DOI: 10.17816/KMJ2022-617

Selectins and their involvement in the pathogenesis of cardiovascular diseases

R.E. Kalinin, N.V. Korotkova*, I.A. Suchkov, N.D. Mzhavanadze, A.N. Ryabkov

Ryazan State Medical University named after I.P. Pavlov, Ryazan, Russia

Abstract

The review presents current data on the structure and functional role of cell adhesion molecules belonging to the selectin family (selectins P, L and E), and their involvement in the pathogenesis of cardiovascular diseases. On the one hand, intercellular adhesion molecules of the vascular wall endothelium, platelets and leukocytes are an important link in the processes of vasculogenesis, development and regeneration of the vascular system. On the other hand, these molecules participate in the earliest stages of endothelial dysfunction with the subsequent development of pathology. For this reason, figuring out the mechanisms of activity of this group of molecules is very important for understanding the molecular basis of the cardiovascular diseases pathogenesis. The adhesion of molecules, both between cells and between cells and a component of the extracellular matrix, is the most important stage of physiological and biochemical processes. According to present knowledge, five classes of intercellular adhesion molecules are known: integrins, cadherins, immunoglobulins (including nectins), selectins and addressins. All of them are bonded to a cytoplasmic membrane and provide the interaction of cells with each other. Some of them are transmembrane and associated with the cytoskeleton of the cell. On the cell surface, intercellular adhesion molecules can be located in clusters, forming multipoint binding sites and thereby determining the degree of avidity. One of the most significant functions of selectins is participation in the initial stage of the leukocyte adhesion cascade, which results in their binding to the endothelium, rolling and further extravasation into tissues. The first stage of this process is mediated by specific non-covalent interactions between selectins and their glycan ligands, with the glycans functioning as an interface between leukocytes or cancer cells and the endothelium. Targeting these interactions remains one of the main strategies aimed at developing new methods of treating immune, inflammatory and oncological diseases.

Keywords: P, L, E selectins, intercellular adhesion molecules, cardiovascular diseases.

For citation: Kalinin RE, Korotkova NV, Suchkov IA, Mzhavanadze ND, Ryabkov AN. Selectins and their involvement in the pathogenesis of cardiovascular diseases. *Kazan Medical Journal.* 2022;103(4):617–627. DOI: 10.17816/KMJ2022-617.

Background

Selectins (differentiation cluster 62, or CD62) belong to the family of cell–cell adhesion proteins (cell adhesion molecules, or CAMs). These cell membrane glycoproteins provide adhesive interactions between hematopoietic cells, cancer cells, leukocytes, platelets, and endothelium. Cell adhesion is significant in inflammatory, infectious, metastatic, and immune processes and in the niche-defining ability of stem cells [1].

Selectins also determine the behavior of aberrant leukocytes in chronic and acute inflammatory diseases [2]. Adhesive interactions between cells and between cells and the extracellular matrix were found to play an important role in processes such as embryonic development, organ morphogenesis, inflammatory reactions, wound healing, immune surveillance, hemostasis, and tumor metastasis [3].

Known selectins have a common structural organization, and their molecule consists of five different domains:

1) An N-terminal calcium-dependent lectin domain, which is consists of 120 amino acids and is responsible for the recognition of carbohydrates.

2) A domain similar to the epidermal growth factor (EGF).

3) Short consensus repeat (SCR) domain, containing 2–9 repeats of approximately 60 amino acids, related to complement-regulatory proteins.

4) A transmembrane domain of approximately 25 amino acids.

5) Short cytoplasmic C-terminal domain (Fig. 1).

The N-terminal domains of all three selectins have a lectin domain that is 60% identical to C-type lectins [4].

Selectins can bind to ligands represented by oli-

*For correspondence: fnv8@yandex.ru

Submitted 01.11.2021; accepted 11.01.2022; published: 10.08.2022.

Table 1. Description of L-, E-, and P-selectins and their general biological and biochemical properties [cit. by 7, mod.]

Selectin	L (MEL-14, CD62L)	E (ELAM-1, CD62E)	P (GMP-140, PADGEM, CD62P)
Expression	All leukocytes (T cells, monocytes, and polymorphonuclear neutrophils)	Activated endotheliocytes	Activated endotheliocytes/activated platelets
Tethered cell types	Activated endotheliocytes	Neutrophils/monocytes	Neutrophils/monocytes
Expression control	Constitutive	Proinflammatory cytokines	Thrombin, histamine, proinflammatory cytokines, and reactive oxygen species
Molecular weight of the molecule, kDa	75–110	116	140
Molecular weight of the protein part of the molecule, kDa	~45	~64	~90
Share of carbohydrates in the composition, %	50	50	28.8
N-glycosylated sites	10	11	12
Ligand	PSGL-1 GlyCAM-1 MAdCAM-1 CD-34 Podocalyxin	PSGL-1 ESL-1 L-Selectin Podocalyxin	PSGL-1 CD24

