron binding
Angiotensinogen	Renin substrate
Complement factors: C3, C4, C9, factor B, C1 inhibitor, C4b-binding protein, mannose-binding lectin	Enhancing phagocytosis of antigens, attracting macrophages and neutrophils, lysis membranes of foreign cells, clumping of antigen-bearing agents, altering the molecular structure of viruses
Coagulation and fibrinolysis factors: fibrinogen, plasminogen, tissue plasminogen activator, urokinase, protein S, vitronectin, plasminogen-activator inhibitor 1	Coagulation, degradation of blood clots, trapping invading microbes, chemotaxis
Ceruloplasmin	Contains copper, has histaminase-and ferroxidase-activity; scavenges Fe^{2+} and free radicals
Haptoglobin (Hp)	Binds haemoglobin; binds to CD_{11b}/CD_{18} integrines
Alpha1-acid glycoprotein (AGP)	Influences T-cell function; binds steroids
Interleukin1-receptor antagonist	modulates a variety of interleukin 1 related immune and inflammatory responses
Alpha1-Antitrypsin (AAT)	Inhibits proteolytic enzymes, immune-modulatory activity
Alpha1-Antichymotrypsin (ACT)	Inhibits proteolytic enzymes
Alpha2-macroglobulin	Inhibits proteolytic enzymes
Proteins whose concentration decrease	
Albumin	Regulates the osmotic pressure of blood
Transferrin	Carrier protein, immunoregulation
Transthyretin	Binds to aromatic compounds, carrier of retinol
Alpha-fetoprotein	Binds various cations, fatty acids and bilirubin
Alpha2-HS glycoprotein	Carrier protein, forms soluble complexes with calcium and phosphate
Thyroxine-binding globulin	Binds thyroid hormone

Table 1. Diverse functional activities of APPs.

7. Haptoglobin

Haptoglobin (Hp) is constitutively present in the plasma (normal plasma levels 0.3 to 3.0 mg/ml) and functions mainly as a scavenger protein for hemoglobin (Hb) that is released from

erythrocytes. Hp-Hb complexes are rapidly cleared from the circulation predominantly in the liver (Kupfer cells) expressing the Hp-Hb receptor CD163 (Graversen et al., 2002). Hp not only prevents loss of Hb/iron by renal excretion and protects from iron-driven oxidative tissue damage, but also acts as a bacteriostatic protein. Hence, Hp restricts access of bacteria to iron that is essential for bacterial growth.

Plasma levels of Hp rise rapidly up to 2 to 5 folds during inflammation, specifically under conditions when there is an extensive amount of necrotic tissue in the wound. Like for other APPs, Hp synthesis is induced by various cytokines but also by ciliary neurotrophic factor. While IL-6 is the most efficient Hp inducer, IFN-γ blocks IL-6-induced Hp synthesis and TNF-β attenuates glucocorticoid-dependent expression of Hp (Baumann et al., 1990; Marinkovic & Baumann, 1990; Raynes et al., 1991; Yoshioka et al., 2002; Yu et al., 1999).

Although the liver is the major site of Hp expression, inducible expression of Hp is also found in lung, skin, spleen and kidney. This suggests that tissue levels of Hp are most likely regulated differently and vary from those in the blood (Abdullah et al., 2009). Therefore, locally expressed Hp, for example in the lungs, might be an important component of a local protection system with antioxidant, bacteriostatic and anti-inflammatory effects (Abdullah et al., 2012).

Hp influences almost every immune cell type of the innate as well as the adaptive immune response. As an example, binding of Hp-Hb to CD163 receptor on the monocytes and tissue macrophages (Kristiansen et al., 2001), induces anti-inflammatory and protective genes such as heme oxygenase-1 (HO-1) (Schaer et al., 2006). HO-1 is involved in heme catabolism that ends up with carbon monoxide, bilirubin and ferritin - all are known to exert potent anti-inflammatory and cytoprotective effects (Otterbein et al., 2003).

