===== REVIEW =====

T Lymphocytes as Targets for SARS-CoV-2

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Abstract—Despite numerous data on the absence or weak expression of the main functional receptor of SARS-CoV-2 angiotensin-converting enzyme 2 (ACE2) by T cells, it was recently demonstrated that the new coronavirus can efficiently infect T lymphocytes. Here, we analyze the data on the alternative (ACE2-independent) pathways of cell infection, identified T cell subpopulations that serve as the most plausible targets of SARS-CoV-2, discuss the mechanisms of virus–cell interaction, including both infectious and non-infectious pathways of T lymphocyte regulation, and estimate the role of the virus-dependent damage of T lymphocytes in COVID-19 pathogenesis. Particular attention is paid to regulatory T cells as potential targets of SARS-CoV-2, as well as to the possible involvement of exosomes in the sensitivity of peripheral T cells to the virus.

INTRODUCTION

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), a cause of pandemic of coronavirus disease 2019 (COVID-19), has an affinity for a wide range of cells and tissues, primarily, lung and respiratory epithelium, vascular endothelium, and cells of the intestine, liver, kidneys, and brain [1], which determines the variety of clinical manifestations and post-COVID complications. The affinity of the virus depends on the presence of receptors for various viral surface structures on target cells, above all, for the virus spike protein (S protein). The main receptor for SARS-CoV-2 is angiotensin-converting enzyme 2 (ACE2). ACE2 recognizes viral S protein, while cell serine proteases, acting as co-receptors, ensure virus entry into the cell [2]. The pattern of ACE2 distribution in human tissues generally coincides with the SARS-CoV-2 infection profile [1].

Cells of the immune system, including T lymphocytes, had not been originally considered as potential targets of SARS-CoV-2, based on the lack of ACE2 expression in lymphoid organs (human spleen, thymus, and lymph nodes) [3] and subpopulations of circulating T lymphocytes [4]. However, recent studies have identified alternative SARS-CoV-2 receptors, some of which are presented on the T cell membrane. For example, the transmembrane glycoprotein CD147 [5] is constitutively expressed by intact CD4$^+$/CD8$^+$ T lymphocytes of human peripheral blood. Its expression, as well as expression of receptor tyrosine kinase AXL (another candidate receptor for SARS-CoV-2) is significantly upregulated in response to the cell polyclonal activation [5-7]. Also, expression of the gene encoding Kringle containing transmembrane protein 1 (KREMEN1) was detected in a subpopulation of regulatory T lymphocytes (Tregs) [8, 9]. Although these receptors play an auxiliary role in traditional virus-targeted tissues [7, 8], they can come to the fore in ACE2-deficient cells, for example, in immune cells.

These data have raised the question on T lymphocytes as potential targets of the new coronavirus. To date, there are six independent studies that demonstrated with

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Abbreviations: ACE2, angiotensin-converting enzyme 2; ASGR1, asialoglycoprotein receptor 1; AXL, AXL receptor tyrosine kinase; CD, cluster differentiation; COVID, coronavirus disease; KREMEN1, Kringle containing transmembrane protein 1; MOI, multiplicity of infection; N protein, nucleocapsid protein; RBD, receptor-binding domain; SARS-CoV, severe acute respiratory syndrome coronavirus; S protein, spike protein; TCR, T cell receptor; Treg, regulatory T lymphocyte; TMPRSS2, transmembrane protease serine 2.

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more or less detail the ability of SARS-CoV-2 to infect human T lymphocytes. Here, we analyze the data of these studies and discuss the possible mechanisms of T cell infection and the contribution of these mechanisms to COVID-19 pathogenesis.