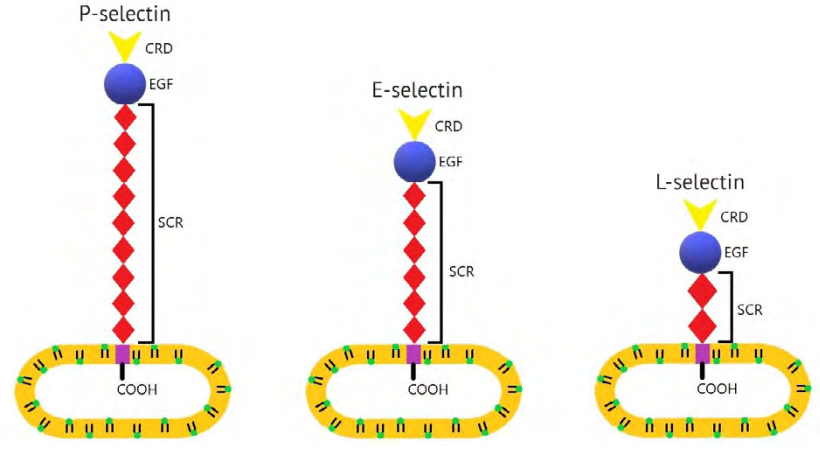

Fig. 1. Schematic representation of the structures of P-, E-, and L-selectins; interpretation of symbols is given in the text

gosaccharides with the involvement of calcium ions. In many respects, current ideas about the structure of selectins are due to the studies of Ashwall et al., who revealed more than 40 years ago that hepatocytes contain a Ca^{2+}-dependent carbohydrate-binding protein, or lectin, which interacts with serum glycoproteins [5]. Then, all three selectins recognize a common motif, namely, sialylated and fucosylated tetrasaccharide Sialyl Lewis X (sLeX) with its isomeric form Sialyl Lewis A (sLeA), which is a terminal component of some *N*- and *O*-glycans.

The binding affinity of glycan determinants sLeX and sLeA is in the millimolar range, and they are important components of many glycoproteins and glycolipid ligands that are often present on proteins and participate in multivalent interactions. Subsequently, the discovery was confirmed using modern methods of molecular and cellular biology. Currently, the term “selectin” is used for this group of molecules, instead of the previously used term lectin–EGF complement–binding-cell adhesion molecule (LEC-CAM) [6].

The general characteristics of selectins are presented in Table 1.

Selectins are nearly not expressed on the membrane of non-activated cells. With the activation of

endothelial cells, leukocytes, and platelets, which occurs under certain conditions (changes in blood flow rate, pH, and temperature, cell structure disturbance, and exposure to biologically active molecules), the expression of selectins increases.

P-selectin

The amino acid sequence of human P-selectin is represented by 120 amino acids. It has a molecular weight of approximately 140 kDa and extends approximately 40 nm from the endothelium surface. When expressed on the platelet membrane, the reduced molecular weight of P-selectin is approximately 149 kDa and contains 28.8% carbohydrates by weight. For P-selectin, nine consensus repeats in the SCR domain are typical. It can associate with a homodimer through the interaction of transmembrane domains. The dimerization of P-selectin and its main ligand, the P-selectin glycoprotein ligand (PSGL-1), promotes the binding of leukocytes to endotheliocytes. PSGL-1 is a transmembrane protein of leukocytes [8].

A soluble form of P-selectin (sP-selectin) is formed by alternative splicing of the messenger ribonucleic acid (mRNA) precursor. This fraction of sP-selectin enters the bloodstream from activated platelets. Both soluble and membrane forms of selectins are expressed by stimulated endothelial cells and platelets.

P-selectin is located in the α-granules of platelets and secretory granules of Weibel–Palade bodies of endothelial cells and participates in the primary interaction of polymorphonuclear neutrophils and endotheliocytes, particularly in the focus of inflammation. It can regulate the synthesis of integrins, acting in conjunction with cytokines. Its maximum level is achieved 5–10 min after cell activation, and P-selectin is separated from the cell surface within 0.5 or 1 h [9].

P-selectin is delivered to the cell surface in two pathways. Pathway 1 is fast (2 min) mobilization from Weibel–Palade bodies, with a maximum on minute 10 and a duration of up to 3 h. During its implementation, new molecules are not synthesized. This pathway is induced by exposure to histamine, thrombin, reactive oxygen species, and proinflammatory cytokines [10].

Pathway 2 is associated with increased transcription of P-selectin mRNAs and an increase in its synthesis in endothelial cells *in vitro* and *in vivo* under the influence of proinflammatory cytokines, namely, tumor necrosis factor-α, interleukin-1β, and lipopolysaccharides of the outer membrane of bacteria. The transcription factor NF-κB and the activating transcription factor 2-ATF-2 are involved in this process. Unlike other mammals, humans and primates do not have this pathway. In human endothelial cells, tumor necrosis factor-α slows down the transcription of P-selectin mRNAs in vitro and reduces P-selectin-mediated cell adhesion in vivo [11].

According to the study by Chaitanya et al., P-selectin expression can be regulated under the influence of nitric oxide [12]. For example, the administration of the nonselective nitric oxide synthase inhibitor NG-nitro-L-arginine methylester is accompanied by an increase in P-selectin expression [13]. In addition, the expression of P-selectin on the surface of endotheliocytes increases under the influence of hypoxia and decreases against hypoglycemia.

Evidence reveals that the heterogeneity of the synthesis of cell adhesion molecules is inherent in the endothelium. Thus, certain aortic endotheliocytes do not contain P-selectin in contrast to the endothelial cells of the umbilical vein.

E-selectin

E-selectin, a glycoprotein with a molecular weight of approximately 116 kDa, is expressed on the plasma membrane surface of vascular endothelial cells. The human *Sel E* gene is located on chromosome 1q22–q25 and consists of 12 exons. The E-selectin molecule comprises a lectin domain, an EGF domain, and six cysteine-rich consensus repeats of the SCR domain, followed by a 119-residue N-terminal lectin domain responsible for binding to the oligosaccharide component. E-selectin production, in contrast to P-selectin production, is inducible. After cellular activation, it requires de novo transcription. Intact endothelium practically does not express it. Shear stress and proinflammatory cytokines influence the expression of E-selectin on the endotheliocyte membrane [14].