It has also been demonstrated that Hp inhibits respiratory burst in fMLP, arachindonic acid or opsonised zymosan-stimulated neutrophils (Oh et al., 1990). Moreover, Hp exerts inhibitory effects on fMLP-driven chemotaxis, and shows intracellular bactericidal activity against *E. coli.* (Rossbacher et al., 1999). Evidence exists for an intracellular uptake of Hp by peripheral blood neutrophils and monocytes via endocytosis and for the subsequent exocytosis of Hp following exposure to *Candida albicans* or TNF- α (Berkova et al., 1999; Wagner et al., 1996). Hp reduces LPS-induced pro-inflammatory effects by the selective suppression of TNF-α, IL-10 and IL-12 production *in vivo* and *in vivo*. The importance of anti-inflammatory and immune modulatory effects of Hp is confirmed by enhanced sensitivity of Hp knockout mice to LPS shock compared to wild type mice (Arredouani et al., 2005).

In addition to its effects on innate immunity, Hp also dampens adaptive immune response. It is a powerful inhibitor of the proliferative response of lymphocytes to phytohemagglutinin and concanavalin A, and depending on the concentration used Hp significantly inhibits or enhances mitogenesis in B-cells in response to LPS (Baseler & Burrell, 1983). Using highly purified human T lymphocytes Arredouani et al. presented evidence for a specific binding of Hp to resting and anti-CD3 stimulated CD4+ and CD8+ T cells and for a direct anti-proliferative effect of Hp on T lymphocytes (Arredouani et al., 2003).

Further evidence for the high importance of Hp as anti-oxidative and immunoregulatory compound arises from the existence of different Hp subtypes and their influence on different

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pathologies. Hp gene has been studied as a candidate gene for rheumatoid arthritis, systemic lupus erythematosus, primary sclerosing cholangitis, inflammatory bowel disease and diabetes mellitus type 2 (Marquez et al., 2012).

In human two allels code for Hp1 and Hp2 proteins resulting in Hp1-1, Hp2-2 homozygous and Hp2-1 heterozygous genotypes. Clinical studies show that Hp2-2 individuals suffering from diabetes mellitus have a higher risk of vascular complications, especially diabetic nephropathy, compared to Hp2-1 and Hp1-1 individuals (Asleh & Levy, 2005). Epidemiological data also show that Hp2-2 genotype is a major determinant of susceptibility to diabetic cardiovascular disease (Levy et al., 2010).

Functional differences between Hp1-1 and Hp2-2 on molecular level can be in part explained by the finding that the Hp1-1-Hb complex is endocytosed more rapidly by the CD163 pathway than Hp2-2-Hb. This results in a more effective clearance of Hb and less oxidative stress in Hp1-1 individuals (Asleh et al., 2003). Moreover, Hp2-2 individuals show greater immunological reactivity including higher antibody titers after vaccination compared to Hp1-1 and Hp2-1 individuals (Nevo & Sutton, 1968). When compare to Hp2-2-Hb, Hp1-1-Hb is related to a much greater production of anti-inflammatory cytokines, therefore, Hp1-1Hp results in a more Th2 directed balance between Th1 (inflammatory) and Th2 (anti-inflammatory) T helper cells. Recent findings provide evidence that Hp1-1 individuals are better protected against oxidative stress and Hp1-1 seems to have higher immunomodulatory effects than Hp 2-2 (Guetta et al., 2007).

8. Alpha-1-acid glycoprotein

Alpha-1-acid glycoprotein (AGP) also known as orosomucoid (ORM) is a heavily glycosylated (45 %) protein (Schmid et al., 1977) APG belongs to the immunocalin family, a lipocalin subfamily. Whereas the lipocalins function as carriers for small hydrophobic compounds, the immunocalins were shown to modulate inflammatory and immune responses (Logdberg & Wester, 2000; Hochepied et al., 2003). Though, the main biologic function of AGP remains unclear. Indeed, APG was found to be a major carrier for neutral and basic drugs in the blood (Kremer et al., 1988). Evidence also exists supporting a role for AGP in the maintenance of normal capillary permeability and selectivity by binding to the capillary vessel wall putatively as part of the glycocalyx, a dynamic endothelial surface layer of glycosaminoglycans, proteoglycans and absorbed plasma proteins (Curry et al., 1989; Fournier et al., 2000; Pries et al., 2000). Moreover, AGP stabilizes the biological activity of plasminogen activator inhibitor-1 (Smolarczyk et al., 2005).

