Influence of Increased sCD56 and Scd16 Serum Concentrations on the Secretory and Cytotoxic Activities of Peripheral Bloodmononuclear Cells in Healthy People Living in Arctic Russia

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Article

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Abstract

Objectives.

The CD56 differentiation cluster has been found on cells of neurogenic origin, muscle, natural killer cells, and on various populations of T lymphocytes, neutrophils, monocytes, epithelial and dendritic cells; this cluster sends signals to activate the secretion of chemokines, integrins, enzymes, cytokines, and other biologically active substances that are characteristic for this cell type. The CD16 third receptor for Fc immunoglobulins (FcγRIII) has been found on the membranes of granulocytes, mast cells, monocytes, macrophages, natural killers, and lymphocytes. The Fc fragment of antibodies provides the cytophilicity of immunoglobulins and frequently binds to IgM, IgA, and IgE. The aim of this study was to evaluate the effect of elevated concentrations of sCD56 and sCD16 on the secretory and cytotoxic activity of peripheral blood mononuclear cells in healthy people.

Methods.

An immunological examination was performed on 178 healthy people aged 21 to 55 years, including 112 women and 66 men, living in the Murmansk region and on the Spitsbergen (Svalbard) archipelago. The peripheral venous blood was analyzed; specifically, the hemogram, phagocytic activity of neutrophilic leukocytes, and contents of lymphocyte phenotypes (CD3+, CD4+, CD8+, CD10+, CD16+, CD56+, CD25+, CD71+, HLADRII, CD95+) were determined using an Epics XL instrument (Beckman Coulter, USA). The concentrations of free sCD16, sCD56, cytokines IL-1β, IL-6, TNF-α, IL-10, cGMP and cAMP, and circulating immune complexes (CICs) to IgA, IgM, and IgG were evaluated using an Evolis automatic analyzer (Bio-Rad, Germany).

Results.

Increases in the serum concentrations of sCD56 and sCD16 in healthy adults of working age are associated with an increase in the content of circulating mononuclear cells with the corresponding membrane clusters. An increase in sCD16 concentration is associated with a decrease in circulating leukocytes in the blood, and an increase in sCD56 concentration is associated with an increase in cytokines. Concentrations of CICs increase in parallel with increases in sCD16 and sCD56 concentrations. An increase in signal-sending activity with an increase in circulating CD16 + and CD56 + leukocytes and the shedding of these signaling molecules occur in parallel with decreases in the cAMP and cGMP concentrations.

Conclusion.

The increase in serum concentrations of sCD56 and sCD16 reflects the specificity and activity of the functions they perform. Membrane CD56 sends a signal that activates cell secretory activity, which results in increases in serum cytokine and immunoglobulin concentrations. In addition, membrane CD56 initiates cell interaction with immunoglobulins. The interaction of mCD16 and sCD16 with immunoglobulins causes a decrease in circulating lymphocytes in the blood and an increase in serum CIC concentration. The activation of signal transduction through CD56 and CD16 and their shedding occur in parallel with a twofold decrease in the extracellular cAMP and cGMP concentrations.

1 INTRODUCTION

The CD56 differentiation cluster is found on neurogenic cells, muscle cells, natural killer cells (including those of thymic origin), as well as on various populations of T lymphocytes, neutrophils, monocytes, epithelial and dendritic cells [1, 2, 3]. The appearance of CD56 on the cell surface is one of the signs of cell maturity [4, 5]. CD56 sends a signal to activate the secretion of chemokines, integrins, enzymes, cytokines, and other bioactive substances that are characteristic for this cell type [6]. $CD56^{dim}$ and $CD56^{bright}$ mononuclear cells circulate in the blood with predominant secretion of lytic granule perforins, granzymes, and cytokines [1, 7].