E-selectin is synthesized on the plasma membrane of endothelial cells 4–6 h after exposure to tumor necrosis factor-α, interferon-γ, and interleukin-1. This selectin is involved in the initiation of the adhesion of activated leukocytes to endotheliocytes in the inflammation site [15]. The maximum concentration of E-selectin can persist for 1–2 days. The magnitude of the shear stress and its duration influence the cytokine-induced expression of E-selectin. Under the combined effect of shear stress and cytokines, E-selectin is maximally expressed after 8–12 h. Signaling pathways c-Jun N-terminal kinases and mitogen-activated protein kinase p38 increase the expression level of E-selectin. Moreover, its expression is NF-κB-dependent [16].

Sialylated oligosaccharides (Sialyl Lewis A/X), including those contained in glycoproteins such as E-selectin ligand-1 (ESL-1) and PSGL-1, are ligands for binding E-selectin. They are present

in greater amounts in granulocytes and smaller amounts in monocytes and T-lymphocytes [17]. Glycosphingolipids containing sialic acids can be E-selectin ligands.

The biological significance of E-selectin includes ensuring the attraction of leukocytes to the inflammation site and the slow rolling of neutrophils along the surface of activated endothelial cells [18]. With E-selectin deficiency, the slow rolling of leukocytes and severity of the inflammatory reaction decrease. E-selectin is also involved in the adhesion of endothelial cell precursors, which promotes the migration of the latter and formation of capillaries. The administration of the E-selectin adenoviral vector accelerates capillary formation and reduces the severity of ischemia-induced necrosis. Thus, E-selectin overexpression confirms its involvement in the adhesion of endotheliocyte progenitors and neoangiogenesis [19].

L-selectin

L-selectin has a similar organization of extracellular domains with P- and E-selectins, and structurally, it contains two short SCR domains of the complement-regulatory protein with a molecular weight of approximately 75 and 110 kDa, depending on the cell type. N-terminal 9 amino acids are decisive in the mechanism of binding of a ligand molecule to L-selectin [20]. This part of the molecule is also necessary for the binding of lymphocytes into the high endothelium of the postcapillary venules of peripheral lymph nodes and the invasion of neutrophils into the inflammation site. Evidence shows that P- and L-selectins bind to *O*-glycans, sulfated tyrosine (another possible post-translational modification), and other amino acids near the N-terminus of PSGL-1. L-selectin binds to sialylated, fucosylated, and sulfated *N*- and *O*-glycans on glycoproteins expressed on the endothelial cells of high endothelial venules in the lymph nodes [21].

L-selectin is involved in the migration of leukocytes to inflamed tissues, and high levels of L-selectin ligands initiate its expression. In addition, L-selectin plays an important role in the adhesion of circulating leukocytes to leukocytes attached to the blood vessel wall, known as secondary binding.

L-selectin is continuously produced on leukocytes and releases the cell surface very quickly after its activation. This enables the adhesion of leukocytes to the cells of the lymph nodes and activated endothelium.

Involvement of selectins in cardiovascular diseases

To date, accumulated data show that adhesion molecules are involved not only in cell fixation in certain areas inside tissues but also in the transfer of biochemical information from the extracellular environment through the initiation of intracellular signaling pathways.

In the past 25 years, selectins, particularly P-selectin, contribute to the development of inflammation and thrombosis in many preclinical disease models, including atherosclerosis [22], ischemic damage [23], and arterial thrombosis [24, 25].

Unregulated adhesion and activation of leukocytes lead to tissue damage, which is associated with the development of inflammatory, ischemic, and reperfusion injuries [26]. Moreover, cardiovascular diseases are the main cause of morbidity and mortality; therefore, changes in individual biochemical signaling pathways typical for them must be actively explored [27].

Accordingly, knowledge of the molecular mechanisms of the functioning of adhesive molecules will enable establishing individual links in the pathogenesis of cardiovascular diseases to determine further the strategic points of application of therapeutic intervention [28].

Selectins and myocardial infarction

Glycans serve as the main ligand of selectins and play an important role in the adhesion of leukocytes and endothelial cells. Recently, they are increasingly used as biomarkers of metabolic disorders, particularly in myocardial infarction.

In myocardial infarction, neutrophils are the first type of cells that enter the injury site, and this occurs through the expression of selectin ligands that initiate adhesion to activated endothelial cells. The already extravasated neutrophils phagocytize cell debris, release proteolytic enzymes, and generate reactive oxygen species, which result in the degradation of the extracellular matrix and initiation of wound healing [29]. In this case, a cytotoxic effect was observed on viable cardiomyocytes and blood vessels, which exacerbates reperfusion-associated myocardial damage [30]. The excessive intravascular accumulation of neutrophils contributes to capillary damage and microvascular occlusion, prolonging the duration of ischemic injury [31].

Clinical trials on the suppression of P-selectin by the recombinant monoclonal antibody inclacumab have demonstrated positive results. According to Jean-Claude Tardif et al., inclacumab reduced myocardial injury after percutaneous coronary intervention in patients with non-*ST* elevation myocardial infarction [32].