SARS-CoV-2 RECEPTORS

The ACE2 molecule, a key component of the renin−angiotensin system, has been identified as the major entry receptor for SARS-CoV-2 [1, 2], as well as for the related 2003 coronavirus SARS-CoV-1 [10]. ACE2 binds to the S protein of SARS-CoV-2 via the C-terminal domain of its S1 subunit, the so-called receptor-binding domain (RBD) [1, 2]. The next step in the ACE2-dependent cell infection by SARS-CoV-2 is proteolytic cleavage of the viral S protein between the S1/S2 subunits and at the S2' site, which leads to the release of fusogen, a factor ensuring the fusion of the viral envelope with the host cell membrane [2]. The fusion can occur in two ways: at the plasma membrane after receptor engagement or in the endosome after the virion uptake. In the latter case, the viral envelope fuses with the endosomal membrane. The S protein is cleaved by host serine proteases, primarily, TMPRSS2 (transmembrane protease serine 2) and furin [2, 11]. Endosomal cysteine proteases cathepsins B and L (CatB/L) also contribute to this process, although only in the case of alternative virus entry, after virion endocytosis [2]. ACE2 is widely represented in human tissues, especially on the surface of alveolar and bronchial epithelial cells, enterocytes, and vascular endothelium [1, 3]. This pattern of receptor distribution coincides with the SARS-CoV-2 infection profile [1], but does not explain the predominant lung and airway damage. Furin is a ubiquitous protease, while TMPRSS2 has a more limited expression, with maximum expression in the pneumocytes, which apparently contributes to the specifics of virus spread and pathology [12, 13].

However, ACE2 is not the only SARS-CoV-2 receptor. Recent studies have identified a number of new candidates for this role. The first and main one is CD147, a transmembrane protein of the immunoglobulin family (also known as basigin or EMMPRIN) involved in *Plasmodium falciparum* invasion [14], as well as in some bacterial and viral infections [15, 16], including 2003 coronavirus SARS-CoV-1 [17]. In 2020, Wang et al. reported direct interaction of CD147 with SARS-CoV-2 S protein and involvement of the former in the cell infection with the virus based on the association of SARS-CoV-2 infectivity with the level of CD147 expression by the target cells [5]. Of note, two 2021 studies have failed to confirm these results [18, 19] as they found no direct interaction between the host cell CD147 and recombinant SARS-CoV-2 S protein [18, 19], as well as no changes in the infectivity of the virus in the cells with knocked

down CD147 gene [18] or functionally blocked CD147 [19]. Nonetheless, the latest work [20] supports the findings of Wang et al. Therefore, the question on the role of CD147 in cell infection with SARS-CoV-2 has not been finally resolved and requires further investigations. It is possible that CD147 participates in the process indirectly. CD147 is ubiquitously present in human tissues; it is expressed by epithelial and neuronal cells, as well as by leukocytes (hence its name CD147, in accordance with the nomenclature of leukocyte differentiation antigens) [4].

Other candidates for the molecules ensuring SARS-CoV-2 entry are receptor tyrosine kinase AXL [7], transmembrane protein KREMEN1, and asialoglycoprotein receptor 1 (ASGR1) [8].

Receptor tyrosine kinase AXL is widely expressed in human tissues, where it regulates many physiological processes, including cell survival, proliferation, and differentiation [21, 22]. It specifically interacts with the N-terminal domain of the S1 subunit of SARS-CoV-2 S protein (but not with the classical RBD [7]) and mediates virus entry to the cell. The blockade of AXL expression significantly reduces SARS-CoV-2 infection of cultured pulmonary cells, while its overexpression promotes viral infection [7]. However, blocking AXL only moderately reduces viral replication in lung cells [7], implying its secondary role among traditional SARS-CoV-2 targets.

Two other virus receptors are transmembrane proteins ASGR1 and KREMEN1. ASGR1 mediates endocytosis and lysosomal degradation of some glycoproteins, playing a critical role in their homeostasis [23], while KREMEN1 is involved in the regulation of WNT signaling [24]. Both proteins serve as the entry receptors for many viruses [25], including the new coronavirus. ASGR1 and KREMEN1 interact directly with the SARS-CoV-2 S protein (both N-terminal domain and RBD), and their binding affinity is comparable to that of ACE2 [8, 26]. Ectopic expression of ASGR1 or KREMEN1 is sufficient to enable SARS-CoV-2 entry [8]. However, the overexpression of these receptors in ACE2-negative cells only partially restores SARS-CoV-2 infectivity, with significantly less efficiency than in ACE2-positive ones [8].

Each of the four alternative receptors (CD147/AXL/KREMEN1/ASGR1) can potentially mediate SARS-CoV-2 entry independently of ACE2, providing additional pathways for the virus infection in different tissues, although their role is secondary to that of traditional ACE2-positive targets of the virus.

In addition to the independent receptors, there is a number of membrane molecules capable of enhancing SARS-CoV-2 infectivity, such as neuropilin-1 [27], sialic acids [28], heparan sulfates [29], and lectin receptors [30].

