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STATUS OF FUNCTIONALLY ACTIVE COMPONENTS OF C4A AND C4B OF THE HUMAN COMPLEMENT SYSTEM IN THE CHILD POPULATION IN CONNECTION WITH THE IMMUNE RESPONSE TO THE PRESENCE OF BACTERIAL ANTIGENS

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ABSTRACT

The analysis of the immune response of a 3-4-year-old child population to cell wall polysaccharides and the protein toxoid of *Corynebacterium diphtheriae* was performed by determining the functionally active isotypes C4A and C4B of human complement system component C4 in a micropanel in the reaction of inhibition of covalent binding of activated C4b to IgG (in the case of C4A) or lipopolysaccharide (in the case of C4B). The different efficacy of *C. diphtheriae* antigens in inhibiting the formation of C3/C5 convertase (EC 3.4.21.43) from C4A and C4B has been shown. The binding of the activated fragment C4b was judged by the activity of C3/C5 convertase, that is, by the amount of bound to the antigenic target, determined using a conjugate of monospecific polyclonal IgG rabbit antibodies with peroxidase. The polysaccharide antigen inhibited the formation of convertase from the C4B isotype, and the protein antigen inhibited the formation of convertase from the C4A isotype. The incidence of C4A and C4B deficiencies in children with high, medium, and low levels of antitoxic and antibacterial IgG antibodies to *C. diphtheriae* differed from the normal population. At the same time, C4A deficiencies were correlated with a decrease in anti-toxic immunity, while C4B deficiencies were correlated with a decrease in antibacterial immunity. The results are important for predicting the resistance of the child population to the emergence and development of socially significant diseases. They are also useful for standardizing vaccine

preparations and will contribute to further progress in determining the network activities of multifunctional proteins in the defense systems.

KEYWORDS: complement system; deficiencies of C4A and C4B; C3/C5 convertase; ELISA; functional analysis of protein; diphtheria antigens; vaccine, immune reply.

ABBREVIATIONS

CR1	complement receptor 1
DT	diphtheria toxoid
Fc	Fc-region of IgG
GC	glycoconjugates
HCS	human complement system
EIA	enzyme immunoassay
PSB	phosphate saline buffer
VSB^{++}	veronal saline buffer with Ca^{2+} and Mg^{2+} cations

1. INTRODUCTION

The study of the functional status of activated components of the body's defense systems, including those related to infectious diseases and antigen presentation, is relevant and promising.[1-4] It can help in assessing the population's predisposition to the occurrence and development of autoimmune diseases, gastritis, ulcers, and others.

The C3, C4, C5 components of the human complement system (HCS) and α_2-macroglobulin (inhibitor of serine proteinases EC 3.4.21.) belong to a family of highly homologous proteins that originated from a common precursor as a result of gene duplication.[5] The presence of an intramolecular thiol-ester bond in these proteins allows them to form covalent complexes with molecular targets. After proteolytic activation of such proteins, the thiol-ester bond becomes exposed and capable of reacting with nucleophilic chemical groups. It forms a covalent bond between the acyl group of the thiol-ether and the amine or hydroxyl group of the target. The C4B isotype of the C4 HCS component predominantly forms an ester bond with the OH groups of carbohydrates and proteins (C4B as a lectin-like reagent), while the C4A isotype predominantly forms an amide bond with proteins.[6] After C4 activation, a cascade of reactions leads to the formation of a membrane-attack complex on target cells and the production of biologically active peptides, including anaphylatoxins.

The binding of activated C4 molecules to microbial or other surfaces leads to the removal of immune complexes by erythrocytes and macrophages through interaction with receptors with lectin (glycoconjugates [GC] recognizing and binding) properties: CR1 (complement receptor 1) and the Fc-domain receptor of IgG (Fc-receptor).[7] At the same time, CR1, which plays an important role in the clearance of immune complexes, binds activated C4Ab significantly better than C4Bb.[8] In addition, protein antigens that are opsonized by C4A induce a secondary immune response that switches from IgM to IgG antibodies.[9]

In view of the above, the aim of the study was to investigate the differences in the inhibition of C4b covalent binding by protein and carbohydrate antigens of microorganisms (on example of using the antigens of the symbiotic bacteria *Corynebacterium diphtheriae* tox-) when determining the functional activity of C3/C5-converase (EC 3.4.21.43, EC – Enzyme Classification.[10] formed from C4A or C4B HCS components.

