

# Expression and structural-functional alterations of $\alpha$ -1-acid glycoprotein at the pathological state

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*The review analyzes up-to-date knowledge on structure and biological functions of  $\alpha$ -acid glycoprotein. A special attention is given to alterations in fucosylation, sialylation and branching of orosomucoid at the acute, chronic inflammation and oncotrans formations.*

*Keywords:  $\alpha$ -acid glycoprotein, glycosylation, inflammation, oncopathology.*

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**Introduction.** Comprehensive analysis of molecular mechanisms of developing pathological states is of both theoretical and practical importance for creation sensitive and specific diagnostics and search for new medicines. Nowadays it is known that the majority of pathological states are connected with the changes in synthesis and posttranslational modifications of certain proteins, which received a common name of acute phase proteins (APPs). One of the most well-known APPs is  $\alpha$ -acid glycoprotein (AGP), or orosomucoid – an acute inflammation protein of all mammals. Despite a significant number of studies, many issues remain unclear, including structural and functional changes of this glycoprotein during diseases.

This review generalises modern literature data on AGP expression, peculiarities of its glycolysation at the development of pathological states, and perspectives of further investigation.

**Structural Organisation of AGP.** The only polypeptide chain of orosomucoid consists of 181 amino acid residues and contains two disulfide bonds between cysteine residues, namely Cys5-Cys147 and Cys72-Cys164. At pH 7.4, a protein part of AGP molecule contains 15% of  $\alpha$ -helixes, 41% of  $\beta$ -sheets, 12% of  $\gamma$ -helixes, and 24% of non-ordered structures. The secondary and ternary structures of this protein are foreseen by IR and Raman-spectroscopy. The protein is supposed to consist of eight antiparallel  $\beta$ -structures, forming so called  $\beta$ -cylinder with hydrophobic pocket in the middle, which participates in binding some medicines due to the presence of three tryptophan residues [1]. Nishi et al. in their experiments with desialylated and restored AGP revealed a natural tendency to form  $\alpha$ -helixes while disulfide bonds are intermediate links between  $\beta$ -sheet and  $\alpha$ -helix structures. Moreover, the absence of histidine residue in position 172 prevents the formation of  $\alpha$ -helixes and the interaction between protein and biomembranes [2].

The AGP structure is characterized by high level of glycosylation, i.e. it contains five complex N-glycans, which bind to asparagine residues and make up 41-45% of total molecular weight. AGP has a high negative charge ( $pI=2.7-3.2$ ) owing to significant content of sialic acids (12%). The molecular weight of plasmatic AGP, according to different authors, varies from 35-37 to 41-43 kDa and depends on the structure of carbonic component and the place of synthesis [3]. For instance, AGP secreted by activated neutrophils has a higher molecular weight due to the fucosylation of its glycans and the presence of poly lactoseamine residues [4].

Genetic polymorphism of desialylated AGP was found by the method of isoelectrofocusing. Polypeptide variants of AGP are encoded by three neighbouring genes, AGP-A, AGP-B, AGP-B', the first and second being identical. These genes are located in q31-q34.1 locus of the ninth human chromosome and encode two molecular forms different in 21 out of 181 amino acid residues, AGP-1 having four and AGP-2 five cysteine residues. It is not known whether the additional fifth Cys149 residue plays any role in the formation of disulfide bond in AGP-1 molecule. At normal conditions, AGP-1 exceeds AGP-2 in human blood plasma by about three times, but there are data that this ratio changes in different pathological states [5]. The amino acid sequence and location of introns in three genes demonstrate close similarity of AGP with lipocalins and partial similarity with a receptor of epithelial growth factor [6].

**Synthesis and expression of AGP.** AGP is predominantly synthesised by hepatocytes, but its unhepatic synthesis, including that in tumour tissues, is also known. Recently it has been shown that AGP can be synthesised by myelocytes and secreted by secondary granules of polymorphonuclear neutrophils [4].

The AGP synthesis and glycolysation are independently regulated by cytokines and glucocorticoids. Lipopolysaccharide (LPS) of gram-negative bacteria, some cytokines (interleukine-1b, tumour necrosis -factor, and interleukine-6) and glucocorticoids are the inducers of AGP synthesis. On the contrary, other cytokines (interleukine-1ra, interleukine-4, interleukine-10 and TGF- ) inhibit the synthesis of this protein [7].

