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# THE COMPLEMENT AS THE SUPERSYSTEM OF INNATE IMMYNITY OF ORGANISM: COMMUNICATION WAYS BETWEEN THE HUMAN COMPLEMENT AND OTHER PROTECTIVE SYSTEMS AT THE LEVEL OF INTERACTING AND RECOGNIZING MOLECULES AND RECEPTORS

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## ABSTRACT

It is shown for the first time that a lot of proteins and their fragments (more than 120 types) and non-protein participants of the human complement system (HCS) are involved in the network of communicative relationships with other protective systems. Such a variety demonstrates extended and deep relationships between HCS and other protective systems of organism at the level of interactions between molecules and/or receptors. Many participants are involved in recognition and communication with and between natural glycoconjugates involving signals and other regulator types. A feature of the protective super-network of HCS, the blood coagulation system, cytokines, Toll-like receptors and CD antigens of the body is the wide participation of serine proteinases EC 3.4.21.-., which function through different mechanisms (including their assembly, cascade action, to be as activation or inhibition factorsin respect of other proteinases), their inhibitors, activators and stabilizers in the communications. Despite the large number of molecular and receptor participants linking defense systems in the case of infectious diseases, the communication relationships between HCS and other human defense systems are predictable due to the known pathways, their cascade properties and knowledge of the switching locations between systems. Important (key) for studying the super-protective innate system of the body remain the close cooperation of Lectins—Glycoconjugates interactions/ recognition and the net of action by serine proteinases. The deeper knowledge

on the extended HCS as protective super-network will help against the strategies of microbial and viral pathogens which are able to use the human innate immunity in some cases of diseases.

**KEYWORDS:** Human innate immunity, Extended complement system, Components and Participants, Glycoconjugates, Lectins, Serine proteinases, Assembling.

## 1. INTRODUCTION

The number of recognized protein components and participants in the human complement system (HCS) varies, but is constantly growing. The components C1-C9, Factor D, Properdin and C1-inhibitor (C1-inh) were originally described. As component substructures and component receptors were identified, the total number of HCS components continued to grow. By 1994, more than 20 serum HCS proteins were known, and by 1997 the total number of HCS participants reached over 30 (Mostly soluble, including the $C1r_2$ complex).[1]

The aim is to summarize the data[1-16] on protein (in addition to the known minimum number of complement components) and non-protein participants of HCS associated with the functioning of classical, alternative and lectin pathways (CCP, ACP and LCP, respectively), taking into account a network of biochemical transformations involving complexes of proteins (including lectins, GP and factors), proenzymes/ zymogens and activated serine proteinases (Enzyme Classification [EC] 3.4.21.-.[3]) and their protein modulators (Inhibitors, activators and stabilizers), other soluble and receptor modulators, factors and cofactors.

## 2. The main content

The following proteins, their fragments and complexes are involved in the functioning of HCS (abbreviations of proteins, fragments, complexes, activated states are highlighted in bold):

### 2.1. *Proteins involved in the initiation of HCS, the development of the initial stages of CPP, ACP and LCP involving amplification and implementation of terminal stages common to all pathways*

**hexameric C1q** (spontaneously activated or inactivated; inhibited by synthetic peptides); **C1r/C1r*** (zymogen or activated serine proteinase EC 3.4.21.41.; activates C1s); **C1r2**; **C1s/C1s*** (zymogen or activated serine proteinase EC 3.4.21.42.); **$C1r_2C1s_2$** (tetrameric proteolytic complex EC 3.4.21.-.); **C1/C1*** (zymogen or activated serine proteinase EC 3.4.21.41-42; represented by the C1q+C1r+C1s complex; C1 is preparatively simply divided