2. MATERIALS AND METHODS

During the EIA, flat-bottomed micropanels with high sorption (Biomedical, Russia) were used. Reagents uncluded: Twin-20 (Sigma, USA), horseradish peroxidase (NPO Biochemreactive, Olaine, Latvia), 3,3',5,5'- Tetramethylbenzidine (TMB) – peroxidase substrate (Medac, Germany); *Salmonella typhi* lipopolysaccharide Ty2 ("Pyrogenal", in sealed ampoules, 100 μ/ml at a phosphate saline buffer pH of 7.4 [PSB]; *N.F. Gamalei* State Research Institute of Medical Sciences, Moscow), others. Reagent R4 (human blood serum deprived of C4 activity) was prepared according to the work.[11] C3, C4, antibodies to C3 and C4, peroxidase conjugates to antibodies were prepared in laboratory. Other reagents were of domestic production and were at least of brand "Pure for Analysis" in quality. Purified non-sorbate diphtheria toxoid (DT) (State Institute for Standardization and Control of Medical Biological Products named after *L.A. Tarasevich*) and experimental production series of diphtheria bacterial subcellular vaccine Codivac (*G.N. Gabrichievsky* Research Institute of Epidemiology and Microbiology) were used as diphtheria antigens. The work examined blood serum of healthy children aged 3-4 years. Antitoxic antibodies (antigen – DT) and antibacterial antibodies (antigen – Codivac) of the IgG class were determined as described earlier.[12] The calculation of C4A and C4B deficiencies in the sera was performed using protocols for determining the functional activities of C4A and C4B.[13,14]

2.1. Determination of C4A functional activity in a micropanel

Immunochemically pure IgG was dissolved in 0.05 M Na-carbonate buffer, pH 9.5, at concentrations of 10-100 μg/ml, and 100 μl of the solution was added to each well of the plate and left overnight at 4°C. The microplate was washed with veronal saline buffer (VBS^{++}) pH 7.4, containing 0.15 M NaCl, 0.15 mM Ca^{2+}, and 0.5 mM Mg^{2+}, at a volume of 150 μL per well. 100 μL of a solution containing the test C4 in VBS^{++} and 10 μL of reagent R4 were added to each well. After incubation for 1 h at 37°C, the wells were washed with PSB pH 7.4 with 0.05% Tween-20 (PSB-Tween), and 100 μl of peroxidase conjugate with antibodies against human C3 component was added to the wells in the same buffer at a selected dilution. After 1 h incubation at 37°C, washing with PSB-Tween, 100 μl of TMB solution in substrate buffer was added to the wells. After 30 min incubation in the dark, the reaction was stopped by adding 50 μl of 4% sulfuric acid to the wells. The results were recorded using a vertical beam spectrophotometer by measuring the optical density at 450 nm (D_{450}). The functional activity of C4 was calculated using a standard curve, and a pool of 10 healthy donor sera was used as the standard.

2.2. Determination of the functional activity of C4B in a micropanel

Pyrogenal was heated in a boiling water bath for 1.5 h, diluted with hot PSB to a concentration of 10 μg/ml, cooled to 40-50°C, and added at a concentration of 10 μg/ml to the wells of a flat-bottomed polystyrene plate with increased sorption capacity. The plate was covered and incubated for 2 h at 37°C and then for 18 h at room temperature in the dark. Such sensitized microarrays can be stored at -20°C for up to 3 months without significantly affecting the determination of C4B. The plate was washed with VBS^{++} and 100 μl of the solution with the test C4 in VBS^{++} and 5 μl of the R4 reagent were added to the wells. After incubation in a thermostat for 1 h at 37°C, the microplates were washed with PSB-Tween, dried, and 100 μl of the peroxidase conjugate with antibodies against human C3 in the working dilution in the same buffer was added to the wells. After incubation for 1 h at 37°C and washing with the same buffer, the working solution of TMB was added to the wells. After 30 min, the reaction was stopped with a solution of H_2SO_4. The results were registered at 450 nm. The functional activity of C4B was calculated using a standard curve.