The normal AGP content in blood is 0.55-1.4 g/l. The AGP concentration in blood plasma of healthy adults does not depend on age, but is defined by gender. The level of orosomuroid in blood plasma of men is somewhat higher (0.81 g/l) than that of women (0.67 g/l), and AGP content varies throughout the menstrual period [8, 9]. Embryonic orosomuroid is detected in foetus blood during the 16th week of embryonic development and constantly increases with gestational aging. The AGP concentration in newborns is 0.25-0.93 g/l and increases with age reaching the level of adults at 10 months [10].

During acute phase response, i.e. at] inflammation, trauma, surgical intervention, malignant transformation etc. the AGP level in blood plasma increases 2-5-fold [11]. The increase in AGP content was proven for HIV-infection [12]. According to this research, high concentration of AGP prevents intracellular accumulation of protease inhibitors *in vitro*. Therefore, the binding of mentioned inhibitors to AGP is supposed to play a significant role in the decrease in antiviral activity, though the sites of their binding in AGP molecule are yet to be defined.

A new trend in AGP study has been recently developed. It has been proven that the increase in AGP level in urine is an early marker of dysfunction of endothelium under the conditions of diabetic nephropathy and cardiac complications [13]. It is believed to be the consequence of disorder in proangiogenic properties of this glycoprotein [14].

**Biological role of AGP.** The variety of AGP biological functions has not been yet studied completely, however, participation of AGP in regulation of immune reactions, protection from bacterial infections, maintaining the barrier for transendothelial transport of macromolecules, and inhibition of cell apoptosis has been shown. The moment of its occurrence in blood as well as a significant affinity to main substances allow considering this glycoprotein to be an immunomodulator, binding endo- and exogenic mediators of inflammation. Together with retinol-binding protein and -1-microglobulin, AGP is a member of the family of immunocalins, subfamily of lipocalins, modulating immune and inflammatory reactions. It is also notable for the ability to protect an

organism under conditions of excess production of inflammatory cytokines, in particular, at endotoxic shock [15]. A protective activity of AGP was also demonstrated in experiments with bacterial infection in mice [16].

Particular significance is attributed to the transport properties of AGP. It was revealed that it is capable of binding and transporting about 300 neutral and alkaline substances of exo- and endogenous origin, the interaction with medical preparations being dependent on human genotype [17]. AGP in blood plasma is the main carrier of positively charged medical substances and contains at least three binding sites for: 1) medical substances (lipocalin "pocket"), 2) plasma proteins, and 3) receptors of cell surface. It binds steroids (progesterone, androstenedione, and cortisol) and anion ligands (warfarin, phenobarbital, and retinol), as well as serotonin, melatonin, histamine, and factor of activation of thrombocytes. Pregnant women and newborns demonstrate weakening in AGP interaction with medical substances, which results in higher than expected level of "free" fractions of medical substances [6, 11].

#### **Glycosylation of AGP under normal conditions.**

AGP is present in blood in several molecular forms, identical in primary sequence of polypeptide part, but different in biological activity and composition of carbohydrate chains, which determines microheterogeneity of this protein. The AGP concentration and ratio of its glycoforms depend on the age, physiological condition of a person and change during acute and chronic inflammation and tumour formation [8]. Up till now a complete sequences of five desialylated N-glycans of human AGP have been described and the sites of their binding to the polypeptide chain have been determined [18]. N-glycans of AGP belong to a "complex type": they contain the links gal-glcNAc, joined to the general central area, which consists of two residues of  $\alpha$ -mannose, one residue of  $\beta$ -mannose and one residue of chitobiose. One residue of  $\beta$ -mannose, bound to C-3 residue of  $\alpha$ -mannose, has antennas at C-2 and C-4, while the second  $\beta$ -mannose at C-2 and C-6 (Fig.1). The reason of such asymmetry is the substrate specificity of different N-acetylglucosaminyltransferases, responsible for binding during the formation of chain of each N-acetylglucosamine residue to the preceding chain. It