Neuropilin-1 directly binds to the polybasic motif in the furin-cleaved S1 subunit of the S protein and significantly promotes cell infection. Blocking this interaction using RNA interference or selective inhibitors reduces

SARS-CoV-2 entry [27]. It is important that neuropilin-1 cannot induce cell infection alone, but efficiently does this when coexpressed with ACE2 and TMPRSS2 [27]. Heparan sulfate is another necessary factor that promotes SARS-CoV-2 infection in various target cells [29]. It interacts with the RBD of SARS-CoV-2 S protein at a site that does not overlap with the motif involved in the contact with ACE2. The binding of heparan sulfate initiates S protein transition from the closed conformation into the open one, thereby increasing the accessibility of the RBD for the ACE2 engagement [29]. Some lectin receptors are also involved in the SARS-CoV-2 infection through binding to glycans associated with the S protein [30]. Most of C-type lectins interact with the S protein regions outside the RBD. Although virus capture by the lectin receptors cannot induce direct cell infection with SARS-CoV-2, these receptors promote virus entry into ACE2-positive cells by serving as non-specific attachment molecules for SARS-CoV-2 [30]. In addition, the N-terminal domain of the S1 subunit of SARS-CoV-2 S protein contains sialic acid-binding motifs that mediate virus interaction with various sialoproteins, glycoproteins, or gangliosides on the cell membrane [28]. Hence, although these non-specific molecules are not self-sufficient, they contribute markedly to the SARS-CoV-2 infection of the cell – either by providing better virus attachment to the surface of host cells or by changing the conformation of the S protein, which furnishes additional receptor binding sites or increases RBD accessibility for the ACE2 engagement.

EXPRESSION OF SARS-CoV-2 RECEPTORS BY T LYMPHOCYTES

The presence of the main functional SARS-CoV-2 receptor on T lymphocytes is currently controversial. In 2004, Hamming et al. demonstrated by immunohistochemical analysis the absence of ACE2 expression in the lymphocytes of central and peripheral lymphoid organs, namely, thymus (number of samples studied, $n = 4$), spleen ($n = 4$), and lymph nodes ($n = 6$) [3]. Until recently, most authors referring to this work had doubted the possibility of T cell infection with SARS-CoV-2 [31]. In support of these data, in 2020, Radzikowska et al. [4] showed the lack of ACE2 and TMPRSS2 gene expression in various subpopulations of human peripheral blood T lymphocytes, including naive CD4$^+$/CD8$^+$ T lymphocytes and terminally differentiated effector CD4$^+$/CD8$^+$ T cells – however, again in a small sample ($n = 4$). At the same time, Bertram et al. demonstrated, also by immunohistochemistry, a high stable expression of ACE2 and TMPRSS2 in lymphoid cells in the tissues of respiratory and gastrointestinal tracts, including respiratory sinus, tonsil mucosa, and intestinal villi [32]. Furthermore, in another study, single-nucleus RNA sequencing showed a marked expression of genes encoding TMPRSS2 and, in

trace amounts, ACE2 by T lymphocytes in healthy lung tissue of cancer patients ($n = 12$) [33]. There is no contradiction in the data above. In the first case, the object of study was predominantly T cell precursors or naive T lymphocytes, while in the second case, it seems to be either mucosa-associated lymphoid tissue or activated T lymphocytes infiltrating peripheral tissues. In addition, the size of the studied groups was small, while expression of ACE2 is genetically determined. Hence, the available data indicate the absence of constitutive expression of ACE2 and TMPRSS2 by the main population of T lymphocytes, naive αβT cells, but do not exclude the presence of these molecules in individual T cell subpopulations, as well as their appearance upon stimulation or under pro-inflammatory conditions, especially considering that the ACE2 gene is interferon-stimulated [34] and T lymphocytes actively respond to interferons.

Another mechanism for ACE2 acquisition by T cells is also possible, which is associated with exosomes. Cells that do not express or weakly express SARS-CoV-2 receptor can receive this receptor from other cells through extracellular microvesicles released from the surface of cells under normal conditions or undergoing stimulation. Such microvesicles contain biomolecules, e.g., RNA and proteins, and carry out intercellular communication [35]. It is known that ACE2 is a traditional component of microvesicles that can transfer it in a co-culture from ACE2-overexpressing cells to the recipient cells lacking this protein [36]. Moreover, recent study has shown the presence of ACE2$^+$ microvesicles in the plasma of patients with COVID-19; the content of these microvesicles varied a lot and was generally comparable to that in healthy donors. However, the number of ACE2$^+$ microvesicles in the group of COVID-19 patients correlated with the severity of disease [37].

