ISSN 0006-2979, Biochemistry (Moscow), 2006, Vol. 71, No. 10, pp. 1051-1059. © Pleiades Publishing, Inc., 2006.
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REVIEW

Molecular Interactions of Acute Phase Serum Amyloid A: Possible Involvement in Carcinogenesis

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Received April 11, 2006
Revision received May 22, 2006

Abstract—Acute phase serum amyloid A (A-SAA) is a well-known marker of inflammation. The present review summarizes data on the regulation of A-SAA expression, signaling pathways which it is involved in, its effects, and possible influences on progression of malignant tumors.

DOI: 10.1134/S0006297906100014

Key words: inflammation, malignant tumor, serum amyloid A, NFκB, matrix metalloproteinase

Acute phase amyloid A (A-SAA) was first discovered as a soluble precursor of amyloid A, a protein responsible for amyloid deposits in chronic inflammation [1, 2]. The blood concentration of A-SAA in inflammation increases to 1 mg/ml and more, whereas the normal level is 1-10 μg/ml [3].

The family of serum amyloids A (SAA) includes a number of homologous proteins with molecular weight of 11-12 kD. In humans, there are two nearly identical genes encoding A-SAA: *SAA1* and *SAA2*. Both *SAA1* and *SAA2* are represented by several alleles. In mice, acute phase serum amyloid is encoded by two highly homologous genes *Saa1* and *Saa2*, and also by the gene *Saa3*. The protein Saa3 is 63 and 65% identical with the proteins Saa1 and Saa2, respectively [3]. In humans, the *Saa3* homologous sequence contains an insertion responsible for a frame shift and appearance of a stop codon. Nevertheless, stimulation with prolactin or the inflammation inducer LPS initiates transcription of *SAA3* in the mammary gland epithelial cells [4]. But no translation product of this mRNA has been detected.

In addition to the acute phase proteins, the family of serum amyloids A also includes constitutive proteins (C-SAA), SAA4 in humans and Saa5 in mice, characterized by more or less constant level of expression. The amino acid sequence of these proteins is about 50% identical with that of the acute phase proteins [3].

The proteins of the serum amyloid A family are evolutionarily ancient and present in all vertebrates studied, including fishes [5], and in echinoderms [6].

Similarly to acute phase proteins, A-SAA is mainly generated in the liver but is also synthesized in leukocytes, epithelial cells of different organs (stomach, intestine, lungs, kidneys, etc.), and brain neurons [7]. A high level of this protein is also observed directly in regions of inflammation, including synoviocytes in rheumatoid arthritis [8] and atherosclerotic patches [9, 10].

An increased blood level of A-SAA was found in patients with cancer even some decades ago [11-13]. Moreover, the level of A-SAA correlated with the stage of the disease and was the highest at the stage of metastasis [13]. The blood level of A-SAA was also studied in correlation with the prognosis of the disease [13]. The mean survival of patients with the late stage of cancer was significantly less at A-SAA concentration higher than 10 μg/ml than in patients with concentration lower than 10 μg/ml [13]. This observation supports the idea about the possible influence of A-SAA on cancer progression.

New proteomic approaches of investigation, such as mass spectrometry and immunochips, have shown A-SAA to be promising as a biomarker of ovary [14], lung [15], kidney [16], and nasopharyngeal [17] cancer.

Earlier, A-SAA in cancer patients was suggested to be of liver origin, and its elevated level in the blood was

Abbreviations: A-SAA) acute phase serum amyloid A; C/EBP) CCAAT enhancer binding protein; HDL) high density lipoprotein; IL) interleukin; LPS) lipopolysaccharide; MMP) matrix metalloproteinase; NFκB) nuclear factor κB; SAF1) SAA-activating factor; TIMP) tissue inhibitor of matrix metalloproteinase; TNF) tumor necrosis factor.

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thought to be a consequence of the body's systemic response to inflammation concomitant with cancer. However, an increased expression of *A-SAA* was found in the tissue of human colon carcinoma [18], as well as in the cells of trophoblastoid choriocarcinoma and in the placenta of human first trimester trophoblast [19].

The correlation between A-SAA and various human diseases, such as rheumatoid arthritis, atherosclerosis, and cancer, has attracted the attention of researchers. Based on the recent data on the A-SAA features, this protein is suggested to play an active role in pathogenesis of these diseases.