AGP is a positive acute phase protein that under normal conditions circulates in human plasma at a concentration of 0.6 -1.2 mg/ml and rises up to 2- to 7-fold during acute phase response (Colombo et al., 2006; Kremer et al., 1988). Besides the liver, a main source for the circulating AGP levels, production of AGP occurs in human microvascular endothelial cells, pneumocytes, alveolar macrophages, neutrophils, monocytes and B and T lymphocytes (Sirica et al., 1979; Sorensson et al., 1999; Crestani et al., 1998; Martinez Cordero et al., 2008; Fournier et al.,

1999; Theilgaard-Monch et al., 2005; Rahman et al., 2008; Gahmberg & Andersson, 1978; Dirienzo et al., 1987). Hepatic AGP expression is induced by the IL-1β, IL-6 and TNF-α and inhibited by the growth hormone (Barraud et al., 1996; Mejdoubi et al., 1999).

The immunomodulatory activities of AGP are specifically directed against exaggerated inflammatory response to tissue damage. For example, AGP in a concentration-dependent manner regulates neutrophil chemotactic migration and superoxide generation (Costello et al., 1984; Hochepied et al., 2003; Laine et al., 1990). AGP also inhibits monocyte chemotaxis and diminishes cellular leakage caused by histamine and bradykinin. Moreover, AGP induces secretion of soluble TNFα receptor and IL-1 receptor antagonist from peripheral blood monocytes. (Tilg et al., 1993; Samak et al., 1982; Muchitsch et al., 1996).

The effects of AGP on lymphocytes are mainly immunosuppressive. AGP significantly suppresses induced synthesis of IL-2 and proliferation of lymphocytes (Chiu et al., 1977; Elg et al., 1997). Notably, different glycan variants of AGP show different degrees of inhibition of lymphocyte proliferation (Bennett & Schmid, 1980). The Con A non-reactive fraction of AGP (AGP-A) inhibits anti-CD3 stimulated lymphocyte proliferation stronger than Con A reactive AGP forms emphasizing the importance of the carbohydrate moiety of AGP (Pos et al., 1990).

In vivo AGP has been found to protect mice against TNF-α induced lethal shock but not from LPS-induced lethality or Fas-mediated cell death in lethal hepatitis. These findings imply that the protecting effects of AGP are, most likely, TNF-α -specific (Muchitsch et al., 1998; Van Molle et al., 1999).

Pro-inflammatory and immuno-stimulatory effects of AGP have been described, too. Previous studies demonstrated that AGP activates monocytes to produce IL-1β, IL-6, IL-12, TNF-α and tissue factor (Su & Yeh, 1996; Tilg et al., 1993). Moreover, AGP has found to potentiate the effect of suboptimal concentrations of LPS to induce IL-1β, IL-6 and TNF-α in peritoneal and alveolar macrophages (Boutten et al., 1992). Nakamura and collaborators presented evidence that monocytes stimulated with inflammatory cytokines produce AGP and suggested that high expression of AGP may potentially create a positive feedback loop for further production of IL-1β (Nakamura et al., 1993). The observation that AGP-induced secretion of TNFα can be inhibited by protein tyrosine kinase inhibitors led to the proposal that AGP involves tyrosine kinase signalling pathway (Su et al., 1999). This is in line with the finding that AGP binds to chemokine receptor CCR5 on macrophages and signals via tyrosine kinases (Atemezem et al., 2001). In neutrophil models AGP interacts with lectin-like receptors (Siglecs), Siglec-5 and/or Siglec-14, directly induces an intracellular calcium rise and regulates expression of L-selectin (Gunnarsson et al., 2007).

Recently, it has been reported that AGP up-regulates the expression of the Hb scavenger receptor CD163 on monocytic cells *in vitro* (Komori et al., 2012). *In vivo*, in the phenylhydrazine-induced hemolysis mice model AGP induced CD163 expression with a subsequent increase in Hb clearance and reduced oxidative stress. The effect of AGP on CD163 expression seems to be indirect and mediated by the IL-6 and IL-10, known inducers of CD163. According to Komori and co-workers AGP induces CD163 expression via the TLR4/CD14 pathway (Komori et al., 2012).

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Taken together AGP seems to exhibit both pro- and anti-inflammatory effects. The resulting net function of AGP most likely depends on contextual factors, e.g. interacting cell type, additional stimuli, inflammatory status of the host.