Unlike ACE2, the transmembrane glycoprotein CD147, which has been recently identified as a new functional SARS-CoV-2 receptor [5], is constitutively expressed on the membrane of non-stimulated human peripheral blood CD4$^+$/CD8$^+$ T lymphocytes. Its expression is significantly upregulated in response to polyclonal cell activation [5], as well as expression of tyrosine kinase AXL, which is another candidate for the SARS-CoV-2 receptor [6]. Besides, expression of the transmembrane protein KREMEN1 was also detected in a subpopulation of regulatory T lymphocytes [9].

To summarize, although the question on the ACE2 expression by T lymphocytes remains unclear, the presence of alternative SARS-CoV-2 receptors on the cell membrane has been convincingly confirmed. Even if these receptors play an auxiliary role in traditional SARS-CoV-2 targets, they can come to the fore in cells with low or no expression of ACE2, for example, in immune cells.

It is also important to note that recent structural computer analysis of immune receptors has identified a number of new potential targets for SARS-CoV-2. It

has been shown that CD26, CD2, CD56, CD7, CCR9, CD150, CD4, CD50, XCR1, and CD106 molecules have theoretically a higher binding affinity for the RBD of viral S-protein than the classical receptor ACE2 [38]. Many of these molecules are expressed by T lymphocytes and even serve as markers of T cell subpopulations (e.g., CD2, CD7, CD4), but their involvement in infection requires experimental confirmation.

T LYMPHOCYTES AND SARS-CoV-2

T lymphocyte infection with SARS-CoV-2. Despite the data on the absence of ACE2 expression by T lymphocytes [3], related coronavirus SARS-CoV-1, which uses the same functional receptor, efficiently infects T cells. The presence of viral particles (electron microscopy) and mRNA (*in situ* hybridization and RT-PCR) was detected in circulating T lymphocytes (CD3+ cells), as well as in secondary lymphoid organs (spleen and lymph nodes) in 27% patients with SARS-CoV-1 infection [39]. Accordingly, the authors attributed lymphopenia, which accompanies this disease, to the defeat of the immune system by the virus [39].

It is no wonder that similar research on the new coronavirus SARS-CoV-2 has begun since its identification.

The first published study was by Wang et al. [5], who identified SARS-CoV-2 virions in T lymphocytes (CD3+ cells) infiltrating lung tissues of COVID-19 patients [5]. Using luciferase reporter analysis, the authors also demonstrated a dose-dependent infection of human peripheral blood CD4+/CD8+ T lymphocytes (*n* = 6) by SARS-CoV-2 pseudovirus, which was much more efficient in the case of preliminary polyclonal activation of T cells (anti-CD3/CD28) [5].

In March 2022, Shen et al. presented a study in which they used an expanded range of methods to confirm the previously obtained data [40]. Thus, the presence of the SARS-CoV-2 antigen (nucleocapsid protein, N protein) has been shown in peripheral blood T lymphocytes (CD3+ cells) and post-mortem lung sections of COVID-19 patients [40]. Moreover, the level of N protein in CD4+ T lymphocytes of the patients' peripheral blood was significantly higher than that in CD8+ T cells. [40]. When CD4+ T lymphocytes of Jurkat or MT4 cell lines were infected with SARS-CoV-2 *in vitro* (multiplicity of infection, MOI = 0.01), the presence of viral RNA (RBD-coding region), subgenomic viral RNA (a marker of viral replication in the cell), viral N protein (Western blot/flow cytometry), and viral particles (electron microscopy) were demonstrated in the cells. The assessment of virus infectivity in primary peripheral blood T lymphocytes of healthy donors (*n* = 3) also showed the presence of viral RNA (RBD), which was more abundant in pre-activated (CD3/CD28/IL-2) T cells [40]. Furthermore, the authors reported massive apoptosis of

virus-infected T lymphocytes *in vitro*, as well as an increased content of apoptotic T lymphocytes in the peripheral blood of COVID-19-patients compared with T cells of healthy donors [40].

Two more works directly related to the problem under discussion are currently at the preprint stage. However, they deserve discussion, since they have much in common with the previous studies. The first work shows the ability of SARS-CoV-2 (MOI = 0.1) to infect *in vitro* CD4+, but not CD8+ T lymphocytes of the peripheral blood of healthy donors, as confirmed at the level of viral RNA, viral protein (SARS-CoV-2 S protein, immunofluorescence), and viral particles (electron microscopy) [41]. Furthermore, negative (antisense) SARS-CoV-2 RNA was detected in infected CD4+ T cells, indicating viral replication [41]. In support of these results, *ex vivo* studies revealed the presence of viral RNA in CD4+, but not CD8+ T lymphocytes, of the peripheral blood of COVID-19 patients, and the viral load was directly related to the disease severity [41].