The CD16 third receptor for Fc immunoglobulins (FcγRIII) has been identified on the membranes of granulocytes, mast cells, monocytes, macrophages, natural killer cells, and lymphocytes [8, 9, 10, 11]. The Fc-fragment of the antibody provides cytophilicity to immunoglobulins and can more often bind IgM, IgA, and IgE. The ability of membrane signaling and receptor proteins to move across the membrane and cluster is not specific; in many types of cells, various integral proteins of the outer layer of the membrane, not only Ig, are able to form aggregates and show a similar recognition ability to that of antibodies [12, 13]. The formation of a complex of different structures with FcR initiates cell contact interactions including adhesion, rosette formation, aggregation, and complement-dependent lysis [9, 14, 15]. The receptor also interacts with the Fc–Fc aggregate [16], with antibody-like structures and a histocompatibility T-cell receptor, as well as fragments of their degradation [17, 18]. Interaction with a peptide bound to the main histocompatibility complex molecule [18] has an inhibitory effect on cells by limiting the transduction of signals through Toll receptors [19].

In this study, our focus was to examine the effect of increased concentrations of sCD56 and sCD16 on the secretory and cytotoxic activity of peripheral blood mononuclear cells in healthy subjects.

2 MATERIALS AND METHODS

2.1 Design and Participants

We performed an immunological evaluation of 178 healthy individuals aged 21–55 years, including 112 women and 66 men, living in the Murmansk (Revda and Lovozero settlements; 67°N, 34°E) region and on the Spitsbergen (Svalbard) archipelago (Barentsburg; 80°N, 10°E). The state of health of the participants

was determined based on the analysis of medical records and the results of examinations by a medical committee during preventive examinations. The examinations were performed in the morning (8.00–10.00) with the consent of the volunteers, according to the requirements of the Declaration of Helsinki of the World Medical Association on Ethical Principles of Medical Research (2000) and with the approval of the Biomedical Ethics Committee of the Institute of Physiology of Natural Adaptations of the Federal State Budgetary Scientific Institution Federal Research Center for Integrated Arctic Studies of the Ural Branch of the Russian Academy of Sciences (Protocol No. 5 of February 11, 2022). Informed consent was obtained from all subjects and/or their legal guardians.

2.2 Laboratory Tests

The immunological evaluation included examination of the hemogram and phagocytic activity of neutrophil leukocytes of peripheral blood. The phagocytic activity of neutrophil granulocytes was determined using the Reakomplex test kit (Russia); the results were evaluated by determining the percent of active phagocytes and phagocytic number (average number of latex particles absorbed by one neutrophil per 100 cells) [20]. Deficiency of active phagocytes was recorded when the result was less than 50%; deficiency of phagocytosis intensity was determined when the phagocytic number was less than 4.

The contents of lymphocyte phenotypes (CD3+, CD4+, CD8+, CD10+, CD16+, CD56+, CD25+, CD71+, HLADRII, and CD95+) in peripheral venous blood were evaluated by indirect immunoperoxidase reaction using monoclonal antibodies (Sorbent, Moscow, Russia); the results of the reaction were evaluated using an Epics XL apparatus (Beckman Coulter, USA).

The enzyme immunoassay method was used to study the concentrations of free sCD16 and sCD56 (Elisa Kit, USA), cytokines IL-1β, IL-6, TNF-α, IL-10 (Bender MedSystems, Germany), cyclic guanosine monophosphate (cGMP) and cyclic adenosine monophosphate (cAMP) (Assay Design, USA) in blood serum using an Evolis automated immunoassay analyzer (Bio-Rad, Germany) and appropriate reagents. The concentrations of circulating immune complexes (CICs) to IgA, IgM, and IgG were studied by precipitation using 3.5, 4.0, and 7.5% PEG-6000, and the reaction was evaluated using the Evolis automated immunoassay analyzer (Bio-Rad, Germany).

2.3 Statistical Methods

Evaluation of the relationship between the concentration in blood of serum receptors (sCD56 and sCD16) and their corresponding membrane forms (CD56 + and CD16+) and the contents of lymphocyte phenotypes, cytokines, CICs, and serum adenylate cyclase activity was performed by dividing baseline values of samples with low and high free sCD56 and sCD16 contents relative to quartiles Q1 and Q4 in the database.