In the present review, we summarize various data on the regulation of expression and molecular interactions of A-SAA, signaling pathways which it is involved in, and pay special attention to the possible influence of this protein on the initiation and progression of cancer.

REGULATION OF *A-SAA* EXPRESSION

Initiation of inflammation is associated with activation of a cascade of inflammatory mediators. In the region of inflammation, monocytes and macrophages generate primary inflammatory mediators among which cytokines of the IL-1 and tumor necrosis factor (TNF) families are the most important. These cytokines, in turn, stimulate the expression by stroma cells of secondary cytokines (including IL-6 and IL-8), which are chemotactic for leukocytes [3]. Inflammation induces in the body various systemic changes, in particular, changes in the expression profile of acute phase proteins including A-SAA. In inflammation, synthesis of A-SAA can increase hundreds and even thousands of times within a few hours, and its expression is regulated mainly on the

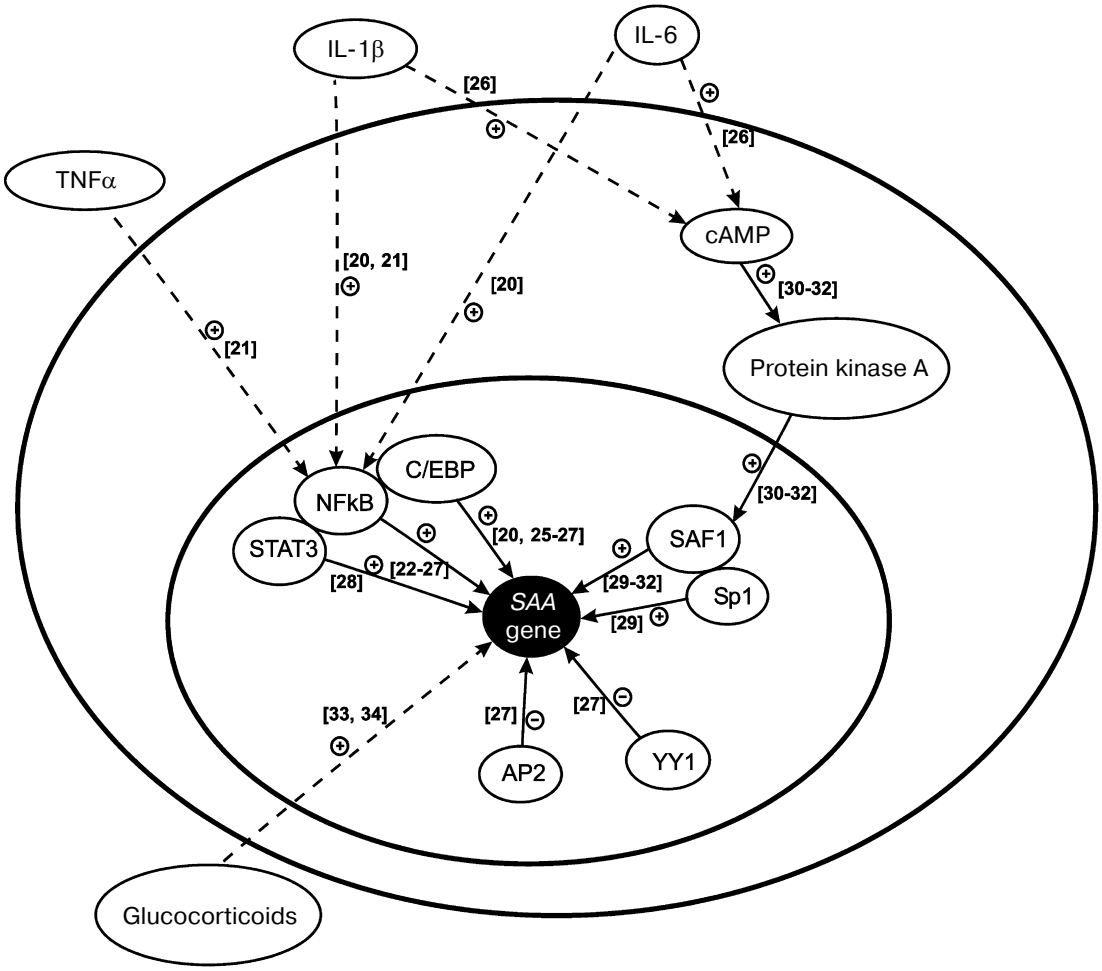

Fig. 1. Scheme of regulation of expression of the acute phase serum amyloid A gene. The *SAA* gene denotes highly homologous genes *SAA1* and *SAA2*. The activating and inhibitory influences are shown by pluses and minuses, respectively. The solid arrows show experimentally proven intermolecular interactions, the dotted lines show interactions mediated through other molecules or interactions through a mechanism that has not been experimentally established.

transcriptional level. The pathways of regulation of the *A-SAA* gene are presented in Fig. 1.