into subcomponents); **MBP** (mannan/Man-binding protein) - penta- and hexamers initiate HCS (tri/tetramers recognize bacteria, but do not initiate HCS); **MBL** (mannan/ Man/ GlcNAc-binding lectin within MBP, C1q-like protein); MBL-associated serine C1s-like proteases **MASP-1** EC 3.4.21.-. (proteolysis of C3 and C2, activation of MASP-2 and MASP-3), **MASP-2** EC 3.4.21.-. (proteolysis of C4 and C2), **MASP-3** EC 3.4.21.-. (inhibition of MASP-2), **MASP-4**; **C2a**, fragment of component C2, responsible for proteolytic activity, and C2b with stabilizing complex C2 activity; **C2** (serine proteinase CF 3.4.21.43; includes C2a+C2b); **oxidized C2**; **RaRF** (Ra-reactive factor, includes MBP+MASP); **Ficolin L** (P35; GlcNAc-binding lectin) or **Ficolin N** (*Hakata* antigen; GlcNAc-binding lectin) in complex with MASP-2, initiating LCP; leukocyte **Ficolin M**; **C3a** (soluble anaphylotoxin); **C3b** (covalently bound to the target through its own thiol complex ester bond); **C3b*** (activated form of C3b with non-hydrolyzed thiol ester bond, prior to covalent binding to the target) (convenient method of binding to C3b* by complement effectors); **iC3b** (inactivated C3b by factor I); **C3c, C3dg, C3e** and **C3f** (fragments of C3 with insufficiently studied functions); **C3** (C3a+C3b); **iC3** (inactivated soluble C3, C3($H_2O$), C3 with spontaneously hydrolyzed thiol ester bond); **C4a** (soluble anaphylotoxin); **C4b** (covalently bound to the target through its own thiol ester bond); **C4b*** (activated form of C4b with non-hydrolyzed thiosulfide ester bond, prior to covalent binding to the target); **C4Ab*, C4Bb*** (activated forms of fragments of C4A and C4B); C4b-like C4 (**C4-μ**, C4b-like C4 with preserved C4a); **C4c** (capable of signally significant dimerization) and **C4d** (soluble fragments of C4 with insufficiently studied functions); **C4c2**; **C4** (C4a+C4b; C4A+C4B); **C5a** (soluble anaphylotoxin); **C5a-desArg** (inactivated anaphylotoxin after the action of serum carboxypeptidase-N EC 3.4.17.10.; without Arg); **C5b** (fragment C5); C5 (C5a+C5b); pore-forming proteins **C6, C7, C8** and **C9**; **Factor B** (serine proteinase - EC 3.4.21.47, zymogenic form activated by active Factor D; includes Ba+Bb); **Ba** and **Bb** without or with a catalytic center, respectively; **Factor D** (EC 3.4.21.46, the zymogenic form activated by C3/C5-convertase EC 3.4.21.47. within the framework of ACP; the possibility of participation of only zymogenic Factors B and D in the activation of ACP); **C3-convertase ACP** (C3b+Bb= C3bBb= further C3bBb); **Factor P** (Properdin, [Gal(galactoside) sulfate]-binding), the trimeric form of Properdin; C3b+Bb+Pn = **$C3bBbP_n$** (serine proteinases EC 3.4.21.-. of ACP); **C5-convertases of ACP** (C3bnBb and C3bnBbP, EC 3.4.21.-); **C3-convertase** EC 3.4.21.43. of CCP (C4b+C2a= C4bC2a= further C4b2a); **C5 convertases of CCP** (C4b+C2a+C3b= C4bC2aC3b= C4b2aC3b=further C4b2a3b; regulation by cytokines, C4b+C2a+C4b= $(C4b)_2C2a$= further abbreviation as C4bC2a; EC 3.4.21.43.); **MAC**

(membrane-attacking pore-forming terminal cytolytic complex= C5b+C6+C7+C8+C9= C5bC6C7C8C9= C5b6789= further C5b-9).

