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СРАВНИТЕЛЬНАЯ ОЦЕНКА РОЛИ ЛИПИДНОГО ОБМЕНА И СИСТЕМНОГО ВОСПАЛЕНИЯ В РАЗВИТИИ АТЕРОСКЛЕРОЗА НА ЖИВОТНЫХ МОДЕЛЯХ

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Системное воспаление вносит весомый вклад в патогенез атеросклероза и является предметом многочисленных исследований. Работы, направленные на анализ механизмов развития атеросклероза, нередко включают эксперименты на животных. Характеристика, обоснование и выбор адекватной модели является первоочередной задачей каждого подобного исследования.

Цель. Оценка особенностей липидного обмена и системного воспаления при хронической обструктивной болезни легких (ХОБЛ) в развитии атеросклероза на моделях животных.

Материалы и методы. Проведен анализ перекрестных связей видоспецифических особенностей липидного обмена и иммунного ответа и биоинформационный анализ различий Toll-подобного рецептора 4 (TLR4) у мышей, крыс и кроликов в сравнении с человеком. Поиск и анализ аминокислотных последовательностей рецептора TLR4 человека, мыши, крысы и кролика выполнен в международной базе данных GenBank Национального Центра Биотехнологической Информации (NCBI) и базе The Universal Protein Resource (UniProt). Множественное выравнивание аминокислотных последовательностей рецептора проведено в программе Clustal Omega, версия 1.2.4. Реконструкция и визуализация молекулярных филогенетических деревьев выполнены с помощью программы MEGA7 по методу ближайших соседей (англ.: Neighbor-Joining) и методу максимальной экономии (англ.: Maximum Parsimony).

Результаты. Показаны видоспецифические различия особенностей липидного обмена и врожденного иммунного ответа у человека, мышей и кроликов, которые необходимо учитывать при анализе результатов исследований.

Заключение. Участвующие в патогенезе атеросклероза при ХОБЛ нарушения липидного обмена и системное воспаление, опосредованное врожденной иммунной системой, имеют видоспецифические особенности, которые необходимо учитывать при анализе результатов исследований.

Ключевые слова: *атеросклероз; системное воспаление; ХОБЛ; липопротеины; врожденная иммунная система.*

ROLE OF LIPID METABOLISM AND SYSTEMIC INFLAMMATION IN THE DEVELOPMENT OF ATHEROSCLEROSIS IN ANIMAL MODELS

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Systemic inflammation makes a significant contribution to the pathogenesis of atherosclerosis and has been the subject of numerous studies. Works aiming to analyze the mechanisms of

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atherosclerosis development often include experiments on animals. A primary task of such research is the characterization, justification, and selection of an adequate model.

Aim. To evaluate the peculiarities of lipid metabolism and systemic inflammation in chronic obstructive pulmonary disease (COPD) in the development of atherosclerosis in animal models.

Materials and Methods. Analyses of cross-links between species-specific peculiarities of lipid metabolism and the immune response, as well as a bioinformatic analysis of differences in Toll-like receptor 4 (TLR4) in mice, rats, and rabbits in comparison with its human homolog, were carried out. A search for and analysis of the amino acid sequences of human, mouse, rat, and rabbit TLR4 was performed in the International database GenBank of National Center of Biotechnical Information and in The Universal Protein Resource (UniProt) database. Multiple alignments of the TLR4 amino acid sequences were implemented in the Clustal Omega program, version 1.2.4. Reconstruction and visualization of molecular phylogenetic trees were performed using the MEGA7 program according to the Neighbor-Joining and Maximum Parsimony methods.

Results. Species-specific differences of the peculiarities of lipid metabolism and the innate immune response in humans, mice, and rabbits were shown that must be taken into account in analyses of study results.

Conclusion. Disorders in lipid metabolism and systemic inflammation mediated by the innate immune system participating in the pathogenesis of atherosclerosis in COPD possess species-specific differences that should be taken into account in analyses of study results.

Keywords: *atherosclerosis; systemic inflammation; COPD; lipoproteins; innate immune system.*

Atherosclerosis (AS) is a global problem of modern humanity and is associated with reduction of the duration and quality of life, as well as an economic and social burden [1]. Therefore, investigation of the mechanisms of development of AS remains an important task at present. In the uneasy history of the study of AS, several paradigms have been formed that determine the modern concepts of this pathological process.