2.3. Determination of C4A and C4B binding inhibition

Inhibition was studied by determining the functional activities of C4A and C4B, as described above, in the presence of different concentrations of inhibitors (DT and Codivac). The

inhibition constant was calculated based on the *Michaelis-Menten* equation, using the degree of inhibition as a function of the inhibitor concentration.

3. RESULTS AND DISCUSSION

C. diphtheriae antigens are a convenient model for studying the immune response, as this diphtheria pathogen elicits a dual immune response in the infected host: the production of antitoxic antibodies against DT and the production of antimicrobial antibodies against the bacterial cell wall polysaccharides. A study was conducted to investigate the inhibitory effect of both types of antigens on the formation of C3/C5-convertase from C4A or C4B. In addition, the children's levels of antitoxic and antibacterial antibodies were determined, and the severity of these antibodies was compared with the incidence of congenital C4A and C4B deficiencies.

The study examined the inhibition of the covalent binding of the activated C4b fragment of the human complement component C4 to its natural target, human IgG. Since the acylation of the protein target is primarily mediated by the C4A isoform, the comparison of the inhibitory effects of different acceptors was limited to the activated C4Ab fragment. Enzyme immunoassay (EIA) was used to compare the opsonizing properties of C4A against predominantly protein antigens. When C4 was activated, C4B also bound to the polysaccharide antigen, but this did not interfere with the covalent sorption of C4A on the IgG target.

Previously,[11] when studying the covalent binding of activated C4b to various acceptors, the functional activity of C4A alone was used to determine the binding inhibition constant for activated C4A. In this work, a new technique was used to study the interaction of acceptors with activated C4A and C4B, separately. This technique involves the separate determination of the functional activities of C4A and C4B in the formation of C3/C5-convertase from the C4 HCS component,[13] where the functional activity of each isoform was determined in the presence of acceptors at varying concentrations.

As for a similar scheme described earlier,[11] the inhibition of C4b binding in micropanel wells, provided that the concentration of the acceptor [I] is much higher than the concentration of the C4 component, is described by an equation similar to the *Michaelis-Menten* equation:

$A = B \times [I] / (Ki + [I])$,

where A is the fraction of activated C4b bound to the inhibitor (the percentage of inhibition), B is the efficiency of the covalent attachment of the inhibitor to C4b (the maximum percentage of inhibition), Ki is the dissociation constant of the reversible complex between the acceptor (the inhibitor) and C4b, and [I] is the concentration of the inhibitor.

The inhibition constants of DT and bacterial antigen (Kodivac vaccine – cell wall polysaccharides of symbiotic *Corynebacterium*) formation of C3-convertase by activated C4b, separately, for C4A and C4B isotypes, i.e. equilibrium dissociation constants of activated C4b–inhibitor complexes, were investigated. The data are given in Table 1.

Table 1: Inhibition constants of anatoxin and Codivac for the formation of C3/C5-convertase involving C4A and C4B.

Antigen	K_i, µg/ml	
	C4A	C4B
Anatoxin	105 ± 10	100 ± 3
Codivac	171 ± 29	26 ± 3
Anatoxin / Codivac	0,6	3,9

It is important to note that the K_i value for C4A and DT (109 ± 47 µg/mL), previously obtained by another method, was almost identical to the value obtained by the new method.

The table shows that the inhibition constant for the anatoxin was the same for both C4 component isoforms, while Codivac inhibited activated C4B 6.5 times better than C4A. Thus, in the inhibition of C4A, DT was 2 times more potent than Codivac, and in the inhibition of C4B, Codivac was 4 times more potent than DT.