### 2.2. *Regulation of HCS by additional soluble proteins*

**C1-inh** (C1 proteinase inhibitor; covalently binds to C1r, C1s or MASP); **Factor J** (C1-inh-like); **C1q-I** (C1q inhibitor, sulfated proteoglycan [PG]); **C3a/C5a-inactivator** (anaphylotoxin inactivator, carboxypeptidase N EC 3.4.17.10); **C4BP** (C4-binding protein); **Factor H** (binding Sialic acid [Sia] clusters); **FHL-1** (factor-H-like; identical to the first 7 domains of HCS regulation in Factor H); **Factor I** (C3b/C4b inactivator, serine proteinase EC 3.4.21.45, substrate α'-chain in C3b complex C3bH); **Protein S** (vitronectin); **C4bBP-S** (complex of C4bBP and S in blood plasma).

### 2.3. *Regulation of HCS by receptor proteins*

**gC1qR** (receptor for globular heads C1q, a new vitronectin-binding factor); **C1qR** (receptor for C1q) on platelets, B lymphocytes, monocytes, granulocytes, fibroblasts; **M-C1q-I** (membrane-bound inhibitor of C1q); **C1qR-like receptor** for MBR on human histiocytes U937; **various forms of CR1** (receptor for C3b> C4b> iC3b or immune adhesion receptor, **CD35**, gp205; also a receptor for C1q; possible **soluble form of CR1** in plasma and serum) on erythrocytes, granulocytes, monocytes, macrophages, B lymphocytes, a number of T and killer cells, kidney podocytes; **CR2** (receptor for C3d, **CD21**, gp140) cytotoxic and other B-lymphocytes, follicular dendritic cells; **CR3** (receptor for iC3b/fibrinogen/molecules of the ICAM group; integrin of the Leu-CAM group; **CD11b/CD18**, gp180/90; β-glucan-binding; modulation by **galectin-1**) on granulocytes, macrophages and killer lymphocytes involved in antibody(Ab)-dependent cytotoxicity; **CR4** (neutrophil receptor for iC3b> C3d> C3g; **CD11c/CD18**, p150/95kDa; binding of iC3b/C3dg $Ca^{2+}$, $Mg^{2+}$-dependent manner); **CR5** (receptor for C3d/C3g; binds C3d and iC3b independently of $Ca^{2+}$ and $Mg^{2+}$); **C3aR** (receptor for C3a) on neutrophils and monocytes; **C3eR** (receptor for C3e) on granulocytes; **C5aR** (receptor for C5a; **CD88**) on all neutrophils, 70% of eosinophils and 30-40% of basophils and monocytes, as well as on immature myelo/monoblasts U937, HL60, Mac6; **RH** (receptor H, stimulating release of Factor I) on B lymphocytes, granulocytes and monocytes; **DAF** (*decay-accelerating factor*, **CD55**; limiting amplification at the C3 convertase stage) on endothelial cells; **MCP** (*membrane cofactor protein*, **CD46**, gp66/56; limiting assembly of C3 convertase); **HRF** (*homological restriction factor*, C8BP= C8-binding protein); **HRF20** (MACIF= inhibition of forming MAC factor 20 kD, MIRL= membrane inhibitor of reactive

lysis, H19, C8/C9-binding protein, protectin, **CD59**) on T lymphocytes, endothelial cells); **inhibitor other than MIRL**; **clusterin**, which prevents C9 polymerization.

### 2.4. *SCR (Short consensus repeats) in HCS regulators*

The regulatory components of HCS (CR1, CR2, DAF, MCP, C4BP, factor H) contain multiple repeats of SCR (short consensus repeats) responsible for binding C4b/C3b derivatives. Such repeats are widely represented in human receptor and soluble lectins - selectins E, L, P; aggrecan (critical component for cartilage structure) and **CD44** antigen (hyaluronate-binding), which, thus, can be considered as regulators of HCS.

The important role of lectins in the functioning of HCS is indicated by the lectin nature of a number of receptors (including solubilized natural or recombinant ones) and originally soluble HCS components. In addition, direct interaction of HCS components in the blood composition with soluble (including those dumped from the cell surface) and surface (including surface cell) lectins has been shown.