The mathematical analysis of the results was performed using Microsoft Excel 2010 and Statistica 7.0 (StatSoft, USA) software. The distribution of immunological values was verified using Pearson's statistical criterion. The null hypothesis of equality of all averages in the studied groups was tested using a single-factor analysis of variance. Descriptive statistics parameters (M – arithmetic mean, σ – standard

deviation, m – standard error of the mean, Md – median, R – range, W – coefficient of variation, 95% confidence interval limits, r – correlation index) were calculated for each of the abovementioned indicators. Statistical significance was assigned at $p < 0.05$.

3 RESULTS

Increases in serum sCD56 and sCD16 contents were found to be associated with an increase in circulating CD56 + and CD16 + concentrations in peripheral venous blood. In this study, we examined the effect of increased sCD56 and sCD16 concentrations on lymphocyte phenotypes, cytokines, CICs, and serum adenylate cyclase activity. The effects on the studied parameters of increasing the gene expression activity of these differentiation clusters and their shedding from the membrane are markedly different. An increase in sCD16 influences a decrease in circulating leukocytes in blood; an increase in sCD56 concentration is associated with an increase in cytokine content (Table 1).

Table 1

Functional relationship of blood concentrations of CD56 + and CD16 + and their serum counterparts with cytokines and immunocompetent cells (M ± m)

Blood content	**sCD56 < 16 ng/ml 15,92 ± 1,35 (n = 38)**	**sCD56 > 25 ng/ml 41,20 ± 6,56 (n = 45)**	**sCD16 < 1 ng/ml 0,57 ± 0,14 (n = 43)**	**sCD16 > 5 ng/ml 8,23 ± 0,90 (n = 46)**
Leukocytes, 10^9 cells/l	5,32 ± 0,38	5,54 ± 0,37	5,46 ± 0,40	5,08 ± 0,27**
Neutrophil granulocytes, 10^9 cells/l	2,59 ± 0,25	2,65 ± 0,26	2,59 ± 0,31	2,60 ± 0,27
Percentage of active phagocytes, %	68,89 ± 4,12	73,49 ± 4,88	72,80 ± 2,85	73,15 ± 2,69
Phagocytic number, pcs.	4,49 ± 0,65	4,28 ± 0,47	5,14 ± 1,03	3,97 ± 0,99*
Lymphocytes, 10^9 cells/l	2,32 ± 0,20	2,46 ± 0,36	2,40 ± 0,29	2,05 ± 0,23**
Monocytes, 10^9 cells/l	0,29 ± 0,06	0,30 ± 0,04	0,34 ± 0,05	0,28 ± 0,04*
Eosinophils, 10^9 cells/l	0,12 ± 0,03	0,13 ± 0,03	0,13 ± 0,05	0,11 ± 0,04
CD3+, 10^9 cells/l	0,67 ± 0,05	0,76 ± 0,06*	0,98 ± 0,11	0,66 ± 0,07***
CD4+, 10^9 cells/l	0,49 ± 0,04	0,56 ± 0,05	0,64 ± 0,06	0,35 ± 0,06***
CD8+, 10^9 cells/l	0,40 ± 0,04	0,45 ± 0,05	0,49 ± 0,06	0,32 ± 0,05**
CD10+, 10^9 cells/l	0,44 ± 0,07	0,66 ± 0,09**	0,51 ± 0,10	0,35 ± 0,07**
CD16+, 10^9 cells/l	0,47 ± 0,05	0,53 ± 0,08	0,42 ± 0,08	0,55 ± 0,09*
CD71+, 10^9 cells/l	0,42 ± 0,05	0,48 ± 0,06	0,44 ± 0,07	0,26 ± 0,05***
CD25+, 10^9 cells/l	0,44 ± 0,04	0,40 ± 0,06	0,40 ± 0,07	0,32 ± 0,03*
CD56+, 10^9 cells/l	0,32 ± 0,07	0,51 ± 0,09***	0,61 ± 0,10	0,43 ± 0,09**
HLA DR II, 10^9 cells/l	0,36 ± 0,04	0,45 ± 0,05*	0,38 ± 0,04	0,25 ± 0,05**

Note: *p < 0.05; **p < 0.01; ***p < 0.001 – the reliability of differences when compared with a low level of sCD.