Proinflammatory cytokines IL-1β, IL-6 [20], and TNFα [21] are primary inducers of A-SAA synthesis. According to data of Hagihara et al., IL-6 plays a key role in the induction of *A-SAA* expression, and this induction is considerably enhanced when IL-6 acts in complex with IL-1β or TNFα. But neither IL-1β, nor TNFα can activate *A-SAA* expression in the absence of IL-6 [21].

Furthermore, *A-SAA* expression can be activated through different pathways, and transcriptional factors involved in the activation also can differ under varied conditions, in different cell, and in different organisms. The following activators of *A-SAA* expression are known: nuclear factor κB (NFκB) [20, 22-27], CCAAT-binding protein (C/EBP) [20, 25-27], STAT3 [28], and the SAA-activating factor (SAF1) [26, 29-32].

During inflammation, the binding of NFκB with consensus DNA sequences is most markedly increased in the lungs, liver, and kidneys [26], whereas SAF1 binding with DNA increases minimally in kidney cells, but occurs in synoviocytes [29] and brain cells [26]. Note that NFκB and SAF1 are activated in both acute and chronic inflammation, but the transcriptional factor C/EBP in many tissues is activated only for a short time and does not play a role in chronic inflammation [26]. Also, NFκB and C/EBP can function as a complex [25]. In a hepatoblastoma cell line, the transcriptional factor NFκB, in complex with STAT3, was shown to be involved in induction of *A-SAA* transcription in response to treatment with IL-1 and IL-6 [28].

The pathway of induction of the *A-SAA* expression with involvement of SAF1 was studied in detail in rabbit synoviocytes. Both IL-1β and IL-6 enhanced the cAMP concentration in the synoviocytes, resulting in activation of protein kinase A, which phosphorylated SAF1 [30-32]. The transcriptional factors SAF1 and Sp1 formed in the synoviocytes a heterodimer [29].

In humans, glucocorticoids are involved in regulation of the *SAA1* expression in the liver and smooth muscles. The synthetic glucocorticoid dexamethasone and also corticosterone and hydrocortisone considerably increase *SAA1* expression [33, 34]. The *SAA2* promoter is insensitive to glucocorticoids because it has a nine-nucleotide insertion in the site responsible for binding with glucocorticoid receptors.

The transcriptional factors YY1 and AP2 are repressors of the *A-SAA* gene. On the promoter of the rat gene *SAA1* the consensus sequence of NFκB is overlapped with the binding sites of the two above-mentioned repressors. However, the strength of YY1 and AP2 interaction with the promoter is significantly different: YY1 is bound more weakly than NFκB but AP2 is bound more strongly. As a result, *SAA1* is repressed in AP2-possessing cells, whereas in the cells unable to synthesize AP2 everything depends on the ratio between YY1 and NFκB [27].

EFFECTS OF THE A-SAA PROTEIN ON BIOCHEMICAL PROCESSES

Much information is now available concerning the A-SAA protein interactions with various partner proteins and following events. A-SAA influences inflammation, induces expression of some matrix metalloproteinases, changes lipid metabolism, and interacts with the intercellular matrix. Figure 2 presents the scheme of molecular interactions of A-SAA.

Cytokine-like features of A-SAA and its influence on inflammation. More than ten years ago it was found that, similarly to proinflammatory cytokines, A-SAA could induce synthesis and secretion by leukocytes of some cytokines and attract leukocytes into the region of inflammation [35, 36].

In particular, A-SAA, both in a free state and inside high density lipoproteins, was shown to induce production of interleukin IL-1β by monocytes [36]. A-SAA also influenced the production of TNFα and IL-8 by neutrophils [37-39]. Note that these effects were observed when the cells were treated with serum amyloid even at a comparatively low concentration, e.g., 30 μg/ml [36]. In most cases the production of cytokines was elevated due to activation of their transcription [36, 39].