A key role in AS development has been assigned to disorders of lipid metabolism, and much clinical effort is spent on correcting such disorders. Moreover, the results of numerous studies evidence an important role of disorders of immune status in the pathogenesis of AS. Indeed, macrophages, being a part of the immune system, make a significant contribution to the development and progression of the disease, in which the obligatory factor is the accumulation of 'foam' cells in the arterial intima.

The causes of initiation of this process are the subject of numerous discussions and include the role of comorbid diseases, for example, chronic obstructive pulmonary disease (COPD); therefore, of interest are works dedicated to the analysis of systemic inflammation in COPD and its participation in the pathogenesis of AS.

Investigations of the role of systemic inflammation and of the innate immune system in the pathogenesis of AS require the selection of adequate models.

In recent years, a better understanding of the connections of disorders in lipid metabolism and innate immunity with the development and progression of AS has been achieved, and today the main role in the pathogenesis of AS is assigned to the immune system. Moreover, it is considered a connecting link between the comorbid course of COPD and AS.

It is believed that, for detection of the standard molecular structures (patterns) specific to large groups of pathogens, including viruses, bacteria, fungi, parasites, and protozoa, the innate immune system relies on a large

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family of pattern-recognition receptors that include Toll-like receptors (TLR) of macrophages. They present a family of type 1 transmembrane receptors and play an important role in the initiation of inflammation in AS and COPD. According to the modern concept, TLR4, a representative of a large group of Toll-like receptors, is responsible for the recognition of gram-negative bacteria (in particular, lipopolysaccharides (LPS) in their cell walls) and is the mechanism providing specificity for the innate immune system. Furthermore, TLR4 may be stimulated by components of tobacco smoke and saturated fatty acids, which emphasizes their important role in the pathogenesis of the considered diseases.

Taking into account the significant role of the innate immune system in the pathogenesis of AS and COPD, it is impossible not to mention species-specific differences formed due to various pathogens faced by people and model animals.

The *aim of the work* was to assess the role of peculiarities of lipid metabolism and of systemic inflammation in COPD in the development of atherosclerosis in animal models.

Materials and Methods

To achieve the stated aim, analyses of cross-links of species-specific peculiarities of lipid metabolism and the immune response, as well as bioinformatic analysis of differences in TLR4 in mice, rats, and rabbits in comparison with its human homolog, were carried out. A search for and analysis of amino acid sequences of the human, mouse, rat, and rabbit TLR4 receptor were performed in the GenBank international database of the National Center for Biotechnological Information and The Universal Protein Resource (UniProt).

Multiple alignments of amino acid sequences of the receptor were performed with Clustal Omega software, version 1.2.4. It is a series of popular computer programs used in bioinformatics for multiple sequence alignment. Clustal Omega is one of the most modern versions of the program that allows the alignment of multiple sequences with sufficient efficiency.

Reconstruction and visualization of molecular phylogenetic trees were performed in the MEGA7 program using the Neighbor-Joining and Maximum Parsimony methods. MEGA7 is molecular evolutionary genetic analysis software program that contains many sophisticated methods and tools for phylogenomics and phylomedicine.

Statistical support for each tree node was provided by 1000 repetitions of bootstrap analysis. To calculate evolutionary distances, the Poisson correction method was used.

Results and Discussion

The calculation results showed that the highest amino acid sequence similarity of TLR4 with that of humans was seen in the rabbit (Figure 1). These results indicate that the amino acid sequence of the human TLR4 receptor shares 67%, 68%, and 73% identity with that of rats, mice, and rabbits, respectively, which may underlie the species-specific characteristics of the immune response. The findings are supported by the data showing some similarities as well as profound differences between the responses of humans and mice to TLR activation [2,3]. The mouse and human TLR4 receptors share 62% amino acid sequence similarity in the extracellular domain, 70% in the transmembrane domain, and 83% in the cytoplasmic domain, whereas the murine and human MD-2 proteins share approximately 57% overall amino acid sequence similarity [3-6]. The extracellular domain of rat and human TLR4 shares 61% amino acid sequence similarity [3,6]. These differences between TLR4 and MD-2 may underlie the species-specific recognition of ligands.