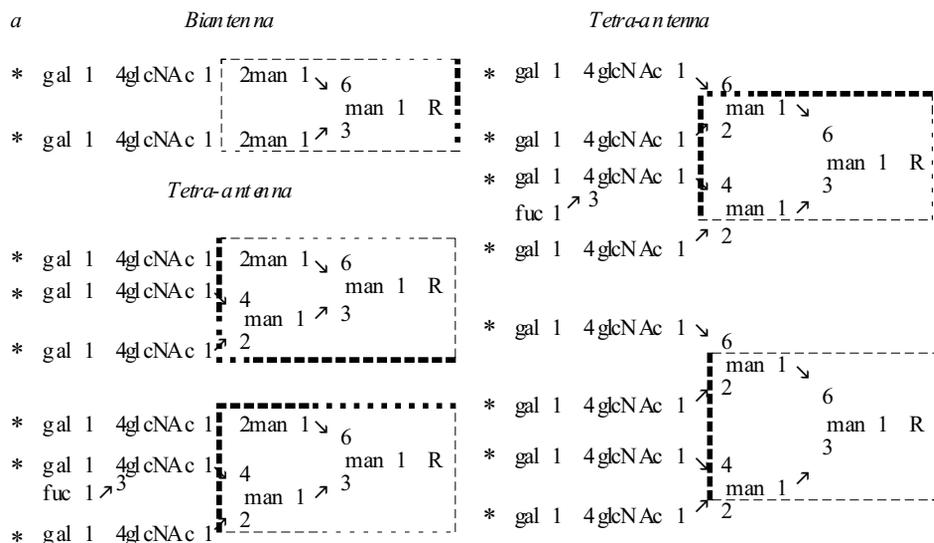
is noteworthy that N-acetylglucosamine with a separation function was not found in the AGP composition. Another notable feature of N-glycans of AGP appeared to be the presence of fucose which binds to the residue of N-acetylglucosamine via 1-3 or 1-4-bond (Fig.1, b).

Five N-glycans of orosomucoid are different in the degree of branching, sialylation and fucosylation. It is known that AGP, containing bi-, tri- and tetra-antenna N-glycans, is synthesized at normal conditions (Fig.1, a). Sialic acids, occupying terminal positions in orosomucoid molecule, may be in two isomeric forms: -2,3-bound residues of sialic acids, which are most frequently expressed at tri- and tetra-antenna glycans, and -2,6-bound residues, expressed at biantennary glycans. Considerable increase in branching and sialylation of orosomucoid glycans is observed during pregnancy [9].

It is noteworthy that foetal AGP is completely different from the AGP of adults. It has three N-glycans of lacto- and poly-lacto- substituted types and three O-glycans, which are absent in AGP from other tissues [10].

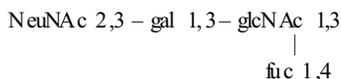
**Structural and functional changes in AGP at inflammation.** Early stage of acute phase is characterized by a considerable increase in the number of AGP glycoforms with biantennary glycans, which reaches its maximum on the 2<sup>nd</sup> day with subsequent decreasing to the control level between 15 and 30 days. Acute inflammation also causes significant changes in AGP fucosylation with kinetics different from that for biantennary glycans. In all the investigated patients with heavy burn and accident injuries the fucosylation level was still increased on the 10th-30th day, while the content of biantennary glycans reached a normal value within 9-14 days after hospitalization [19].

During the acute phase of inflammation the number of fucosylated AGP molecules and fucose residues per each molecule of the mentioned glycoprotein increases (Fig.2), which is in good agreement with the experimental data regarding changes in expression of sialyl-Lewis antigens (SLe<sup>A</sup> and SLe<sup>X</sup>) at inflammation. Sialylated Lewis antigens are insignificant in AGP of a healthy adult, but their level increases considerably at acute and chronic inflammatory processes [20]. It is believed to be related

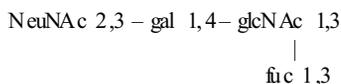


R – glcNAc 1 4glcNAc. Asn.

*b*



*Sialylated Lewis antigen A*



*Sialylated Lewis antigen X*

Fig. 1. Structural variants of N-glycans of 1-acid glycoprotein: *a* – bi-, tri- and tetra-antenna N-glycans; *b* – in the presence of fucose, bound to the residue of N-acetyl glucosamine via 1-3- or 1-4-connection. Keys: gal – galactose; man – manose; fuc – fucose; glcNAc – N-acetylglucosamine; \* – NeuAc (N-acetylneuraminic acid); Asn –

to the increase in hepatic synthesis of such AGP glycoforms under the influence of inflammatory cytokines [21]. AGP may inhibit classic and alternative ways of activation of the complement, and the increase in SLe<sup>x</sup>-antigens in AGP composition enhances such effects considerably. The expression of SLe<sup>x</sup> during acute inflammation affects AGP affinity to E- or P-selectins which, in its turn, results in the increase of leukocytes in the places of inflammation [22].