Currently, the behavior of selectins is being studied at the epigenetic level. Thus, Izzi et al. examined the platelet–endothelial aggregation receptor 1 (PEAR 1), which is involved in platelet

activation and megakaryocytopoiesis, whose expression is a result of the methylation of deoxyribonucleic acid. Their results indicate a negative correlation of PEAR 1 with platelet–monocyte conjugates, P-selectin, and leukocyte count, and a positive correlation with platelet distribution width and L-selectin. This confirms the epigenetic regulation of PEAR 1, inflammation processes, and functioning of selectins [33].

Lampka et al. examined the levels of soluble selectins in myocardial infarction and revealed that the content of sE-selectin increased in parallel with the severity of atherogenic changes in the lipid profile of the blood serum, and the sP-selectin level increased to a greater extent because of inflammatory and prothrombotic processes. However, sE- and sP-selectin do not adequately reflect the degree of endothelial activation. sL-selectin levels are affected by inflammatory processes in the vascular wall. A decrease in sL-selectin levels indicates a functional depletion of leukocytes in patients with myocardial infarction, making assessment of the degree of leukocyte stimulation difficult [34].

Zhang et al. evaluated the deletion of the gene for the chromatin remodeling enzyme *brahma-related gene 1* (*BRG1*) in the endothelium and revealed that such a mutation decreased the infiltration of the focus of myocardial infarction by neutrophils and decreased the level of proinflammatory mediators in the heart tissues after damage caused by ischemia–reperfusion. Further studies have shown that *BRG1* activates the transcription of podocalyxin (PODXL), a sialomucin protein expressed by podocytes, mesothelium, vascular endothelial cells, hematopoietic stem cells, and platelets and is an L-selectin ligand. PODXL is critical for neutrophil adhesion to vascular endothelial cells in response to hypoxia–reoxygenation. The knockdown of the BRG1-encoding RNA suppresses PODXL expression induced by hypoxia–reoxygenation and blocks neutrophil adhesion to endothelial cells [35].

McEver examined the molecular mechanisms of action of selectins in inflammatory and thrombotic diseases in vitro to develop special drugs that inhibit the interaction of selectins with their ligands and revealed that selectins trigger signals in leukocytes, involving ligands to PSGL-1 and the integral cellular glycoprotein CD44. In this case, conformational changes occur in the structure of β_2-integrins, which mediate slow rolling.

The in vitro signaling action of selectins is generally not sufficient to induce superoxide production, tissue factor synthesis, cytokine secretion, or formation of neutrophil extracellular traps. However, selectin signaling enables signals from other agonists, such as chemokines or lipid autocoids, to generate similar responses. Whether such cooperative signaling occurs in vivo requires further investigation. The results of previous studies can lead to an understanding of the pathogenesis of thrombotic and inflammatory diseases and the creation of new drug targets for the treatment of inflammatory diseases [36].

Selectins and thromboses

To some extent, this review has covered the involvement of selectin generation and development of thrombosis. The activation of neutrophils and their consequent interactions with platelets promote thrombogenesis and arterial thrombosis and represent a potential therapeutic target. The interaction of platelets and neutrophils is mediated by adhesion molecules such as P-selectin, E-selectin, and their ligands, which implement physical cellular interactions and intracellular signaling. The release of soluble mediators and direct signaling between platelets and neutrophils leads to their reciprocal activation and the release of extracellular condensed chromatin scaffold traps by neutrophils, which play a prothrombotic role in atherothrombosis [37].

Selectins and atherosclerosis

The risk of atherosclerotic complications, based only on the presence of classical risk factors, is often incompletely analyzed. Thus, the search for polymodal panels of markers indicating the presence of the disease is ongoing. These include primarily peripheral blood markers and markers that indicate deterioration in the arterial wall condition.

Patients with atherosclerosis have high blood levels of classic inflammatory mediators such as cytokines, cell adhesion molecules, including selectins, and acute phase markers, such as highly sensitive C-reactive protein, fibrinogen, and serum amyloid A. A positive correlation was also found between the levels of P- and E-selectins and arterial stiffness, thickness of the media and intima of the carotid artery, stability of atherosclerotic plaques, and presence of clinically apparent cardiovascular diseases in patients with different levels of risk [38].

The functioning of selectins in atherosclerosis is actively studied, both in patients and animals and cell models. Thus, Colijn et al. explored the action of the receptor-interacting serine/threonine-proteinkinase 3 enzyme, whose activity increase is associated with necroptosis, and revealed that it can play an anti-inflammatory role by suppressing the expression of monocyte chemoattractant protein 1 in macrophages and E-selectin expression in endothelial cells. This finding provides new information

about the involvement of the latter in inflammatory vascular diseases and raises issues about the efficacy and safety of its targeting in clinical settings [39].

Zhishuai Ye et al. examined the role of the interaction of P-selectin with its specific ligand PSGL-1 in atherosclerosis. This interaction was found to accelerate the course of atherosclerosis, which is associated with the activation of myeloid differentiation during the primary response of the MYD88-dependent signaling pathway (cytosolic adapter protein involved in signaling through Toll-like receptors) and MyD88-independent signaling pathways of Toll-like receptor 4 [40].