In comparison with mice and rats, rabbit TLR4 is more similar to its human analog, demonstrating approximately 70% amino acid sequence similarity; with this, in the extracellular domain of TLR4, the distal

region demonstrates the highest general similarity (77%, Figure 1) [4,5,7]. Since the similarity of amino acids characteristic of the extracellular domain of humans is higher in rabbits than in mice, rabbit TLR4 may better recognize human pathogens its mouse homolog [3,6]. This factor, along with the higher general similarity between TLR4 in rabbits and humans, makes it possible to suggest that the *immune response of humans to certain pathogens may be better modeled in rabbits than in mice due to a higher phylogenetic closeness to TLR4.* These suggestions are confirmed by reconstruction of the evolutionary history of TLR4 (Figure 2).

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CLUSTAL O(1.2.4) multiple sequence alignment

TLR4_HUMAN   MMSASRLAGTLIPAMAFLSCVRPESWEPCVEVVPNITYQCMELNFYKIPDNLPFSTKNLD 60
TLR4_MOUSE   MMPPWLLARTLIMA-LFFSCLTPGSLNPCIEVVPNITYQCMDQKLSKVPDDIPSSTKNID 59
TLR4_RAT     MMPLLHLAGTLIMA-LFLSCLRPGSLNPCIEVLPNITYQCMDQNLSKIPHDIPYSTKNLD 59
G1SH24_RABIT MMPRLRLAGTLVPAMAFLSYLRPEIWEPCVEVVPNITYQCMEKNLYKIPDNIPFSTKNLD 60
              **    ** **: *  *:* : *   :**:**:********: :: *:*.::* ****:*

TLR4_HUMAN   LSFNPLRHLGSYSFFSFPELQVLDLSRCEIQTIEDGAYQSLSHLSTLILTGNPIQSLALG 120
TLR4_MOUSE   LSFNPLKILKSYSFSNFSELQWLDLSRCEIETIEDKAWHGLHHLSNLILTGNPIQSFSPG 119
TLR4_RAT     LSFNPLKILRSYSFTNFSQLQWLDLSRCEIETIEDKAWHGLNQLSTLVLTGNPIKSFSPG 119
G1SH24_RABIT LSFNLLEHLGSHSFLHVSELHFLDLSRCKIHTIEDDAYQGLKNLSTLILTGNPIQSLSPQ 120
              **** *. * *:**  . :*: ******:*.**** *::.* :**.*:******:*::

TLR4_HUMAN   AFSGLSSLQKLVAVETNLASLENFPIGHLKTLKELNVAHNLIQSFKLPEYFSNLTNLEHL 180
TLR4_MOUSE   SFSGLTSLENLVAVETKLASLESFPIGQLITLKKLNVAHNFIHSCKLPAYFSNLTNLVHV 179
TLR4_RAT     SFSGLTNLENLVAVETKMTSLEGFHIGQLISLKKLNVAHNLIHSFKLPEYFSNLTNLEHV 179
G1SH24_RABIT AFSGLSNLQKLVAVETHLTSLGDFPIGHLKTLKELNVAHNLIHSFSIPDYFSNLSSLEHL 180
              :****:.*::******:::** .* **:* :**:******:*:* .:* *****:.* *:

TLR4_HUMAN   DLSSNKIQSIYCTDLRVLHQMPLLNLSLDLSLNPMNFIQPGAFKEIRLHKLTLRNNFDSL 240
TLR4_MOUSE   DLSYNYIQTITVNDLQFLRENPQVNLSLDMSLNPIDFIQDQAFQGIKLHELTLRGNFNSS 239
TLR4_RAT     DLSYNYIQTISVKDLQFLRENPQVNLSLDLSLNPIDSIQAQAFQGIRLHELTLRSNFNSS 239
G1SH24_RABIT DLSNNKIQSIYHKDLRVLHQMPLGTLSLDLSLNPIDFIQPGAFEAIRLHELILKSNFKST 240
              *** * **:*  .**:.*:: *  .****:****:: **  **: *:**:* *:.**.*