To find a receptor responsible for manifestation of the cytokine-like features of A-SAA, leukocytes were cross-desensitized with A-SAA and other chemoattractants. By such an approach A-SAA was shown to interact with a low affinity receptor FPRL1 (formyl peptide receptor-like 1) to the bacterial peptide fMLP, which was confirmed by data on the binding of radiolabeled A-SAA with cells transfected with the *FPRL1* gene [40].

FPRL1 is a receptor with seven transmembrane domains and is associated with the G_i-protein [40]. In addition to A-SAA and fMLP, eicosanoid lipoxin A4, produced during inflammation and capable of inhibiting the immune response, is also a high affinity ligand of FPRL1 [41]. FPRL1 is expressed in very different cells, including neutrophils [38], synoviocytes [42], and hepatocytes [43].

The FPRL1-including signaling pathway resulting in IL-8 secretion by neutrophils in response to stimulation with A-SAA was studied in detail [38]. Interaction of A-SAA with FPRL1 increased the cell concentration of calcium and activated MAP kinases ERK1/2 and p38 through their phosphorylation. A-SAA also activated the transcriptional factor NFκB through both its increased expression and the promoted degradation of its inhibitor IκBα. A correlation was also demonstrated between the activation of NFκB and the increase in IL-8 secretion [38]. In work [44], the interaction of NFκB with the promoter of the gene *IL-8* and increased transcription of the latter were shown. The ability of A-SAA to activate NFκB was also shown on mouse intestine epithelium cells [44] and fibroblast-like human synoviocytes [45, 46].