To examine the contribution of adhesion molecules to the pathogenesis of atherosclerosis, genetic modeling of atherosclerosis in experimental animals is used. Thus, Collins et al. created a mouse model of a deficiency of intercellular adhesion molecules P-selectin and intercellular adhesion molecule 1 (ICAM-1), and the animals received excess amounts of fats. With this combination of conditions, the atherosclerotic area decreased. In mice knocked out for *Apo E* and *ICAM-1* genes, compared with mice knocked out only for the *Apo E* gene, the atherosclerotic area in the aorta significantly decreased. This may indicate the involvement of adhesion molecules in the early stages of the development of atherosclerosis. In addition, a targeted effect on certain genes influences the atherosclerotic area [41]. In addition, a study of soluble P-selectin targeting showed its negative role in atherosclerosis [42]. The heterogeneity of the production of intercellular adhesion molecules by endotheliocytes may reflect the heterogeneity of the different parts of the vascular bed for infiltration by leukocytes and, possibly, the development of atherosclerotic lesions.

Selectins and varicose veins of the lower extremities

In recent years, phlebology has rapidly developed, and the latest ideas about the pathogenesis of venous diseases and mechanisms of damage to the venous wall have been formulated. Moreover, phlebostasis in combination with leukocyte aggression remains one of the theories of vein pathology, which can also be implemented with the participation of adhesion molecules [43].

Moñux et al. analyzed the level of P-selectin among other markers of endothelial dysfunction to assess the correlation between its concentration in the blood plasma and the state of the vascular wall. Thus, compression therapy was found to improve the condition of the varicose vein wall by affecting the levels of biomarkers associated with endothelial functionality, inflammation, oxidative stress, and coagulation [44].

Mikuła-Pietrasik et al. directly compared the blood sera of patients with varicose veins with those of healthy donors and showed that the pathological serum contained high concentrations of intercellular adhesion molecules, including P-selectin, whereas the level of the latter correlates negatively with chronological age [45]. Moreover, the researchers exposed that the aging of endothelial cells of the umbilical veins was related to the action of blood serum in patients with varicose veins and noted an increase in the levels of ICAM-1, vascular cell adhesion molecule 1, P-selectin, uPA (plasminogen activator, urokinase), plasminogen activator inhibitor-1 and endothelin-1 (ET-1), produced by these cells.

Goshchynsky et al. reported the presence of significant pathomorphological and pathophysiological changes in the wall of deep veins with impaired integrity of the endothelial lining. On days 10 and 60 postoperatively, the concentrations of endothelial dysfunction markers were high, namely, P-selectin, E-selectin, tissue-type plasminogen activator, ET-1, type 1 vascular endothelial adhesion molecules, and circulating endothelial cells. Despite surgery, indicators of endothelial dysfunction decrease but do not return to normal in the late postoperative period [46].

Selectins and mitral valve prolapse

Yagoda et al. revealed in patients with mitral valve prolapse the hyperproduction of circulating cell adhesion molecules, namely, E-selectin, VCAM-1, and ICAM-1, which is an indicator of the endothelial activation process, leading to possible changes in vascular homeostasis. Simultaneously, patients showed decreased levels of platelet/endothelial cell adhesion molecule 1, which probably proves the protective function of this molecule against thrombosis development. In addition, a decrease in RESAM-1 levels may be associated with certain early low rates of collagen-induced platelet aggregation in patients with mitral valve prolapse [47].

Over the past 5 years, the number of publications on instrumental molecular visualization of inflammation has been increasing. For this purpose, P-selectin is used as a marker of inflammation, particularly in cardiovascular diseases, which require early diagnostics. Thus, preclinical molecular visualization of P-selectin was demonstrated by positron-emission computed tomography, single-photon emission computed tomography, magnetic resonance imaging, and ultrasonography using various agents, particularly fucoidan or antibodies against P-selectin [48].

Li et al. also evaluated the effect of fucoidan capsules. They showed that fucoidan capsules

could bind to P-selectin and activated platelet aggregates, even under high-flow conditions. This property can be used for molecular diagnostics and/or treatment of cardiovascular diseases characterized by increased expression of P-selectin [49].

In addition, numerous studies have discussed targeted therapeutic approaches aimed at the interactions of the receptors/ligands of selectins that can be used to suppress inflammatory response or improve leukocyte migration into tissues. For example, the migration of phagocytic leukocytes can be purposefully controlled by modifying the expression of selectin receptors [50].

Conclusion

To date, numerous studies, including in vitro and in vivo models, have demonstrated the significant role of selectins in the initiation of intracellular signaling pathways and regulation of intercellular interactions between leukocytes and the vascular wall. Through participation in the regulation of selectin-dependent activation and adhesion of leukocytes, these cell adhesion molecules function in various physiological and pathological processes, including the development of cardiovascular diseases.

The interruption of the leukocyte and endothelial cell interaction cascade is one of the main research areas, and its therapeutic potential is under intense investigation. The development of the real inhibitors of interactions of selectins with their ligands in vivo is a difficult task because of the dual role of selectins. Thus, more studies of the biochemical signaling pathways associated with selectin-dependent cellular interactions will allow a better understanding of the mechanisms involved in the pathogenesis of cardiovascular diseases and help in the search for new approaches to the development of therapeutic interventions.

Author contributions. R.E.K. and I.A.S. developed the concept and design of the study and edited the text; N.V.K., N.D.M., and A.N.R. performed the data analysis and wrote and edited the text.

Funding. The work was supported from the budget of the I.P. Pavlov Ryazan State Medical University of the Ministry of Health of Russia.

Conflict of interest. The authors declare no conflict of interest.

REFERENCES

1. Wayne Smith C. Adhesion molecules and receptors. *J Allergy Clin Immunol*. 2008;121(2):S375–S379; quiz S414. DOI: 10.1016/j.jaci.2007.07.030.