TLR4_HUMAN   NVMKTCIQGLAGLEVHRLVLGEFRNEGNLEKFDKSALEGLCNLTIEEFRLAYLDYYLDDI 300
TLR4_MOUSE   NIMKTCLQNLAGLHVHRLILGEFKDERNLEIFEPSIMEGLCDVTIDEFRLTYTNDFSDDI 299
TLR4_RAT     NVLKMCLQNMTGLHVHRLILGEFKNERNLESFDRSVMEGLCNVSIDEFRLTYINHFSDDI 299
G1SH24_RABIT NIMKICIQGLSGLEVHRLVLGEFKNERNMKNFDKSALEGLCNLAIEEFRLAYIDDLEGNI 300
              *::* *:*.::**.****:****::* *:: *: * :****:::*:****:* :   .:*

TLR4_HUMAN   IDLFNCLTNVSSFSLVSVTIERVKDFSYNFGWQHLELVNCKFGQF-PTLKLKSLKRLTFT 359
TLR4_MOUSE   VK-FHCLANVSAMSLAGVSIKYLEDVPKHFKWQSLSIIRCQLKQF-PTLDLPFLKSLTLT 357
TLR4_RAT     YN-LNCLANISAMSFTGVHIKHIADVPRHFKWQSLSIIRCHLKPF-PKLSLPFLKSWTLT 357
G1SH24_RABIT TDLFDCLENVSVMALVHMYIDNQEIFPKDFSWKSLEFINCEFSENIFFLKLSSLRRLIFT 360
               . :.** *:* :::. : *.    .  .* *: *.::.*.:      *.*  *:   :*

TLR4_HUMAN   SNKGGNAFSEVDLPSLEFLDLSRNGLSFKGCCSQSDFGTTSLKYLDLSFNGVITMSSNFL 419
TLR4_MOUSE   MNKGSISFKKVALPSLSYLDLSRNALSFSGCCSYSDLGTNSLRHLDLSFNGAIIMSANFM 417
TLR4_RAT     TNREDISFGQLALPSLRYLDLSRNAMSFRGCCSYSDFGTNNLKYLDLSFNGVILMSANFM 417
G1SH24_RABIT ANKGVRTFPELNTPSLEFLDISNNGLSLQSCCSVNSLRLTQLKHLNLSFNGVITMTSNFV 420
               *:   :* ::  *** :**:*.*.:*: .*** ..:  ..*::*:*****.* *::**:

TLR4_HUMAN   GLEQLEHLDFQHSNLKQMSEFSVFLSLRNLIYLDISHTHTRVAFNGIFNGLSSLEVLKMA 479
TLR4_MOUSE   GLEELQHLDFQHSTLKRVTEFSAFLSLEKLLYLDISYTNTKIDFDGIFLGLTSLNTLKMA 477
TLR4_RAT     GLEELEYLDFQHSTLKKVTEFSVFLSLEKLLYLDISYTNTKIDFDGIFLGLISLNTLKMA 477
G1SH24_RABIT GLEQLEHLYFQHSNLRNINEFSIFLSLNNLLYLDISYTHIRVAFRGIFDGLYSLRVLKMA 480
              ***:*::* ****.*:.:.*** ****.:*:*****:*: :: * *** ** **..****
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TLR4_HUMAN   GNSFQENFLPDIFTELRNLTFLDLSQCQLEQLSPTAFNSLSSLQVLNMSHNNFFSLDTFP 539
TLR4_MOUSE   GNSFKDNTLSNVFANTTNLTFLDLSKCQLEQISWGVFDTLHRLQLLNMSHNNLLFLDSSH 537
TLR4_RAT     GNSFKDNTLSNVFTNTTNLTFLDLSKCQLEQISRGVFDTLYRLQLLNMSHNNLLFLDPSH 537
G1SH24_RABIT GNAFQDNRLLNIFTEMTSLTTLDLSSCQLEQVYQGAFESLPRLESLNMSHNNLLVLDTLT 540
              **:*::* * ::*::  .** ****.*****:   .*::*  *: *******:: **