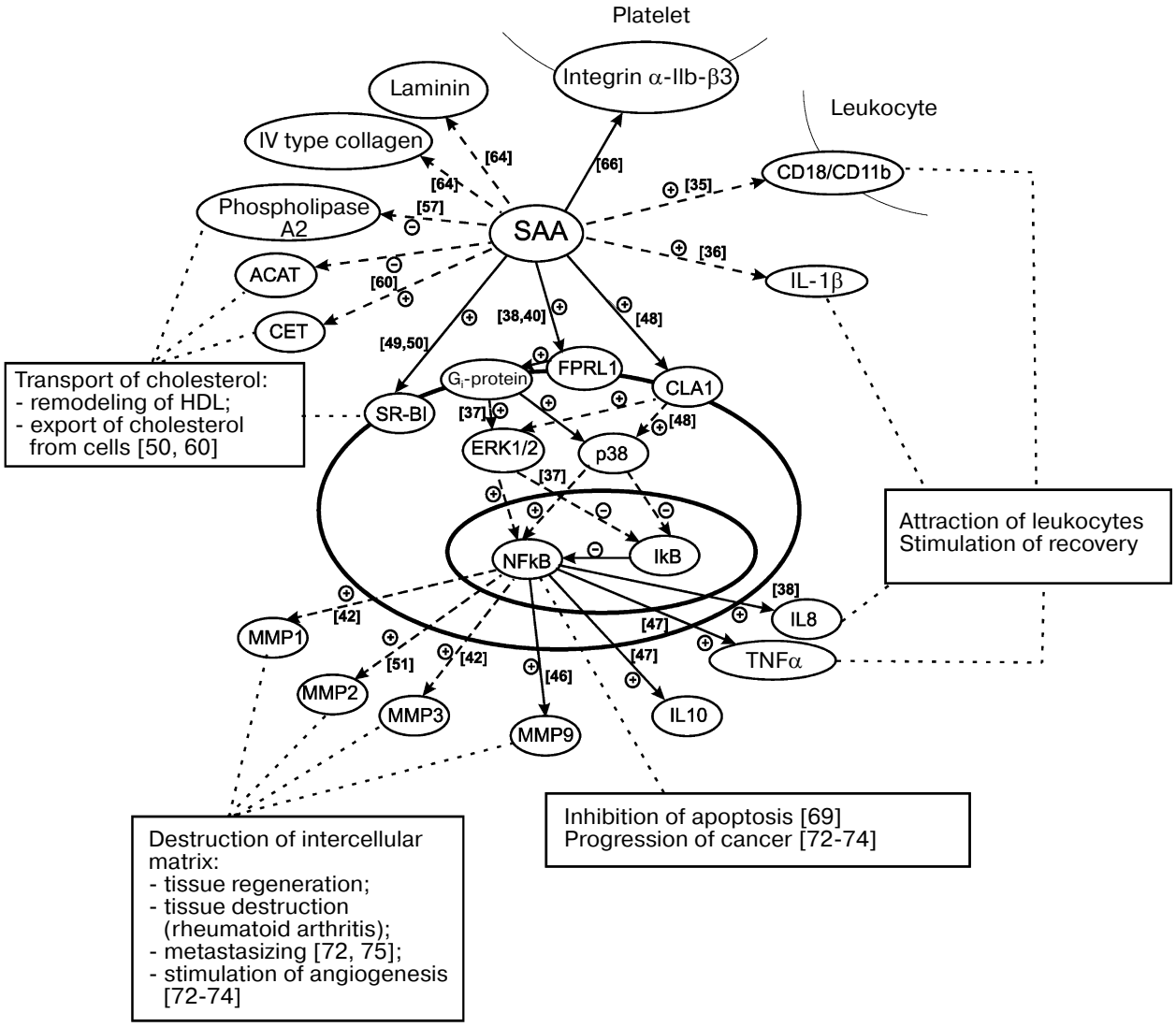

Fig. 2. Scheme of molecular interactions of acute phase serum amyloid A. Activating and inhibitory influences are shown by pluses and minuses, respectively. The solid arrows show experimentally proven intermolecular interactions, and the dotted lines show interactions mediated through other molecules, or interactions by mechanisms that are not yet experimentally established.

Treatment with A-SAA stimulated the expression of TNFα and IL-10 in human monocytes by a pathway that involves NFκB [47]. But TNFα is a proinflammatory cytokine, whereas IL-10 displays anti-inflammatory properties. The expression of TNFα was stimulated with involvement of MAP kinase ERK1/2 and the expression of IL-10 with involvement of p38. It should be emphasized that low concentrations of A-SAA induced TNFα expression and, thus, enhanced inflammation, whereas high concentrations of A-SAA mainly stimulated IL-10 expression and, thus, inhibited inflammation. Moreover, the increase in expression of these two cytokines was characterized by different kinetics: the peak of the TNFα expression was observed 6 h after the treatment of the cells with A-SAA and the maximum of IL-10 expression occurred after 12 h [47].

Apart from proinflammatory cytokines, NFκB is a transcriptional factor for a multitude of genes, including some antiapoptotic ones. Data on the relations of NFκB with carcinogenesis will be considered below.

The CLA1 receptor (an analog of CD36 and LIMPII-1), an ortholog of the human scavenger receptor of the B class type I (SR-BI), is involved in realization of the cytokine-like properties of A-SAA [48]. SR-BI interacts with high density lipoproteins (HDL) and is responsible for the selective uptake of cholesterol by the cells; but, in addition to HDL, this receptor has an affinity for different components of lipoproteins including A-SAA

[49, 50]. The role of A-SAA interaction with SR-BI in the regulation of lipid metabolism will be considered below. In HeLa cells transfected with the *CLA1* gene and in the monocyte cell line, the interaction of A-SAA with CLA1 was accompanied by internalization of A-SAA and activation of the signaling pathway, which was similar to the above-described pathway with the involvement of MAP kinases ERK1/2 and p38 and induction of IL-8 synthesis [48].

The role of A-SAA in induction of expression of matrix metalloproteinases. Significantly elevated concentrations of A-SAA mRNA and the A-SAA protein were found in the synovial tissue of patients with rheumatoid arthritis [8, 51], and the role of A-SAA in pathogenesis of this disease has attracted a great interest. Studies on human and rabbit synoviocytes and monocytes have shown that A-SAA can increase the expression of a number of matrix metalloproteinases, enzymes degrading the intercellular matrix. Thus, increased expressions of MMP1, MMP3 [43], MMP2 [51], MMP9 [45], and MMP13 [52] were shown. In addition to the elevated concentration of A-SAA mRNA, patients with rheumatoid arthritis and other kinds of inflammatory arthritis (psoriatic, sarcoid, and nonspecific arthritis) had an increased level of mRNA of the A-SAA receptor FPRL1 in the fibroblastoid synoviocytes, macrophages, and endothelial cells [42]. Therefore, FPRL1 was suggested to be involved in the induction of matrix metalloproteinase expression. The role of FPRL1 was strictly proven for the induction of MMP9 expression [45]. The MMP9 expression in human monocytes was shown to be induced by a mechanism similar to the above-described induction of the IL-8 expression, i.e., with involvement of FPRL1 and transcriptional factor NFκB [45].