Blood content	sCD56 < 16 ng/ml 15,92 ± 1,35 (n = 38)	sCD56 > 25 ng/ml 41,20 ± 6,56 (n = 45)	sCD16 < 1 ng/ml 0,57 ± 0,14 (n = 43)	sCD16 > 5 ng/ml 8,23 ± 0,90 (n = 46)
CD95+, 10^9 cells/l	0,40 ± 0,08	0,59 ± 0,09**	0,40 ± 0,08	0,30 ± 0,07**
IL-1β, pg/ml	1,46 ± 0,53	2,19 ± 0,46**	3,49 ± 0,41	3,45 ± 1,42
IL-6, pg/ml	4,92 ± 0,35	5,25 ± 0,20*	4,91 ± 0,35	5,33 ± 1,01
TNF-α, pg/ml	1,39 ± 0,35	2,09 ± 0,37**	7,56 ± 0,55	7,66 ± 1,07
IL-10, pg/ml	3,63 ± 0,58	5,24 ± 0,20**	5,27 ± 0,53	4,52 ± 0,49*
CIC IgA, g/l	1,45 ± 0,56	2,45 ± 0,49***	1,51 ± 0,46	2,37 ± 0,58***
CIC IgM, g/l	3,32 ± 1,02	4,99 ± 0,98**	3,72 ± 0,87	4,81 ± 0,94**
CIC IgG, g/l	6,93 ± 2,05	10,06 ± 2,34***	7,12 ± 2,26	9,77 ± 2,48***
cGMP, pmol/l	0,53 ± 0,18	0,15 ± 0,07***	0,61 ± 0,19	0,27 ± 0,13***
cAMP, pmol/l	0,11 ± 0,02	0,07 ± 0,01*	0,12 ± 0,02	0,07 ± 0,01***
Note: *p < 0.05; **p < 0.01; ***p < 0.001 – the reliability of differences when compared with a low level of sCD.				

Signal transduction of cytokine secretion through CD56 resulted in an increase in the proinflammatory cytokine and anti-inflammatory IL-10 concentrations. The decrease in total lymphocyte content in cases of increased CD16 + activity was statistically significant; the insignificant decrease in circulating monocyte and eosinophil concentrations is understandable owing to their low blood levels and predominant presence in tissues. Therefore, even the smallest deviations in the concentrations of circulating monocytes and eosinophils in blood reflect significant changes in the functional activity in these systems. The effect of CD16 + activity on the contents of circulating neutrophil granulocytes and their phagocytic activity was not determined in this study. There are two populations of neutrophil granulocytes: some are predominantly phagocytic, and others mainly provide antibody-dependent lysis. The concentrations of circulating immune complexes increase in parallel with increases in sCD16 and sCD56 without significant statistical differences, depending on the activity of immunoglobulin phenotypes and classes.

An increase in signal transduction activity with increases in circulating CD16 + and CD56 + leukocytes and the shedding of these signaling molecules occurs in parallel with corresponding decreases in the cAMP and cGMP concentrations.

DISCUSSION

The modification of cell activity to external signals is performed by the adenylate cyclase system by activation of protein kinases of catalytic and regulatory subunits. The regulatory subunit is a receptor for cAMP; without an external signal, the complex of catalytic and regulatory parts is inactive. However, as soon as cAMP attaches to the regulatory subunit, the complex dissociates, exposing the active groups. The active groups of adenylate cyclase convert ATP into 3 5 AMP, which activates protein kinases. The guanylate cyclase system is an antagonist of cAMP; cAMP inhibits movement and cell division, while cGMP stimulates these processes [21, 22].