TLR4_HUMAN   YKCLNSLQVLDYSLNHIMTSKKQELQHFPSSLAFLNLTQNDFACTCEHQSFLQWIKDQRQ 599
TLR4_MOUSE   YNQLYSLSTLDCSFNRIETSK-GILQHFPKSLAFFNLTNNSVACICEHQKFLQWVKEQKQ 596
TLR4_RAT     YKQLYSLRTLDCSFNRIETSK-GILQHFPKSLAVFNLTNNSVACICEYQNFLQWVKDQKM 596
G1SH24_RABIT YKCLYSLQVLDLSFNHIGNITEPGQQHFPSNLTLLHLTKNAFVCDCEHQIFMQWIKDQRR 600
              *: * ** .** *:*:* . .    ****..*:.::**:* ..* **:* *:**:*:*:

TLR4_HUMAN   LLVEVERMECATPSDKQGMPVLS-LNITCQMNKTIIGVSVLSVLVVSVVAVLVYKFYFHL 658
TLR4_MOUSE   FLVNVEQMTCATPVEMNTSLVLDFNNSTCYMYKTIISVSVVSVIVVSTVAFLIYHFYFHL 656
TLR4_RAT     FLVNVEQMKCASPIDMKASLVLDFTNSTCYIYKTIISVSVVSVLVVATVAFLIYHFYFHL 656
G1SH24_RABIT LLVEVEQMVCITPPN---MPVLSFTNATCQISKTIISVSVFSVLVVSFAVVLVYKFYFPL 657
              :**:**:* * :* :     **.  * ** : ****.***.**:**: ...*:*:*** *

TLR4_HUMAN   MLLAGCIKYGRGENIYDAFVIYSSQDEDWVRNELVKNLEEGVPPFQLCLHYRDFIPGVAI 718
TLR4_MOUSE   ILIAGCKKYSRGESIYDAFVIYSSQNEDWVRNELVKNLEEGVPRFHLCLHYRDFIPGVAI 716
TLR4_RAT     ILIAGCKKYSRGESIYDAFVIYSSQNEDWVRNELVKNLEEGVPRFQLCLHYRDFIPGVAI 716
G1SH24_RABIT MLLVGRRKYGRGESVYDAFVIYSSQDEDWVRNELVKNLEEGVPPFRLCLHYRDFIPGVAI 717
              :*:.*  **.***.:**********:***************** *:**************

TLR4_HUMAN   AANIIHEGFHKSRKVIVVVSQHFIQSRWCIFEYEIAQTWQFLSSRAGIIFIVLQKVEKTL 778
TLR4_MOUSE   AANIIQEGFHKSRKVIVVVSRHFIQSRWCIFEYEIAQTWQFLSSRSGIIFIVLEKVEKSL 776
TLR4_RAT     AANIIQEGFHKSRKVIVVVSRHFIQSRWCIFEYEIAQTWQFLSSRSGIIFIVLEKVEKSL 776
G1SH24_RABIT AANIIQEGFHKSRKVIVVVSQHFIQSRWCIFEYEIAQTWQFLSSHAGIIFIVLQKVEKSL 777
              *****:**************:************************::*******:****:*

TLR4_HUMAN   LRQQVELYRLLSRNTYLEWEDSVLGRHIFWRRLRKALLDGKSWNPEGTVGTGCNWQEATS 838
TLR4_MOUSE   LRQQVELYRLLSRNTYLEWEDNPLGRHIFWRRLKNALLDGKASNPEQTAEEEQETAT--- 833
TLR4_RAT     LRQQVELYRLLSRNTYLEWEDNALGRHIFWRRLKKALLDGKALNPDETSEEEQEATT--- 833
G1SH24_RABIT LRQRVELYRLLSRNTYLEWEDTVLGRHIFWRRLRKALLDGKTLSPEGMARAENNQQEAMT 837
              ***:*****************. **********::******: .*:       :