### 2.5. *Some conclusions from the above data*

a. At least 100 (glyco) protein participants of HCS have been described, including complexes and active/inactive states of protein products formed on the basis of traditional components of HCS;
b. The complexity of the assembly ensemble of polypeptides result in increase in the polyfunctionality of the ensemble and the emergence of new unique functions;
c. The target type dependent initiation of HCS three pathways increases the reliability of the HCS defense through communications and signaling responses;
d. At the regulatory level of ligand reception by HCS components (to a lesser extent, at the level of soluble components), the principles of co–functioning of HCS with other homeostasis systems and the principles of interaction with microbes and viruses are laid down.

### 2.6. *Other potential HCS Regulators*

These include, first of all, various (glyco)proteins of endogenous origin circulating in human blood, as well as charged compounds with isoelectric point values (pI) that deviate greatly from neutral values, including non-protein ones.

### 2.7. *Other endogenous protein regulators of HCS*

In addition to the immunoglobulin regulators of HCS (**IgM, IgG** and **IgA**), non-immunoglobulin proteins of human blood can Ab-independently modulate the activity of HCS. The latter include oligomeric (assembly) proteins - pentraxins, primarily **SAP** (*serum-amyloid-P-component*) and **CRP** (*C-reactive protein*, acute phase protein). SAP in combination with C4BP participates in the regulation of HCS, in combination with C1q - in the activation initiation reaction of HCS; in combination with histones in the activation process of CCP. SAP is found in complexes with C5b6, iC3b (with exposed Man groups), CRP. CRP complexes with C1q. **Hemoglobin** activates HCS. Aggregated antimicrobial peptides (**defensins** of several classes) are able to associate with the C1*-C1-inh complex and thereby affect HCS. ***Alzheimer*'s amyloid β-peptide aggregates** are involved in CCP and ACP reactions. **Galectin-1** interacts with CR3 of the bone marrow macrophage cell line in a carbohydrate-dependent manner. **$\alpha_2$-Macroglobulin**, interacting with MASP as part of MBP, is able to regulate the MBP-triggered LCP. **Ficolin H** (*Hakata* antigen, MBL-associated serine protease MASP-1 or MASP-3 EC 3.4.21.-.) and **Ficolin L** (associated in human serum with MASP) are able to initiate the LCP of HCS. MBL circulates in the blood in complexes with 4 structurally related serine proteases of the MASP type (that is, there is at least another MASP-4 - see above about MASP–1, 2, 3), and all complexes are involved in the work of HCS.

In model experiments, activation of C4 and C3 can occur due to **kallikrein** EC 3.4.21.34-35. (kinin system of the body), **elastase** EC 3.4.21.36. (connective tissue system) and/or **chymotrypsin** EC 3.4.21.1 (pancreatic system), and regulation of further consumption of C3 fragments in HCS by means of CR3, including **fibrinogen** binding.

C3 can be cleaved by **proteinase of erythrocyte membranes**. Activation of HCS in blood plasma in the presence of $Na_2$-EDTA (sodium salt of ethylenediaminetetraacetic acid) can occur through **coagulation proteases** (EC 3.4.21.22., EC 3.4.21.27., others), which, in turn, can be effectively inhibited by a C1-inh.

### 2.8. *Non-immunoglobulin protein activators of HCS of Viral and Microbial origin*

Non-immunoglobulin protein activators of HCS of viral and microbial origin (for example, of normoflora or pathogens) are constantly present in the body, and, as a rule, have C1q-binding sites. They can include glycoproteins (GP), proteins of the microbial outer membrane, etc. – see below). Many such microbial and viral GP and proteins present in minor amounts in

normally functioning serum and biological fluids are additionally involved in the work of HCS (they are under HCS constant control).