2. Silva M, Videira PA, Sackstein R. E-selectin ligands in the human mononuclear phagocyte system: Implications for infection, inflammation, and immunotherapy. *Front Immunol*. 2018;8:1878. DOI: 10.3389/fimmu.2017.01878.

3. Ludwig RJ, Schon MP, Boehncke WH. P-selectin: A common therapeutic target for cardiovascular disorders, inflammation and tumour metastasis. *Expert Opin Ther Targets*. 2007;11(8):1103–1117. DOI: 10.1517/14728222.11.8.1103.

4. Tvaroška I, Selvaraj C, Koča J. Selectins — The two Dr. Jekyll and Mr. Hyde faces of adhesion molecules — a review. *Molecules*. 2020;25(12):2835. DOI: 10.3390/molecules 25122835.

5. Ashwell G, Modell AG. The role of surface carbohydrates in liver recognition and the transport of circulating glycoproteins. In: Meister A, editor. *Advances in enzymology and related areas of molecular biology.* Vol. 41. New York: John Wiley & Sons; 1974. p. 99–128. DOI: 10.1002/9780470122860.ch3.

6. Sperandio M, Gleissner CA, Ley K. Glycosylation in immune cell trafficking. *Immunol Rev*. 2009;230(1):97–113. DOI: 10.1111/j.1600-065X.2009.00795.x.

7. Kappelmayer J, Nagy BJr. The interaction of selectins and PSGL-1 as a key component in thrombus formation and cancer progression. *Biomed Res Int*. 2017;6138145. DOI: 10.1155/2017/6138145.

8. Ramachandran V, Yago T, Epperson TK, Kobzdej MM, Nollert MU, Cummings RD, Zhu C, McEver RP. Dimerization of a selectin and its ligand stabilizes cell rolling and enhances tether strength in shear flow. *Proc Natl Acad Sci USA*. 2001;98(18):10166–10171. DOI: 10.1073/pnas.171248098.

9. Kansas GS. Selectins and their ligands: current concepts and controversies. *Blood*. 1996;88(9):3259–3287. DOI: 10.1182/blood.V88.9.3259.bloodjournal8893259.

10. Kvietys PR, Granger DN. Role of reactive oxygen and nitrogen species in the vascular responses to inflammation. *Free Radic Biol Med*. 2012;52(3):556–592. DOI: 10.1016/j.freeradbiomed.2011.11.002.

11. Liu Z, Miner JJ, Yago T, Yao L, Lupu F, Xia L, McEver RP. Differential regulation of human and murine P-selectin expression and function *in vivo*. *J Exp Med*. 2010;207(13):2975–2987. DOI: 10.1084/jem.20101545.

12. Hossain M, Qadri SM, Liu L. Inhibition of nitric oxide synthesis enhances leukocyte rolling and adhesion in human microvasculature. *J Inflamm (Lond)*. 2012;9:28. DOI: 10.1186/1476-9255-9-28.

13. Chaitanya GV, Cromer W, Wells S, Jennings M, Mathis JM, Minagar A, Alexander JS. Metabolic modulation of cytokine-induced brain endothelial adhesion molecule expression. *Microcirculation*. 2012;19(2):155–165. DOI: 10.1111/j.1549-8719.2011.00141.x.

14. Huang RB, Gonzalez AL, Eniola-Adefeso O. Laminar shear stress elicit distinct endothelial cell E-selectin expression pattern via TNFα and IL-1β activation. *Biotechnol Bioeng*. 2013;110(3):999–1003. DOI: 10.1002/bit.24746.

15. Huang RB, Eniola-Adefeso O. Shear stress modulation of IL-1β-induced E-selectin expression in human endothelial cells. *PLoS One*. 2012;7(2):e31874. DOI: 10.1371/journal.pone.0031874.

16. Chen TC, Chien SJ, Kuo HC, Huang WS, Sheen JM, Lin TH, Yen CK, Sung ML, Chen CN. High glucose-treated macrophages augment E-selectin expression in endothelial cells. *J Biol Chem*. 2011;286(29):25564–25573. DOI: 10.1074/jbc.M111.230540.

17. Nimrichter L, Burdick MM, Aoki K, Laroy W, Fierro MA, Hudson SA, Von Seggern CE, Cotter RJ, Bochner BS, Tiemeyer M, Konstantopoulos K, Schnaar RL. E-selectin receptors on human leukocytes. *Blood*. 2008;112(9):3744–3752. DOI: 10.1182/blood-2008-04-149641.

18. Sundd P, Pospieszalska MK, Cheung LS, Konstantopoulos K, Ley K. Biomechanics of leukocyte rolling. *Biorheology*. 2011;48(1):1–35. DOI: 10.3233/BIR-2011-0579.

19. Nishiwaki Y, Yoshida M, Iwaguro H, Masuda H, Nitta N, Asahara T, Isobe M. Endothelial E-selectin potentiates neovascularization via endothelial progenitor cell-dependent and -independent mechanisms. *Arterioscler Thromb Vasc Biol*. 2007;27(3):512–518. DOI: 10.1161/01.ATV.0000254812.23238.2b.

20. Ivanov AN, Norkin IA, Puchinyan DM, Shirokov VY, Zhdanova OY. Endothelial cell adhesion molecules. *Uspekhi fiziologicheskikh nauk*. 2014;45(4):34–49. (In Russ.)