TLR4_HUMAN   I- 839
TLR4_MOUSE   WT 835
TLR4_RAT     LT 835
G1SH24_RABIT LI 839
```

Organism	Max Score	Query Cover	E value	Ident%
Rabbit	1211	100%	0.0	72.89%
Mouse	1087	98%	0.0	67.60%
Rat	1094	100%	0.0	66.55%

Notes: «*» – identical amino acid residues; «:» – amino acids with a very high similarity in physical and chemical properties (conservative replacements); «.» – amino acids simply similar in physical and chemical properties (semi-conservative replacements); « » (blank) – absence of similarity; «-» – inserts automatically added by the program for optimal alignment; Max Score – maximal weight; Query Cover – shows the percentage of the length of the initial sequence that aligned with the finding; E value – reflects the extent of occasionality of the obtained alignment; Ident – percentage of coinciding amino acid residues.

Fig. 1. Alignment of amino acid sequences of human, mouse, rat, and rabbit TLR4 (TIR domain-containing protein). Implemented in the CLUSTAL O program, version 1.2.4. The table of identity of amino acid sequences was constructed using the BLAST® tool (Basic Local Alignment Search Tool)

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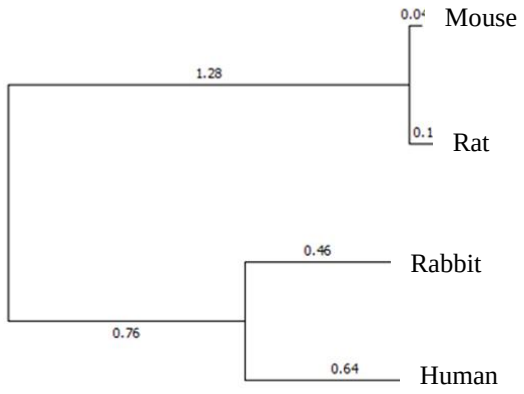

Notes: The tree is constructed to scale, with branch lengths in the same units as the evolutionary distances used for determination of the phylogenetic tree. Evolutionary distances were calculated using the Poisson correction method and were expressed in units of the quantity of amino acid replacements per site. All positions containing blanks and missed data were excluded. Evolutionary analysis was performed in MEGA7

Fig. 2. Phylogenetic tree of TLR4 of humans, mice, rats, and rabbits (protein-containing TIR-domain) constructed using the Neighbor-Joining method

Thus, the cytoplasmic domain of *TLR4 is much more conservative than the extracellular domain,* which is probably because its function is the transduction of a signal to molecules with conservative structures, while the extracellular domain is adapted to the reception of structures determined by the differing ecological niches of humans and rodents [6]. For example, humans and rabbits show an intense reaction to low concentrations of LPS; whereas, the majority of rodents are relatively more LPS-resistant [5]. These differences should be taken into account, since it is known that components of tobacco smoke are capable of activating the TLR4 receptor and its downstream signal pathways.

In 2009, Vasl et al. reported additional functional differences between the human and murine MD-2 components of the CD14/TLR4/MD2 receptor complex that recognizes LPS. Differences include the ability of human, but not murine, MD-2 to be secreted and function as an extracellular endotoxin-binding protein with or without TLR4 [3,8].

Schroder, et al. described differences in the regulation of genes of human and murine microphages after stimulation by LPS [2,3]. Although target genes of TLR4 are more rapidly induced in human than in murine macrophages following the action of LPS, several regulators of negative feedback of the TLR4 pathway are faster and induced to a greater extent in murine macrophages. This enhanced regulation of negative feedback may additionally diminish the primary response to LPS in murine macrophages, thus contributing to lower sensitivity to endotoxin in mice in comparison with that in humans. This phenomenon, called *tolerance to LPS*, is mainly associated with a loss of surface expression of TLR4. The preliminary processing of LPS of murine macrophages suppresses production of inflammatory cytokines depending on the time and dose and considerably reduces the activity of NF-κB [3]. Thus, LPS increase the expression of TLR4 in human macrophages and monocytes; whereas, in peritoneal macrophages and neutrophils of the mouse, the expression of TLR4 decreases after exposure to LPS and remains unchanged in murine monocytes [3].

In addition to the abovementioned dif-