### 2.9. *Some conclusions on protein regulators of HCS*

a) (Glyco) proteins of human biological fluids (not called HCS components) can be involved in the work of HCS as part of supramolecular ensembles;
b) The total number of the above identified human protein participants in the work of HCS is more than 120 (also see above for additional participants – lectins and additional proteinases);
c) HCS works according to the "waste–free" principle - all the proteolytic fragments formed are physiologically active, signaling or structurally demanded components of complexes;
d) HCS has low target specificity and reacts to many agents (protein and non–protein), both endogenous (a variety of spontaneous HCS initiation reactions - see below) and exogenous foreign to the human body;
e) The relatively small variety of types of HCS receptor components (mainly as GP) indicates their key role in the modulation of HCS, and the universality of such regulation regardless of the type of cells in the body;
f) Modeling of human HCS cascades *in vitro* (for example, in micropanels) has more possibilities in cascade construction schemes compared to *in situ* and *in vivo* (both in terms of diversity and reliability of ensuring the planned development of the cascade), since there are no supervisory hierarchical constraints, which is positive for the rapid and effective achievement of the goal – for example, the creation of a directed diagnostic test system or biosensor technique.

### 2.10. *Non-protein regulators of HCS in ligand consumption reactions*

It is established that:

a) HCS reacts to all amine- and/or OH-containing compounds (Reacts to varying degrees), including drugs useful to the body, therefore, the task is to create drugs with minimal anti-HCS action (for example, forms encapsulated in liposomes);
b) Reacting with polysaccharides (PS) and the carbohydrate part of natural glycoconjugates (GC) (GP, PG and others), various components of HCS can be considered as carbohydrate-recognizing (lectin and lectin-like) opsonizing and presenting HCS antigens to the body as a whole, which is a broader representation compared to the designation in HCS only the lectinic (third) pathway (LCP). Thus, the lectin properties of HCS consist in

its functioning according to lectin principles at the stages of initiation and development of HCS reactions. At the same time, C4B and C3 exhibit lectin-like properties: carbohydrate antigens serve as targets of recognition, and the ability of C4 to covalently bind to glycans acts as a more reliable and evolutionarily advanced compared to the reversible binding of lectins to glycans. Moreover, we can talk about the cooperative coordinated action (synergism) of C4 and C3 with a set of typical lectins in HCS, which includes MBL, Ficolines, Sia-binding Factor H, Properdin reacting with acidic glycans, iC3b as oligomannoside binding in micropanels, carbohydrate-binding complement receptors CR1, CR2 and CR3. C3 and isotypes C4B and C4A, reacting to the presence of hydroxyl groups (OH-) of carbohydrates, can be considered as communicative lectin-like proteins. The assembly of a number of multipolypeptide components of HCS involves the recognition of glycans and metal cations. That is, an important factor in interactions in HCS and using HCS is the ability of components (and derivatives of protein components and their complexes) to sense target carbohydrates (not necessarily bind carbohydrates, but require their presence to preserve recognizable surface configurations - patterns). The ability to sense carbohydrates should also be attributed to the manifestation of lectin-like properties of proteins. For example, C1q exhibits lectin-like properties because it is Sia-sensitive and sensitive to the conformational structure of Asn glycans in the $CH_2$ domain of the Fc-fragment of human IgG, and also binds to the proteoglycan complex C1q-I.

### 2.11. *Interaction of Microbial and Viral constituents with HCS*

When microorganisms enter the human body, blood plasma lyzes them, due to the ability of exposed structures of microorganisms to initiate HCS. Such initiators of HCS activation include lipopolysaccharides (**LPS**) and lipooligosaccharides (**LOS**) of Gram-negative bacteria; peptidoglycans (**Pg**) and **(lipo) teichoic acids** of Gram-positive bacteria; **porins** in the composition of OMP (encoded by omp= *outer membrane proteins* genes), bacterial **lipoproteins** and **lipopeptides**. Microbial and viral GP and other GC can play the role of external foreign HCS regulators, and such regulation is carried out through a system of proprietary HCS factors.