The interaction of A-SAA with FPRL1 resulted in activation of matrix metalloproteinases, whereas another high affinity ligand of FPRL1, eicosanoid lipoxin A4, was likely to act oppositely: it decreased the expression of MMP3 and stimulated the expression of tissue inhibitors of metalloproteinases TIMP-1 and TIMP-2 [53].

Although matrix metalloproteinases are responsible for some important physiological functions associated with tissue rearrangements, a long-term increase in their activities underlies such pathologic processes as tissue destruction in rheumatoid arthritis. The role of matrix metalloproteinases in progression of cancer will be considered below.

Influence of A-SAA on lipid metabolism. In the blood A-SAA is mainly present as a component of HDL, which replaces in them apolipoprotein A1 [3]. HDLs play the central role in the back transport of cholesterol from the body cells to the liver [54]. But the replacement of apolipoprotein A1, which is the main protein component of HDL, by A-SAA can significantly affect properties of these lipoproteins. Moreover, there is a correlation between the increase in the A-SAA blood concentration and progress of atherosclerosis [55]. Therefore, the influence of serum amyloid on lipid metabolism, especially on metabolism of cholesterol, is very interesting.

Many data have accumulated about the influence of A-SAA on lipid metabolism, but they are rather contradictory.

Initially, A-SAA was reported to provide for an increase in the rate of cholesterol utilization. Thus, A-SAA was shown to bind cholesterol and strengthen its uptake by cells. This effect was demonstrated on hepatoma HepG2 cells and aorta cells of a newborn rabbit [56].

The increase in cholesterol uptake by cells is supported by data on AA-induced activation of secretory phospholipase A_2 catalyzing hydrolysis of HDL surface phospholipids [57]. Hydrolysis of these phospholipids was accompanied by displacement of cholesterol molecules from the core region of HDL to the surface, and this promoted an increase in the ability of HDL to transport cholesterol into the cells [58]. But it is unclear whether this effect exists in HDL enriched with A-SAA.

Later it was found that, in contrast, A-SAA provided for a decrease in cholesterol uptake by cells and an increase in its export [49, 50, 59]. Some of these data concerned changes in the interaction of acute phase HDL with its receptor SR-BI responsible for the selective uptake by the cells of cholesterol esters and some other lipids of HDL.

It was shown on the Chinese hamster ovary cells expressing SR-BI and on the hepatoma cell culture HepG2 that HDL enriched with serum amyloid, as well as free A-SAA, were high affinity ligands of SR-BI and inhibited cholesterol uptake by the cells [49], promoting its export from the cells [50].

An increase in cholesterol export was also shown on mouse macrophages after phagocytosis of the cell membranes. SAA2.1 as a component of HDL inhibited acyl-CoA-cholesterol acyltransferase (ACAT), which catalyzed production of cholesterol esters and activated cholesteryl ester hydrolase (CEH) catalyzing hydrolysis of cholesterol esters. Changes in the ratio between esterified and free cholesterol increased its active export with involvement of the ATP-binding cassette transporter (ABCA1) [60]. This seems to be a mechanism for removal of excess cholesterol obtained by macrophages from cell membranes degraded during inflammation.

Some other features of A-SAA are also associated with lipid metabolism. Thus, A-SAA inhibits lecithin:cholesterol acyltransferase (LCAT) in human blood and thus prevents esterification of cholesterol in HDL [61]. A-SAA was also shown to lower the rate of lipid biosynthesis in smooth muscles [62].

On summarizing, note that data supporting the increase in cholesterol export from cells under the influence of A-SAA seem more justified. Disorders in back transport and cholesterol utilization can increase the risk

of atherosclerosis at chronically elevated blood level of A-SAA [63]. Obviously, the effect of A-SAA on lipid metabolism also depends on the cell type.