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ferences, the existing typical animal models used in AS studies pose several disadvantages associated with significant differences in lipid metabolism between animals and humans and between different animal models, as well as the connections between lipid metabolism and the innate immune system. For example, mice are highly resistant to AS due to the species-specific peculiarities of lipoprotein metabolism. In humans, the most common subtype of apolipoprotein B (ApoB) is ApoB-100, which is synthesized only in the liver and is the main component of the apolipoprotein in very low-density lipoproteins (VLDLP), intermediate-density lipoproteins (IDLP), and low-density lipoproteins (LDLP). The isoform ApoB-48 is synthesized in the intestine and is located in chylomicrons, providing transfer of lipids from the intestine to muscle, fat, and other tissues. However, some rodents, such as rats and mice, can also synthesize ApoB-48 in the liver. Therefore, in mice, most (about 70%) of the LDLP produced in the liver transfers ApoB-48 in contrast to the ApoB-100 form transferred by liver-produced LDLP in humans. ApoB-48, the main component of intestinal chylomicrons, is characterized by accelerated metabolism in plasma, compared with the ApoB-100 protein. This leads to faster clearance of atherogenic ApoB-containing lipoproteins by the liver.

Another feature of lipid metabolism is that the blood plasma of rodents (mice and rats), in contrast to that of humans and also to that of primates, rabbits, and hamsters, does not contain cholesteryl ester transfer protein (CETP), which transfers cholesteryl esters from HDLP to ApoB-containing LDLP and VLDLP [9,10]. Thus, wildtype mice have a low natural level of LDLP and a high level of HDLP, in which up to 90% of cholesterol is transferred, and have low susceptibility to the development of AS [11,12]. Transgenic mice expressing human CETP have enhanced reverse cholesterol transport, probably due to enhanced LDLP receptor-dependent clearance of ApoB lipoproteins in the liver [13]. They also demonstrate enhanced postprandial triglyceridemia, enhanced absorption of LPS by the liver, and increased survival in endotoxemia [13].

Thus, participation in lipid homeostasis is not the only function of CETP. Recent findings have improved our understanding of the links between CETP and the inflammatory response. Experimental data strongly suggest that CETP in macrophages, as well as in the liver, prevent the interaction of LPS with TLR4, thereby reducing the inflammatory response [14]. It also plays a useful role in reducing the inflammatory response to bacterial endotoxins by removing LPS. The anti-inflammatory function of CETP is realized by its membership in the family of proteins that includes lipopolysaccharide-binding protein (LBP) and bactericidal protein increasing permeability (BPI) [14-17]. CETP shares structural homology with LBP, which participates in the innate immune response by binding to LPS and causing an inflammatory response mediated by the TLR4 receptor and ultimately leads to activation of the transcription factor NF-kB [17,18]. Thus, owing to CETP, LPS binds with circulating HDLP, LDLP, and VLDLP, which makes it inaccessible for stimulation of the innate immune system [12,19-21]. Although CETP has a weak ability to bind LPS compared with LBP or BPI, it is associated with resistance to sepsis [12,22]. Human CETP transgenic mice have lower mortality after introduction of LPS, compared with wildtype mice [12,14].

There are several lines of evidence confirming that LPS is cleared from the circulation mainly by the liver, although the exact mechanisms remain undefined. The mechanism of LPS elimination includes the involvement of CETP, which facilitates transfer of LPS from HDLP to LDLP [12], and LDLP receptor-mediated absorption of LPS-associated lipoproteins by the liver [12,17,23]. Absorption of HDLP by the SR-B1 receptor of hepatic cells also participates in LPS clearance [12]. Kupffer cells absorb

the majority of free LPS and also inactivate LPS through deacylation by acyloxyacyl hydrolase [17,24].

CETP decreases both in hamsters and in mice transgenic for human CETP in response to LPS [12]. This agrees with the results of a small study conducted on humans, which reported the connection of increased mortality with the level of reduction of CETP in patients hospitalized with sepsis [12,14]. CETP deficit is a genetic disease that leads to an extremely high level of HDLP cholesterol. However, this does not lead to the expected prolongation of the life span. Thus, the CETP inhibitor dalcetrapib increases the levels of HDLP but does not reduce the risk of repeated cardiovascular events in patients with recent acute coronary syndrome [25], and torcetrapib increases infectious and oncological morbidity [17,26].

Furthermore, rodents also have other peculiarities of lipoprotein metabolism: a high level of circulating lipases and of a specific protein – phospholipid transporter *(specific phospholipid transfer protein*, PLTP), which also explains their resistance to AS. Knockout mice for PLTP exhibit increased mortality associated with endotoxins, delayed absorption of LPS by lipoproteins, and reduced LPS clearance [12,27].