These findings are consistent with the idea that C4A binds better to proteins, while C4B binds better to carbohydrates and GC.

Since the antitoxic immune response is triggered by the protein antigen DT, and the antibacterial response is triggered by the cell wall antigens of *Corynebacterium* (predominantly polysaccharides[12]), it can be assumed that individuals with congenital C4A or C4B deficiencies should have different antitoxic and antibacterial immune responses. Since the prevalence of congenital C4A and C4B deficiencies in the population is approximately 15% each, significant differences in the immune response can be expected.

In the blood sera of healthy children aged 3-4 years, antibacterial and antitoxic antibodies were determined[13] as well as the ratio of C4A and C4B, which revealed the presence of deficiencies. The results are shown in Table 2.

Table 2: The content of antibacterial and antitoxic antibodies against the background of C4A and C4B deficiency in the sera of healthy children.

No. serum	Antibody content		Isotype content*, % of control		C4A/C4B	Deficit**
	Antibacterial	Antitoxic	C4A	C4B		
1	Medium	High	130	264	0,49	C4A
2	Medium	High	139	72	1,94	C4B
3	Medium	Low	98	175	0,56	No
4	Medium	Medium	67	80	0,83	No
5	Medium	Medium	64	142	0,45	C4A
6	Medium	Medium	136	24	5,79	C4B
7	Medium	Medium	53	47	1,13	No
8	Medium	Medium	77	77	1,00	No
9	Medium	Medium	172	12	14,40	C4B
10	Medium	High	80	69	1,17	No
11	Medium	Medium	142	35	4,10	C4B
12	High	Medium	1	87	0,01	C4A
13	High	Medium	1	23	0,04	C4A
14	Low	Medium	23	85	0,27	C4A
15	High	Medium	13	46	0,29	C4A
16	Medium	Medium	37	57	0,65	No
17	Low	Medium	41	23	1,80	C4B
18	High	Low	51	30	1,71	C4B
19	Low	Low	24	20	1,18	No
20	High	Low	16	27	0,60	No
21	Low	Medium	22	10	2,30	C4B
22	High	High	23	10	2,20	C4B

Comments.* Determination of C4 isotypes in a micropanel using a developed method; ** isotype deficiency confirmed by chemiluminescent analysis on a blot.

As it was established (Table. 1), Codivac showed significant differences in binding to C4A and C4B, binding 6.5 times better to C4B, therefore, the effect of C4B deficiencies on the antibacterial immune response could be expected. Indeed, the low content of antibacterial antibodies was accompanied by a high incidence of C4B deficiency. In contrast, the high frequency of C4A deficiencies did not interfere with maintaining a high level of antibacterial response. In the case of antitoxic immunity, there was no pronounced dependence of the antibody content on the presence of C4A deficiency. However, with a high (strong) immune

response, C4A deficiencies were twice as low as with a normal response. It should be noted that the results of the express procedure in the micropanel were fully consistent (Table. 1) chemiluminescent immunoblotting analysis of the functional activity of the isotypes of the C4 component of HCS, which has been also shown for other objects of study.[14,16]

4. CONCLUSION

The results obtained suggest that the presence of C4B deficiencies correlates with the level of the antibacterial immune response against *C. diphtheriae*. Deficiencies of C4B interacting with GC of the polysaccharide type are one of the factors predisposing to bacterial transmission and survival of the pathogen. The results point to the prospects of using functional analysis of the C4 system, including C4A and C4B (isotypes, as well as their subisotypes) of blood for the evaluation and further standardization of vaccine ingredients. In the diagnosis and prognosis of the status of a single defense system or one associated with other defense systems of the body, it is promising to combine such independent methods as microarray and chemiluminescent immunoblotting procedures for analyzing the functional activity of C4A and C4B. This has made it possible to provide a preliminary prognostic assessment of additional aspect of children's population predisposition to pathologies. The results are important for the further development of functional analysis of network and cascade targeting assembly technologies involving the main defense systems of the body, including HCS.[7,16-18]

Disclosure of conflict of interest

The authors declare no conflict of interest.

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