In the second work, *in vitro* infection of peripheral blood mononuclear cells of healthy donors (*n* = 5) with SARS-CoV-2 (MOI = 1) showed the presence of viral antigens in both CD4+ and CD8+ T cells (~13-14% by flow cytometry using hyperimmune serum from mice immunized with SARS-CoV-2) [42]. The process was accompanied by a pronounced apoptosis of both T cell subpopulations: up to 70% of SARS-CoV-2-infected cells had apoptotic changes [42]. In addition, the presence of virus-infected CD4+ T lymphocytes in the peripheral blood was shown in COVID-19 patients (*n* = 22, by immunofluorescence analysis using the serum of recovered patients against viral antigens), and the majority of T cells carrying viral antigens had SARS-CoV-2 double-stranded RNA (a marker of replication) [42]. The data of post-mortem immunohistochemical studies showed the presence of virus-infected CD4+ T lymphocytes in the lung tissues of COVID-19 patients [42].

Along with the works above, viral RNA was detected in T lymphocytes (CD3+ cells) in the samples of bronchoalveolar lavage (*n* = 6) and sputum (*n* = 2) from the patients with severe COVID-19 [43]. SARS-CoV-2 proteins and virions were also detected in the cells of spleen and lymph nodes in the post-mortem tissues of COVID-19 patients [44], although in the latter case, the type of infected cells was not determined.

Receptors mediating T lymphocyte infection with SARS-CoV-2. In almost all of the above works on the SARS-CoV-2 infection of T lymphocytes, the main viral receptor and co-receptor ACE2/TMPRSS2 were either not detected on infected T cells [5, 43] or not involved in the infection, as confirmed by the inhibitory analysis using suppression of the ACE2 gene and/or functional blockade of the receptors [40]. The only exception is the work by Davanzo et al. [41], in which SARS-CoV-2 infection of peripheral blood CD4+ T lymphocytes *in vi-*

T lymphocyte infection* with SARS-CoV-2

Type of T cells	T cell location	Receptor/co-receptor	Detected viral component	References
T lymphocytes in the tissues of COVID-19 patients				
CD3+ T cells	lungs	nd	viral N protein	[40]
			viral antigens**	[42]
			virions	[5]
	bronchoalveolar lavage, sputum	nd	viral RNA	[43]
CD4+/CD8+ T cells	peripheral blood	nd	viral N protein	[40]
CD4+ T cells	peripheral blood	nd	viral RNA	[41]
			double-stranded viral RNA	[42]
			viral antigens	[42]
Healthy donor T lymphocytes infected *in vitro*				
CD4+/CD8+ T cells	peripheral blood	CD147***	viral RNA	[5]
		AXL?	viral RNA	[40]
		nd	viral antigens	[42]
CD4+ T cells	peripheral blood	ACE2/	viral RNA	[41]
		TMPRSS2	antisense viral RNA	
		CD4	viral S protein; virions	

Note. nd, not determined.

* The table presents data only on the infection of primary T lymphocytes and not T cell lines. See the text for the information on the methods used for detecting viral components and assessing the contribution of specific receptors to the cell infection, and the size of study groups.

** Viral antigens were not identified; the presence of viral components was detected using sera from mice immunized with SARS-CoV-2 or recovered patients.

*** Only receptors/co-receptors for which the involvement in T lymphocyte infection with SARS-CoV-2 has been experimentally confirmed.

tro was effectively reduced by the blockade of ACE2 and TMPRSS2 [41].

At the same time, the involvement of alternative SARS-CoV-2 receptors in the infection process has been shown. Thus, expression of CD147 was found in the target cells and increased significantly in response to the cell activation [5, 43]. Moreover, *in vitro* infection of human CD4+/CD8+ T lymphocytes with SARS-CoV-2 pseudovirus was abolished by the monoclonal antibodies against CD147 [5]. Another alternative SARS-CoV-2 receptor, AXL tyrosine kinase, was detected at the mRNA level in the virus-infected T lymphocytes of COVID-19 patients [40]. In addition, in Jurkat T cells, AXL overexpression promoted (1.5-fold) cell infection with the virus, although the knockdown of the corresponding gene had no effect on this process, indicating that AXL is not the main receptor for the virus entry into Jurkat cells but may contribute to the infection [40].