Thus, *wildtype mice and rats are mammals with a predominantly high level of HDLP; whereas, both humans and rabbits are mammals with a high level of LDLP*. Nevertheless, certain differences also exist between rabbits and humans in terms of lipoprotein metabolism.

Rabbits are known to have approximately twice as much CETP activity in the plasma as humans [11,12], and they are very sensitive to diet-induced AS [12,28], the risk of which is reduced by inhibition of CETP [12,29]. Given the involvement of CETP in the innate immune response, it is logical to suggest a difference in LPS stimulation between rabbits and humans. Moreover, rabbit plasma does not contain ApoA-II [30,31], an important protein component of HDLP in humans. A similar ApoA-II gene exists in the rabbit genome, but it is still unclear whether it is an actual functional gene or a pseudogene [31].

ApoA-II is the second most widespread protein component of human HDLP and is also widely represented in rodents, but it is either absent or has low expression in rabbits [32-34]. In humans, mice, and rats, ApoA-II is primarily synthesized by the liver and to a considerably lesser extent, by the intestine [34,35]. However, the amino acid sequences of murine and human ApoA-II differ by approximately 40%, and they produce the opposite effect on lipoprotein metabolism when expressed in transgenic mice [34]. Some studies suggest that the increase in the level of ApoA-II may be proatherogenic due to reduction of reverse cholesterol transport and reduction of protection against oxidative modification of LDLP [34,36]. However, experiments with expression of human ApoA-II in rabbits showed a pronounced anti-atherogenic effect, the probable mechanism of which can be attributed to the anti-inflammatory activity of ApoA-II [37]. These data contradict the information that murine ApoA-II HDLP can potentially be pro-inflammatory. The indicated differences may be attributed to differences in the structure of murine and human ApoA-II [37]. The role of ApoA-II in atherogenesis can also be demonstrated by the fact that HDLP stimulates endothelial nitric oxide synthase (eNOS) in cultured endothelial cells. Here activation of eNOS induced by HDLP can only be inhibited by antibodies against ApoA-I but not by those against ApoA-II. In this context, it can be suggested that, unlike ApoA-I, ApoA-II does not participate in activation of eNOS [34].

Is should be also noted that the activity of rabbit liver lipase is approximately 10 times below that of rat liver [31,38]. These differences are supposed to be responsible for the high susceptibility to rapid development

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of AS in rabbits kept on a high-cholesterol diet.

Besides the described differences, a specific lipoprotein is present in human plasma, similar to LDLP, termed lipoprotein (a) (Lp (a)) that is produced via disulfate bonding between ApoB-100 and Apo (a). Although Lp (a) is not usually present in the plasma of rabbits and mice, studies of transgenic mice showed that ApoB-100 of rabbits, but not that of mice [31,39], can bind to Apo (a) of humans with the formation of Lp (a) to enhance the development of AS [31,40].

Besides, VLDLP receptors, which participate in the production of foam cells, are highly expressed in macrophages of rabbits and humans but not those of mice [31,41].

It is worth mentioning the differences in the synthesis of nitric oxide (NO) by murine and human macrophages. It is known that NO, produced by inducible NO synthase (iNOS, NOS-2), is an important component of macrophage-mediated immune protection from numerous pathogens. Murine macrophages produce NO under stimulation by the classic iNOS inductors interferon gamma (IFN-γ) and LPS, whereas human macrophages under similar conditions produce low levels of NO or do not produce it altogether. Although activated human macrophages may express iNOS mRNA and protein, *the question of whether they possess a complete mechanism of NO synthesis remains in dispute* [42,43]. Theoretically, the absence of high activity of NO synthesis *in vitro* may not correlate with the data obtained *in vivo* during inflammatory processes; that is, *one should exercise caution when transferring data obtained in rodents* [42,43].

Conclusion

In summary, lipid metabolism and systemic inflammation, mediated by the innate immune system that participate in the pathogenesis of atherosclerosis in COPD possess species-specific peculiarities that should be taken into account in the analysis of study results.

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