The increase in the content of SLe<sup>x</sup>-antigens is notable for tri - and tetra-antenna glycans which correlates with the data on specificity of glycosylation enzymes. It is known that 2-6-sialyltransferase has a weak ability of sialylating N-glycans with tri - and tetra-antenna structures compared to biantennary structures. On the contrary, 2-3-sialyltransferase and

1-3-fucosyltransferase, which are responsible for the expression of SLe<sup>x</sup>-antigens, demonstrate enhanced affinity to more branched glycans. It was also proven

that there is a positive correlation between the level of branching of N-glycans and the activity of 1-4-fucosyltransferase, responsible for the SLe<sup>x</sup>-antigens synthesis [23]. Therefore, both the changes in activity of abovementioned enzymes, induced by inflammation, and the changes in the level of branching of glycans may determine the expression of Lewis-antigens in AGP composition.

**Structural and functional changes in AGP at malignization.** The Table presents main trends in structural changes of AGP at different pathological states, including oncological diseases. It is known that neoplastic processes are related to hypersecretion of AGP, but the source of this protein is yet to be elucidated. The paradox is the absence of changes in AGP concentration in blood at hepatocellular carcinoma, though in the patients with active forms of lung cancer and cancer of gastrointestinal system a considerable increase in AGP concentration is found.

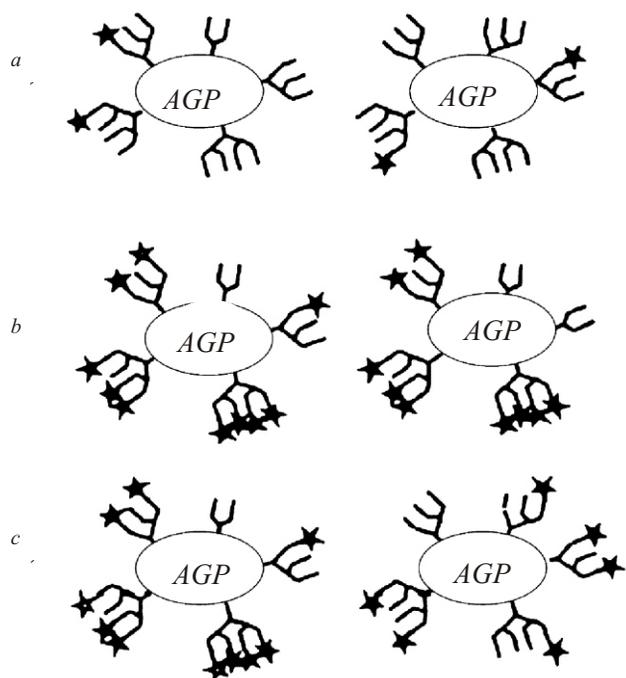


Fig. 2. Glycoforms of  $\alpha$ -1-acid glycoprotein, present in blood under physiologically normal conditions (a), at acute (b) and chronic (c) inflammation [15]. Stars indicate fucose.

The level of AGP is an objective prognostic factor of survival for patients with non-small-cell lung cancer: at AGP concentration less than 1.11 g/l average patient's life duration is 15.6 months, while at the concentration of 1.85 g/l and more it is only 5.5 months [35]. There are experimental data proving that AGP in high concentration activates cell proliferation decreasing the efficiency of tyrosine kinase inhibitor [36].

The data on changing AGP carbohydrate component at neoplasia are limited to the investigation on N-glycans] branching, sialylation and fucosylation. A characteristic feature of oncological disease is a higher] content of polyantenna glycans due to the increase in expression of 1,4- and 1,6-branched tri- and tetra-antenna structures. Similar regularity was also determined in our investigations on AGP structure in patients with leukaemia or tumours of pancreatoduodenal zone [27]. These patients demonstrate considerable decrease in the amount of biantennary glycans and proportional increase in the amount of tri- and tetra-antenna structures in AGP molecules, circulating in blood. It should be mentioned that at mechanic jaundice, caused by oncological

diseases, there is a sharp decrease in the amount of biantennary structures almost to their complete disappearance [34].