#### 2.11.1. *LPS and LOS interacting with HCS*

LPS of *Salmonella*, *E.coli* and LOS of *Neisseria* can interact with CCP in an Ab-independent manner. The lipid part of LPS (lipid A) activates CCP by binding to C1q. The binding of Re-LPS (Re as core region of LPS) to C1q occurs with the collagen-like region of C1q. The

length of the PS chain in LPS is important for the successful reaction with HCS. There is a cooperation of lipid-A and PS from LPS in the activation of HCS. The time required for CCP activation increases with an increase in the LPS glycan chain in the Re-, Ra-, Rc-chemotype series (a larger LPS size does not lead to activation even after 3 hours of incubation). The LPS of the *Salmonella* Ra chemotype (Ra as a relatively shot glycan) is recognized by penta/hexameric lectin – MBL, a key component to initiate LCP. In model animals (mice) defective in C3 and C4, it was shown that the mammalian body becomes significantly more susceptible to the action of LPS (endotoxin) due to the lack of its binding and neutralization by HCS. LPS and LOS are able to initiate activation of all three HCS pathways. Therefore, the phenomenological picture of Ab-independent launch and consumption of HCS components - is usually complex for many genera and species of Gram-negative bacteria. It has been shown that LPS of *E.coli* M17 binds human C1q, which leads to a more effective consumption of human C4 in CCP compared with *Pyrogenal* (commercial LPS from *Salmonella typhi*) and less effective compared with Blastolysin. LPS of *Shigella sonnei* is a good acceptor of the activated C4b (C4b*) human C4B isotype. As a result of the release of LPS during incubation of *E.coli* J5 with normal human serum, a decrease in the hemolytic activity of CCP is observed. C1q forms an Ab-independent complex with serum-sensitive *Salmonella*, S- and R-forms of *Salmonella minnesota*. Promising initiators of HCS activation are synthetic analogues of GC including lipid A and LPS.

#### 2.11.1.1. *The aggregated state of LPS and LOS and their interaction with supramolecular blood complexes*

The degree of aggregation of LPS, as well as the size of LPS, is functionally important for interaction with HCS. The state of LPS aggregation is important for CCP activation, as in the case of *Serratia marcescens*. The presence of supramolecular aggregated protein complexes in the blood creates additional possibilities for regulating HCS by constituents of the surface of microorganisms, for example, bacterial LPS. LPS are able to form complexes with various blood proteins.

### 2.11.2. *Interaction of capsular PS of Bacteria and Fungi with HCS*

The anti-HCS effects of capsular PS is usually less pronounced than that of LPS. Capsular PS are usually resistant to the bactericidal action of serum. In the case of *Neisseria meningitidis*, capsular PS of serogroups A, B and C bind to human activated C4b, and the effectiveness of

inhibiting the binding of C4b to endogenous components of HCS decreases in the row PS-A > PS-C > PS-B, in accordance with a decrease in the degree of immunogenicity of these PS.

PS of yeast *Candida albicans* and *C. stellatoidea* (unlike PS of other *Candida* species), as well as PS of *Saccharomyces cerevisiae* and *Cryptococcus neoformans* bind to iC3b and C3d, but not C3b. Yeast mannan, interacting with the whey protein MBP (C1q-like), binds to activated C4b and initiates LCP.

### 2.11.3. *Interaction of proteins of the bacterial Membrane and The viral envelope with HCS components*

Bacterial OMPs are usually represented by porins, proteins involved in the formation of pores in membranes, including when interacting with GP-components of HCS, especially with Factor H, FHL and C4bBP.