9. C-reactive protein

Human C-reactive protein (CRP) belongs to a family of pentraxins (Myles et al., 1990) and is composed of five identical 23 kDa subunits (protomers), linked together non-covalently to form pentameric CRP. The liver is the main source for circulating CRP. Hepatic secretion of CRP is primarily regulated by IL-6 and IL-1 (Weinhold et al., 1997; Zhang et al., 1995). Plasma CRP is a highly dynamic protein with a concentration range from 0.05 to 500 μg/ml (Shine et al., 1981; Pepys & Hirschfield, 2003). Plasma CRP levels rise up to 10.000-fold in response to acute tissue injury or inflammation and decline rapidly due to a relatively short half-life (about 19 hours) (Macintyre et al., 1982; Claus et al., 1976; Vigushin et al., 1993). Cardiovascular disease is correlated to chronic inflammation and serum CRP above 3 μg/ml is a good predictive of increased risk for the disease (Black et al., 2004).

Both *in vitro* and *in vivo* CRP exists in a monomeric form (mCRP) with a molecular weight of 23 kDa, too (Taylor & van den Berg, 2007). The pentameric native form of CRP (nCRP) is usually found in the plasma whereas the momomeric form of CRP (mCRP) is present in tissues and at sites of inflammation (Diehl et al., 2000; Potempa et al., 1987; Rees et al., 1988). pCRP also undergoes conformational rearrangement in the absence of calcium and dissociates into mCRP (Eisenhardt et al., 2009). The modified CRP isoform is generated *in vivo* when pCRP binds to damaged membrane surfaces such as activated platelets, apoptotic microparticles (Habersberger et al., 2012), liposomes containing lysophosphatidylcholine (Volanakis & Narkates, 1981), and oxidized but not native low-density lipoprotein (Chang et al., 2002). Modified CRP displays an antigenicity that is distinct from pCRP. In fact, modified CRP may exist as aggregates of mCRP on cell membrane surfaces (Ji et al., 2007).

One critical function of modified CRP is binding to C1q and activation of the immune system's complement cascade (Ji et al., 2006). In addition to its roles in the regulation of classical and alternative complement pathways, CRP has been shown to interact with ficolin-2 (Ng et al., 2007). Recent study has shown that infection-induced local inflammatory conditions trigger a strong interaction between CRP and ficolin-2; this elicits complement amplification and enhances antimicrobial activation of the classical and lectin pathways (Zhang et al., 2009).

Despite evidence that modified CRP is more strongly associated with inflammation (Zouki et al., 2001) current CRP diagnostics are unable to distinguish between the common isoforms.

Taken together, physiological function of CRP is not fully understood. The most reproducible observations indicate that CRP contributes to innate immunity against bacterial infections like pneumococci (Horowitz et al., 1987). Experimental data provide evidence that transgenic mice over-expressing human CRP are more resistant to *Pneumococci* sepsis than wild-type mice (Szalai et al., 1995). Indeed, CRP is expressed by respiratory epithelial cells and CRP concen-

trations in secretions from both inflamed and non-inflamed human respiratory tract are sufficiently high for an antimicrobial effect. This suggests that CRP is involved in the bacterial clearance in the respiratory tract (Gould & Weiser, 2001).

Recent findings lend experimental support to the hypothesis that biological activities of CRP might be dependent on both, its molecular form and the property to interact with plasma membrane lipid microdomains (Ji et al., 2009).

For example, CRP and two CRP derived peptides, CRP(174-185) and CRP(201-206), but not peptide CRP(77-82) are capable of diminishing attachment of human neutrophils to LPS-stimulated human endothelial cells and consequently limiting leukocyte traffic into inflamed tissues (Zouki et al., 1997). CRP as well as the two peptides rapidly downregulate the expression of L-selectin on the neutrophil surface.

In summary, CRP is used as an indicator of disease outcome and to monitor the disease course. CRP is measured objectively and affordably in clinical practice worldwide.

10. Conclusions

In this chapter we have shown that AAT, only one among many APPs, holds tremendous potential as an anti-inflammatory and immuno-modulatory protein.

Several *in vitro* and *in vivo* studies have been published in which a specific APP switched the pro-inflammatory to the anti-inflammatory pathways necessary for the resolution of inflammation. Although the physiological roles of APPs are not completely understood, existing findings provide evidence that APPs act on a variety of cells involved in early and late stages of inflammation and that their effects are time, concentration and molecular conformation-dependent. It cannot be excluded that these proteins may have more common characteristics and biological effects, however the lack of high quality purified endotoxin or other contaminant free proteins limits current understanding.

The mechanisms of action for the APPs are still being investigated, however, there remain a number of challenges to face in the development of APPs as a true anti-inflammatory therapeutic agents and diagnostic markers.

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