Interaction of A-SAA with intercellular matrix components and its influence on adhesion of cells. Serum amyloid A can interact with some components of the intercellular matrix. A-SAA interacts with high affinity *in vitro* with laminin [64], but virtually did not interact with laminin complexed with entactin. However, just this is a normal form of laminin presence in intercellular matrix. It was supposed that A-SAA should interact *in vivo* not with the intact but with damaged intercellular matrix, which contained entactin partially degraded by proteases. Of the intercellular matrix proteins, entactin is the most liable to proteolysis [64]. In addition to laminin, A-SAA also interacts with type IV collagen [64], vitronectin [65], heparin, and heparan sulfate [64].

Because A-SAA can interact with intercellular matrix proteins, it is reasonable to suggest that HDL enriched with A-SAA should also have the same properties. The increased adhesion of HDL to vascular walls seems to be a connecting link between inflammation and progression of atherosclerosis [63].

Concurrently with the ability to interact with intercellular matrix proteins, A-SAA can influence adhesion of some cells, first, interacting with their receptors to intercellular matrix, and second, inducing the expression of some receptors. Via an RGD-like motif, A-SAA interacts with αIIbβ3 integrin on the platelet surface [66]. The αIIbβ3 integrin plays an important role in thrombogenesis, providing for platelet interaction to one another and with intercellular matrix proteins, such as fibronectin and vitronectin [67].

A-SAA also influences the adhesion of leukocytes through induction of expression of CD11b and LECAM-1 (the molecule responsible for leucocyte adhesion-1), which are receptors for extracellular matrix proteins in polymorphonuclear neutrophils and monocytes [35]. The increased adhesion of lymphocytes to intercellular matrix in the area of inflammation seems to promote their accumulation and aggravate the inflammation.

HYPOTHETICAL MECHANISMS OF THE INFLUENCE OF A-SAA PROTEIN ON CANCER PROGRESSION

Every malignant tumor is always accompanied by inflammation; therefore, the finding of an elevated blood concentration of A-SAA in patients with various malignant tumors is expected. However, recent data on its properties suggest that A-SAA as it is can considerably influence carcinogenesis. In this relation, it is necessary to consider in more detail two features of A-SAA: its ability to activate the transcriptional factor NFκB and induce expression of matrix metalloproteinases.

NFκB: correlation of inflammation and cancer. Transcriptional factor NFκB plays a crucial role in inflammation. In the absence of proinflammatory stimuli, NFκB dimers are located in the cytoplasm in complex with an IκB inhibitor. Proinflammatory cytokines activate IκB kinase (IKK), which phosphorylates IκB and makes it a target for ubiquitin-dependent degradation, whereas the released NFκB dimers acquire the ability to penetrate into the nucleus [68].

NFκB is a transcriptional factor of many functionally heterogeneous genes, among which the cytokine genes and antiapoptotic genes should be especially noted. Activation of these genes enhances inflammation and suppresses apoptosis [69].

Indirect data indicating the association of NFκB with cancer were obtained not long ago. Thus, amplification of the NFκB family genes is often observed in human lymphomas and leukemias, and mutations in the *IκBα* gene have been found in patients with Hopkins lymphoma [70].

In some recent works, the key role of NFκB as a connecting link between inflammation and malignant tumor was shown experimentally. Greten et al. investigated the role of NFκB on a model of colitis-associated cancer in mice. Lines of mice with the *IKKβ* deletion only in the intestinal epithelium or only in the myeloid cells were studied. Inactivation of NFκB in the epithelium resulted in a 75-80% decrease in the tumor incidence, without influencing the tumor size and attenuating the inflammation. This was due to increased incidence of apoptosis caused by the absence in the *IKKβ*-lacking epithelial cells of expression of the antiapoptotic gene *Bcl-X_L*, which is a target gene of NFκB. However, in mice with the *IKKβ* deletion in the myeloid cells the tumor incidence was 50% decreased as compared to the control and the tumor size was also markedly decreased. This was realized through quite another mechanism: the secretion by the myeloid cells of proinflammatory cytokines IL-1β, IL-6, KC, MIP-2, TNFα, COX-2, and ICAM was decreased, and this resulted in a decrease in the rate of the intestinal cell proliferation [68].