The number of processes that cAMP affects is considerable. cAMP is associated with activation of gluconeogenesis, lipolysis, ketogenesis, synthesis of RNA and DNA, cell growth, secretion of almost all hormones, serotonin, histamine, acetylcholine, lysosomal enzymes, and ion transport [23, 24, 25, 26]. The mechanisms of cAMP action are diverse; in some cases, they are very complex and not always directly mediated by adenylate cyclase stimulation. Proteins that activate the catabolic gene play the role of cAMP receptors; thus, as soon as cAMP binds to the catabolism-activating protein, this complex binds to the promoter, which initiates transcription. In addition, the adenylate cyclase system can influence biosynthesis processes independently of RNA polymerase by affecting histones and ribosomal proteins. The possibility of gene activation by the adenylate cyclase system ensures its participation in the regulation of cell proliferation.

Although the cell response will be coordinated by the presence and transfer of cAMP, the level of cell activation and its character will depend on the concentration of the cellular macromolecule with which cAMP interacts, and if the macromolecule necessary for the reaction is not sufficient, activation of only a few cells will result in an enhanced response [26, 27]. In our study, we show that a parallel decrease (actually twofold) in the extracellular cAMP and cGMP concentrations occurs with an increase in the functional activity of CD56 and CD16 clusters. The contents of extracellular cAMP and cGMP are always higher (by a factor of 3–10) and almost never approach the intracellular levels; the difference between the internal and external concentrations is independent of intracellular metabolism and is achieved by the release of adenylate cyclases against the concentration gradient in the cytosol [28]. This unidirectional process is activated by ATP and depends on the concentration of cyclic nucleotides in the cell. Thus, intracellular concentrations of cyclic nucleotides in the cell depend on simple diffusion, reactive membrane changes, and an energy capacity. The absence of changes in cGMP concentration indicates that the increase in CD56 and CD16 gene expression activity and their shedding levels within the fluctuations in this study do not disturb homeostasis, although they condition adaptive responses to preserve it.

Our data confirm the functional importance of CD56 membrane clusters for activation of cytokine secretion and the importance of CD16 for providing cell contacts. We confirmed the previously expressed opinion that the activation of differentiation cluster genes is accompanied by enhancement of their shedding [29, 30]. Thus far, receptor shedding from the membrane has been attributed to various processes; specifically, cell sheds receptor structures at rest [31, 32], for renewal [33, 34], during activity [35, 36], and when there is no need or it is impossible to respond to a signal. The increased concentration of the extracellular pool in blood during various pathological processes and their accumulation in exudates and transudates indicate that receptor shedding occurs during periods of functional cell activity [24, 32, 37].

Shedding is performed by membrane proteases, which are zinc metalloproteinases and, as enzymes, are glycoproteins. They are detected at the sites of signal-receiving molecules and are activated after a receptor–ligand interaction. Membrane surface proteolysis can increase the rate of membrane transport while determining the local concentration of effectors and the threshold of sensitivity of the acceptor system of the cell [38, 39, 40, 41]. The increase in the rate of transport and the decrease in the levels of cAMP induced by proteases suggest that the increase in the activity of surface proteolysis during cell activation is an adaptive regulation that depends on feedback.

Conclusion

Increases in the serum sCD56 and sCD16 concentrations in healthy adults of working age are associated with an increase in the circulating mononuclear cell contents with the corresponding membrane clusters. The increased serum concentration of the differentiation clusters studied in this work reflects the specificity and activity of the functions they perform.

Membrane CD56 transduces a signal that activates cell secretory activity depending on increases in serum concentrations of cytokines and immunoglobulins; in addition, membrane CD56 initiates cell interaction with immunoglobulins. The interaction of mCD16 and sCD16 with immunoglobulins causes a decrease in circulating blood lymphocytes and an increase in serum CIC concentrations.

The activation of signal transduction through CD56 and CD16 and their shedding occur in conjunction with parallel twofold decreases in the extracellular cAMP and cGMP concentrations.

Declarations

Data availability

The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

Author contributions

Liliya K. Dobrodeeva: organization and design of the study, data interpretation; writing – original draft; **Anna V. Samodova:** formal analysis, conceptualization; revision of the article,revision of the final version of the article. All authors read and approved the final manuscript.

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Conflict of interest

The authors declare no potential conflict of interest.

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