21. Jutila MA, Watts G, Walcheck B, Kansas GS. Characterization of a functionally important and evolutionarily well-conserved epitope mapped to the short consensus repeats of E-selectin and L-selectin. *J Exp Med*. 1992;175(6):1565–1573. DOI: 10.1084/jem.175.6.1565.

22. Khodabandehlou K, Masehi-Lano J, Poon C, Wang J, Chung EJ. Targeting cell adhesion molecules with nanoparticles using in vivo and flow-based *in vitro* models of atherosclerosis. *Exp Biol Med (Maywood)*. 2017;242(8):799–812. DOI: 10.1177/1535370217693116.

23. Henning RJ, Bourgeois M, Harbison RD. Poly (ADP-ribose) polymerase (PARP) and PARP inhibitors: Mechanisms of action and role in cardiovascular disorders. *Cardiovasc Toxicol*. 2018;18(6):493–506. DOI: 10.1007/s12012-018-9462-2.

24. Grilz E, Marosi C, Königsbrügge O, Riedl J, Posch F, Lamm W, Lang IM, Pabinger I, Ay C. Association of complete blood count parameters, D-dimer, and soluble P-selectin with risk of arterial thromboembolism in patients with cancer. *J Thromb Haemost*. 2019;17(8):1335–1344. DOI: 10.1111/jth.14484.

25. Schutzman LM, Rigor RR, Khosravi N, Galante JM, Brown IE. P-selectin is critical for *de novo* pulmonary arterial thrombosis following blunt thoracic trauma. *J Trauma Acute Care Surg*. 2019;86(4):583–591. DOI: 10.1097/TA.0000000000002166.

26. Van der Laan AM, Hirsch A, Robbers LF, Nijveldt R, Lommerse I, Delewi RA, van der Vleuten P, Biemond BJ, Zwaginga JJ, van der Giessen WJ, Zijlstra F, van Rossum AC, Voermans C, van der Schoot CE, Piek JJ. A proinflammatory monocyte response is associated with myocardial injury and impaired functional outcome in patients with *ST*-segment elevation myocardial infarction: Monocytes and myocardial infarction. *Am Heart J*. 2012;163:57–65.e2. DOI: 10.1016/j.ahj.2011.09.002.

27. Kalinin RE, Suchkov IA, Klimentova EA, Egorov AA, Povarov VO. Apoptosis in vascular pathology: present and future. *IP Pavlov Russian Medical Biological Herald*. 2020;28(1):79–87. (In Russ.) DOI: 10.23888/PAVLOVJ202028179-87.

28. Weil BR, Neelamegham S. Selectins and immune cells in acute myocardial infarction and post-infarction ventricular remodeling: Pathophysiology and novel treatments. *Front Immunol*. 2019;10:300. DOI: 10.3389/fimmu.2019.00300.

29. Ma Y, Yabluchanskiy A, Lindsey ML. Neutrophil roles in left ventricular remodeling following myocardial infarction. *Fibrogen Tissue Repair*. 2013;6(1):11. DOI: 10.1186/1755-1536-6-11.

30. Timmers L, Pasterkamp G, de Hoog VC, Arslan F, Appelman Y, de Kleijn DPV. The innate immune response in reperfused myocardium. *Cardiovasc Res*. 2012;94(2):276–283. DOI: 10.1093/cvr/cvs018.

31. Heusch G. The coronary circulation as a target of cardioprotection. *Circ Res*. 2016;118(10):1643–1658. DOI: 10.1161/CIRCRESAHA.116.308640.

32. Tardif JC, Tanguay JF, Wright SR, Duchatelle V, Petroni T, Grégoire JC, Ibrahim R, Heinonen TM, Robb S, Bertrand OF, Cournoyer D, Johnson D, Mann J, Guertin MC, L'Allier PL. Effects of the P-selectin antagonist inclacumab on myocardial damage after percutaneous coronary intervention for non-*ST*-segment elevation myocardial infarction: results of the SELECT-ACS trial. Randomized controlled trial. *J Am Coll Cardiol*. 2013;61(20):2048–2055. DOI: 10.1016/j.jacc.2013.03.003.

33. Izzi B, Gianfagna F, Yang Wen-Yi, Cludts K, De Curtis A, Verhamme P, Di Castelnuovo A, Cerletti C, Donati MB, de Gaetano G, Staessen JA, Hoylaerts MF, Iacoviello L, Moli-family Investigators. Variation of PEAR1 DNA methylation influences platelet and leukocyte function. *Clin Epigenetics*. 2019;11(1):151. DOI: 10.1186/s13148-019-0744-8.

34. Lampka M, Grabczewska Z, Krajewska M, Piskorska E, Hołyńska-Iwan I, Kubica J. Soluble selectins in myocardial infarction. *Pol Merkur Lekarski*. 2013;34(202):188–191.

35. Zhang X, Liu S, Weng X. Brg1 deficiency in vascular endothelial cells blocks neutrophil recruitment and ameliorates cardiac ischemia-reperfusion injury in mice. *Int J Cardiol*. 2018;15(269):250–258. DOI: 10.1016/j.ijcard.2018.07.105.

36. McEver RP. Selectins: initiators of leucocyte adhesion and signalling at the vascular wall. *Cardiovasc Res*. 2015;107(3):331–339. DOI: 10.1093/cvr/cvv154.

37. Pircher J, Engelmann B, Massberg S, Schulz C. Platelet-neutrophil crosstalk in atherothrombosis. *Thromb Haemost*. 2019;119(8):1274–1282. DOI: 10.1055/s-0039-1692983.