Other researchers studied the inducible system of the NFκB activation/inactivation on a model of hepatocarcinoma. Mice with knocked-out gene *Mdr2*, which on the background of chronic liver inflammation displayed development of dysplasia/carcinoma/metastasizing tumor, were crossed with mice bearing the super-repressor *IκBα* gene under hepatocyte-specific inducible promoter. In the resulting progeny, the inactivation of NFκB did not affect initial stages of the transformation, but had a critical effect at the stage of tumor malignization increasing the incidence of apoptosis of hepatocytes and preventing the development of carcinoma. But reactivation of NFκB resulted in a fast progression of the malignant tumor [71].

Matrix metalloproteinases: influence on angiogenesis and metastasizing. Matrix metalloproteinases (MMPs) are a large family of zinc-containing enzymes catalyzing

degradation of various components of the intercellular matrix. Normally, MMPs are synthesized only during tissue remodeling, e.g., during embryogenesis, wound healing, and rearrangement of cartilage to bone tissue. Abnormal expression of these enzymes occurs in some diseases, including rheumatoid arthritis and malignant tumors [72].

An increased expression of certain metalloproteinases is found in virtually all types of cancer, and the increase in the MMP concentration correlates with the intensity of metastasizing, and, consequently, negative prediction for the patient [72].

Different MMPs influence various aspects of carcinogenesis. But the role of MMPs, in particular, gelatinases (MMP2 and MMP9), in angiogenesis and metastasizing is best studied.

Stimulation of angiogenesis by MMPs was revealed by studies on the effect of MMP inhibitors on angiogenesis and in experiments on mice with knocked-out MMP-encoding genes. Disorders in MMP functions inhibited angiogenesis both *in vitro* and *in vivo* [73].

A number of mechanisms of stimulation of angiogenesis by matrix metalloproteinases are known. First, the MMP-induced degradation of intercellular matrix proteins promotes migration of endothelial cells into the tissues [73]. Second, MMPs are involved in the release of pro-angiogenic factors bound with the intercellular matrix, such as vascular epithelium growth factor (VEGF) and fibroblast growth factor (bFGF) [72, 74]. It has also been shown that MMP-2 as it is can interact with integrin $\alpha v\beta 3$ and, possibly, activate a signaling pathway leading to proliferation of endothelial cells [73]. Note that the ability of A-SAA to stimulate angiogenesis has been proven experimentally [46].

MMPs also influence metastasizing. First, the MMP-caused degradation of basal membrane components is favorable for penetration of tumor cells into capillaries and lymphatic vessels, as well as for migration of circulating tumor cells from vessels into adjacent tissues. Second, MMPs activate cell migration by destruction of adhesive interactions and presenting new adhesion sites, cleavage of receptors, and release of chemoattractants earlier bound with the intercellular matrix proteins [72, 75]. Moreover, MMP-2 was also shown to cleave laminin-5 with production of a chemoattractant-like fragment favorable for tumor cell migration [75].

There are also data indicating that MMPs contribute to tumor initiation via activation of growth factors and inhibition of apoptosis [74]. MMPs can also influence the immune response, in particular, by degrading some cytokines [74].

The above-presented data indicate an obvious association of acute phase serum amyloid A with both NFκB and matrix metalloproteinases. Both NFκB and various matrix metalloproteinases, in turn, influence carcinogenesis. Antitumor preparations directed against NFκB and matrix metalloproteinases as targets are now actively elaborated.

Thus, some nonspecific inhibitors of NFκB and IKK are used for treatment of malignant tumors. In particular, the known antitumor effect of acetylsalicylic acid [76, 77] is based on suppression of NFκB activity [78]. Specific inhibitors of NFκB and IKK are now searched for, and there are some advances in this line [68].

There are attempts to prepare MMP inhibitors based on different strategies: on the transcription suppression level, activation of proMMPs, or inhibition of active MMPs. However, most of these attempts are still unsuccessful because no sufficient selectivity has been achieved. Inhibitors with a wide spectrum of action sometimes caused effects opposite to the expected ones [74]. The search for new approaches for selective suppression of activities of MMPs involved in the progression of cancer is still urgent.

Suppression of the interaction of A-SAA with the receptor seems promising for inhibition of both NFκB and the MMP-2 and MMP-9 metalloproteinases, which are most significant in pathogenesis. The role of A-SAA in the initiation and progression of malignant tumors is worth attention and requires careful studies on cell cultures and *in vivo*. In particular, assessment of the sensitivity of various tumor cells to A-SAA, i.e., determination of expression of its receptor FPRL1 on cells, remains a current problem.

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