It is known that tumour tissue secretes many fucosylated proteins, including those with Lewis antigens [37]. The increase in expression of SLe<sup>x</sup>- or SLe<sup>a</sup>-antigens in neoplastic cells results in their selectin-mediated extravasation and is closely related to the cell migration and tumour metastases. "Deep" fucosylation may be a factor, preventing adhesion and affecting the formation of metastases. According to [38], the patients with progressing malignization, whose AGP contains highly fucosylated tri- and tetra-antenna carbohydrate chains, had poor prognosis during a long period after surgery, in contrast to the patients who did not have such signs and prognosis for whom was more favourable.

The changes in expression and glycosylation of AGP determine a variety of biological effects, some of which are accomplished by the protein part, while others mainly depend on its carbohydrate part.

A group of Russian scientists confirmed immunomodulating activity of the glycan units [39]. They synthesized pseudo-AGP, which is similar to the native AGP by the molecular weight and carbohydrate units, attached to a polymer carrier. Such semi-synthetic analogue inhibits proliferation of lymphocytes and stimulates the production of anti-inflammatory cytokines by mononuclear leukocytes of peripheral blood just like native AGP. However, it neither affects antioxidant activity nor prevents the complement activation in an alternative way. Since the AGP doses used in these experiments corresponded to the norm (<3 mg/ml), the authors made an assumption that such non-specific activity of AGP may be a cause of a tumour "escape" from immune surveillance, thus preventing effect of immunotherapy.

Therefore, an increased expression of  $\alpha$ -1 acid glycoprotein may be regarded as an adequate reaction of the organism to any pathological process, being non-specific for neoplasia; however, a high level of AGP is likely relates to the disease progression. "Subtle" changes, namely, changes in fucosylation, sialylation and branching of AGP are more sensitive and specific indicator of the development of

*Structural changes in AGP under different pathological conditions*

Disease	AGP level	Branching	Sialylation	Fucosylation	Method of study	Reference
Asthma		Biantenna, polyantenna structures	–	Does not change	REP, CAIEP	[24]
I type diabetes	–	-	–		CAIEP, AEC	[25]
Rheumatoid arthritis		-	–		LBIEA	[26]
Septic shock		Biantenna structures			CAIEP	[27]
Burns		-	–		LBIEA	[28]
Chronic renal disease		-	–	–	-	[29]
Lung cancer		-	–		SDS-EP, WB	[30]
Colon cancer		-			Immunohistochemistry, SDS-EP, WB	[31]
Hepatocellular carcinoma, hepatic cirrhosis	Does not change	-			SDS-EP, IEA, chromatographic strip test	[32, 33]
Leukaemias		Biantenna, polyantenna structures	–	–	CAIEP	[27]
Tumours in pancreaticoduodenal zone		Biantenna, polyantenna structures	–	–	CAIEP	[34]

**Note.** – increase; – considerable increase; REP – rocket electrophoresis; CAIEP - cross affino-immunoelectrophoresis; AEC - anion-exchange chromatography; LBIEA - lectin-binding immunoenzyme assay; SDS-EP - electrophoresis in the presence of sodium dodecyl sulphate; WB – Western-blot analysis; IEA – immunoenzyme assay

pathological process. Further studies on microheterogeneity of AGP are a promising direction in the search for specific diagnostic markers and development of therapeutic preparations with directed immunomodulating activity.

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Експресія і структурно-функціональні зміни  $\alpha$ 1-кислого глікопротеїну за патологічних станів

**Резюме**

*Проаналізовано сучасні дані щодо структури і біологічних функцій  $\alpha$ 1-кислого глікопротеїну. Особливу увагу приділено зміні фукозилюваності, сialьованості і розгалуженості гліканів орозомукоїду за гострого і хронічного запалення та онкотрансформації.*

*Ключові слова:*  $\alpha$ 1-кислий глікопротеїн, глікозилюваність, запалення, онкопатологія.

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Экспрессия и структурно-функциональные изменения  $\alpha$ 1-кислого гликопротеина при патологических состояниях

**Резюме**

*Проанализированы современные данные, касающиеся структуры и биологических функций  $\alpha$ 1-кислого гликопротеина. Особое внимание уделено изменению фукозилированности, сialированности и разветвленности гликанов орозомукоида при остром и хроническом воспалении, а также онкотрансформации.*

*Ключевые слова:*  $\alpha$ 1-кислый гликопротеин, гликозилированность, воспаление, онкопатология.

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