38. Poredoš P, Ježovnik MK. Markers of preclinical atherosclerosis and their clinical relevance. *Vasa*. 2015;44(4):247–256. DOI: 10.1024/0301-1526/a000439.

39. Colijn S, Muthukumar V, Xie J, Gao S, Griffi CT. Cell-specific and athero-protective roles for RIPK3 in a murine model of atherosclerosis. *Dis Model Mech*. 2020;13(1):dmm041962. DOI: 10.1242/dmm.041962.

40. Ye Zi, Zhong L, Zhu S, Wang Y. The P-selectin and PSGL-1 axis accelerates atherosclerosis via activation of dendritic cells by the TLR4 signaling pathway. *Cell Death Dis*. 2019;10(7):507. DOI: 10.1038/s41419-019-1736-5.

41. Collins RG, Velji R, Guevara NV, Hicks MJ, Chan L, Beaudet AL. P-selectin or intercellular adhesion molecule (ICAM)-1 deficiency substantially protects against atherosclerosis in apolipoprotein E-deficient mice. *J Exp Med*. 2000;191(1):189–194. DOI: 10.1084/jem.191.1.189.

42. Woollard KJ, Chin-Dusting J. Therapeutic targeting of P-selectin in atherosclerosis. *Inflamm Allergy Drug Targets*. 2007;6(1):69–74. DOI: 10.2174/187152807780077345.

43. Shanaev IN. Modern theories of pathogenesis of trophic ulcer of venous etiology. *Nauka molodykh (Eruditio Juvenium)*. 2019;7(4):600–611. (In Russ.) DOI: 10.23888/HMJ201974600-611.

44. Moñux G, Serna-Soto M, Plá-Sanchez F, Zamorano-León JJ, Segura A, Rial R, Freixer G, Zekri-Nechar K, Hugo-Martínez C, Serrano J, López-Farré A. Compression stockings attenuate the expression of proteins associated with vascular damage in human varicose veins. *Vasc Surg Venous Lymphat Disord*. 2021;9(2):428–434. DOI: 10.1016/j.jvsv.2020.05.020.

45. Mikuła-Pietrasik J, Uruski P, Aniukiewicz K, Sosińska P, Krasiński Z, Tykarski A, Książek K. Serum from varicose patients induces senescence-related dysfunction of vascular endothelium generating local and systemic proinflammatory conditions. *Oxid Med Cell Longev*. 2016;2016:2069290. DOI: 10.1155/2016/2069290.

46. Goshchynsky V, Migenko B, Riabokon S. Pathophysiological and pathomorphological aspects of relapse of

varicose veins after endovascular laser vein coagulation. *Wiad Lek.* 2020;73(11):2468–2475. DOI: 10.36740/WLek 202011124.

47. Yagoda AV, Gladkikh NN, Gladkikh LN. The specifics of adhesion function of endothelium in various clinical variants of primary mitral valve prolapse. *Kardiovaskulyarnaya terapiya i profilaktika.* 2016;15(1):45–50. (In Russ.) DOI: 10.15829/1728-8800-2016-1-45-50.

48. Perkins LA, Anderson CJ, Novelli EM. Targeting P-selectin adhesion molecule in molecular imaging: P-selectin expression as valuable imaging biomarker of inflammation in cardiovascular disease. *J Nucl Med*. 2019;60(12):1691–1697. DOI: 10.2967/jnumed.118.225169.

49. Li B, Juenet M, Aid-Launais R, Maire M, Ollivier V, Letourneur D, Chauvierre C. Development of polymer microcapsules functionalized with fucoidan to target P-selectin overexpressed in cardiovascular diseases. *Adv Healthc Mater.* 2017;6(4):1601200. DOI: 10.1002/adhm.201601200.

50. Silva M, Videira PA, Sackstein R. E-selectin ligands in the human mononuclear phagocyte system: Implications for infection, inflammation, and immunotherapy. *Front Immunol*. 2018;8:1878. DOI: 10.3389/fimmu.2017.01878.

Author details

Roman E. Kalinin, M.D., D. Sci., Prof., Head, Depart. of cardiovascular, endovascular, operative surgery and topographic anatomy, Ryazan State Medical University; kalinin-re@yandex.ru; ORCID: http://orcid.org/0000-0002-0817-9573

Natalya V. Korotkova, M.D., Cand. Sci., Assoc. Prof., Depart. of biological chemistry with course of clinical laboratory diagnostics, Continuing Professional Education Faculty, Senior Researcher, Central Research Laboratory, Ryazan State Medical University, Ryazan; fnv8@yandex.ru; ORCID: http://orcid.org/0000-0001-7974-2450

Igor A. Suchkov, M.D., D. Sci., Prof., Depart. of cardiovascular, endovascular, operative surgery and topographic anatomy, Ryazan State Medical University; i.suchkov@rzgmu.ru; ORCID: http://orcid.org/0000-0002-1292-5452

Nina D. Mzhavanadze, M.D., Cand. Sci., Assoc. Prof., Depart. of cardiovascular, endovascular, operative surgery and topographic anatomy, senior researcher at the central research laboratory, Ryazan State Medical University; nina_mzhavanadze@mail.ru; ORCID: http://orcid.org/0000-0001-5437-1112

Alexander N. Ryabkov, M.D., Cand. Sci., Assoc. Prof., Depart. of Pharmacology with Course of Pharmacy, Continuing Professional Education Faculty, Ryazan State Medical University; ryabkov.an@tfoms-rzn.ru; ORCID: http://orcid.org/0000-0003-4705-747X