Viral proteins are also capable of being involved in HCS. For example, hemagglutinin of the *influenza* virus with an exposed oligomannoside-type glycan particle aggregate (mannan-like) on the surface of virus-infected BHK-21 cells causes cell lysis by guinea pig serum due to $Ca^{2+}$-dependent binding of serum MBL to glycans and subsequent triggering of CCP. gp120 (possibly in $Ca^{2+}$-dependent glycosylated tetrameric or deglycosylated hexameric aggregates) of HIV-1 (*human immunodeficiency virus*) activates HCS. HCMV (*human cytomegalovirus*) virions can be neutralized with the participation of HCS. HSV(*herpes-simplex-virus*)-1 and HSV-2 are protected from HCS by binding gp-c1 and gp-c2 to C3, C3b and C3c (but not C3d) and subsequent inactivation of HCS; gp-c1 (but not gp-c2) inhibits the binding of C5 and P to C3b, it also inhibits ACP-induced lysis of rabbit erythrocytes. HCV (*hepatitis-C-virus*) induces rheumatoid factor (IgG-IgM complex/ aggregate) involved in cold activation of CCP in patients with rheumatoid arthritis. *Vaccinia* virus contains a 35 kD protein (similar to the C3b/C4b-binding region of human and guinea pig C4bBP) that protects the virus from CCP and ACP. In addition, viral proteins interact with HCS receptor regulators.

### 2.11.4. *Interaction of microbial Pg with HCS*

Pg in their composition combines the properties of proteins/peptides and glycans/oligosaccharides/PS. Compared with proteins and microbial PS, we can expect a wider range of activities in the case of Pg, a greater breadth of options for the effect of Pg on HCS and a more reliable initiation or regulation of complement work for microorganisms (evolutionarily it may be beneficial to the microbe). From the point of view of the evolution

of the body's defense, it seems that methods of recognizing and processing Pg with HCS have been developed, which differ in detail from the recognition of other microbial structures. Ab in complexes with Pg of *Gram*-positive bacteria can trigger and/or consume CCP and ACP components, similar to the examples described above involving LPS of *Gram*-negative bacteria. Such Pg as *Lactobacillus bulgaricus* blastolysin with adjuvant and immunostimulatory properties activates CCP and inhibits the conversion of C3- to C5-convertase by C3b binding (blastolysin is better than LPS from *E.coli* and *Salmonella typhi*, and results in the consumption of human C4, C3 and C2 in CCP and ACP; C3b-Pg dissociation constants for such Pg as blastolysin, MDP [*muramyl dipeptide*] or GMDP [*Glucosaminyl-MDP*] are known).

#### 2.11.5. *Other microbial modulators of HCS*

These include pili neisseria, picornovirus capsids and other tested components of microorganisms that react with the receptor structures of HCS, C4BP and Sia-binding lectin-like factor H. Diphtheria toxoid (inactivated protein toxin) is a C4b acceptor. Potential modulators of HCS, apparently, include lipoproteins and lipopeptides of mycoplasmas, *Salmonella*, staphylococci, streptococci, others. Desialylation of C4 (its α- and β-chains) with sialidase (EC 3.2.1.17.) can increase the functional (hemolytic) activity of some C4 allotypes (individual forms of C4 in individual sera of healthy donors), without affecting the activity of other C4 allotypes.

## 3. CONCLUSION

Despite the large number of molecular and receptor participants linking defense systems in the case of infectious diseases, the communication relationships between HCS and other human immune defense systems are predictable due to the network and cascade properties of such relationships and knowledge of the switching locations between defense systems.

Important (key) for studying the whole innate protective system of the body remain the network of Lectins—GC and serine proteinase system (EC 3.4.21.-.) involving in recognition and interactions between HCS and other innate immune systems, including in connection with the strategies of microbial and viral pathogens to use human innate immunity. Enzymes participate in the work of HCS by few mechanisms including their assembly, cascade action, to be as activation or inhibition factors in respect of other proteinases. There is close cooperation in the functioning of the HCS lectin-GC network and the HCS serine protease network. Moreover, in some cases, enzymes exhibit the properties of lectins (including

zymogens), and lectin participants in HCS exhibit the properties of enzymes (including in assembly processes). In general, many HCS participants act as lectinbiotics and enzymebiotics with a wide range of biological activities. Deeper knowledge of the extended HCS as a protective supernetwork will help to resist the strategies of microbial and viral pathogens capable of using human immunity in cases of certain viral and microbial diseases.

**Disclosure of conflict of interest**

The authors declare no conflict of interest.

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