Particular attention should be given to the work of Davanzo et al., who demonstrated the involvement of CD4 molecule, a marker of T helper cell subpopulation, in the process of T lymphocyte infection. The authors found that SARS-CoV-2 S protein coprecipitated with the recombinant full-length CD4 molecule, and infection of peripheral blood CD4+ T lymphocytes with SARS-CoV-2 *in vitro* was suppressed in a dose-dependent manner by cell pretreatment with anti-CD4 monoclonal antibodies [41], although less effectively than by the blockade of traditional virus receptor ACE2 and TM-PRSS2 protease. It is interesting that the same monoclonal antibodies against CD4 were able to block the entry of human immunodeficiency virus (HIV) into CD4+ T cells [45]. In the case of HIV infection, CD4 alone also cannot ensure the virus entry and acts together with

co-receptors, in particular, chemokine receptors CCR5 and CXCR4 [46].

Therefore, there are six independent studies to date that have demonstrated with more or less detail the ability of the SARS-CoV-2 to infect human T lymphocytes. As a rule, these are T cells that infiltrate affected tissues [5, 40, 42, 43] or present in the peripheral blood of COVID-19 patients [40-42]. However, in four studies, infection with the virus [40-42] or pseudovirus [5] has also been shown *in vitro* for the peripheral blood T lymphocytes of healthy donors. The size of studied groups was small, but the results are in good agreement with each other (table). Thus, most authors note exclusive [41, 42] or predominant [40] infection of CD4+ T cell subpopulation, and the work of Davanzo et al. provide an explanation for this phenomenon by demonstrating the involvement of CD4 molecule in cell infection with SARS-CoV-2 [41]. The damage of both T cell subpopulations (CD4+/CD8+) by the virus shown by Pontelli et al. in the *in vitro* experiment is apparently due to the excess of virions introduced into the culture per target cell (MOI = 1.0) [42], since in other works, this indicator was significantly lower (MO I= 0.1 [41] or MOI = 0.01 [40]). T cells infected with SARS-CoV-2 *in vitro* underwent pronounced apoptosis [40, 42]. The content of apoptotic T lymphocytes in the peripheral blood of COVID-19 patients was also increased compared to the T cells of healthy donors [40]. It should be noted that apoptosis is an expected consequence of cell infection with a virus; it can be either a result of direct effect of the virus or a classical immune system response to the appearance of cells carrying foreign antigens.

The replication of the virus was indicated by the presence of subgenomic viral RNA [40], negative (antisense) RNA of SARS-CoV-2 [41], or double-stranded viral RNA [42] in the virus-infected primary CD4+ T lymphocytes and CD4+ T cell of Jurkat and MT4 lines; however, the data on the assembly of viral particles and their release from the infected cell are not yet available. None of the current works allows us to say unequivocally whether the viral infection of T lymphocytes is productive or abortive. Pontelli et al. confirmed the productivity of infection for an unfractionated pool of peripheral blood mononuclear cells [42], but similar data for T lymphocytes are absent.

Non-infectious mechanisms of virus-dependent regulation of T lymphocytes. When speaking about infection of T lymphocytes with SARS-CoV-2, it should be taken into account that even in the case of non-productive virus interaction with the cell, SARS-CoV-2-dependent signaling can regulate cellular activity, as it was demonstrated by two recent studies.

Using structural computer modeling, it was shown that the S protein of SARS-CoV-2, but not of other coronaviruses, contains structural motifs that are highly similar to those of bacterial superantigens (antigens that cause massive non-specific activation of T lymphocytes) and is able to directly bind to the T cell receptor (TCR) [47]. The consequence of this binding should be excessive activation of T lymphocytes, and this mechanism may contribute to the hyperinflammatory syndrome specific to COVID-19. In support of this hypothesis, an atypical (distorted) TCR repertoire intrinsic to superantigen activation was found in COVID-19 patients with hyperinflammation, in contrast to patients with mild or moderate COVID-19 [47].

Another candidate for a regulator of T cell activation is viral fusogen, a protein that ensures the fusion of the virus envelope with the target cell membrane − rather not the protein itself, but the corresponding domain of the SARS-CoV-2 S protein. It is known that fusogen of the related 2003 coronavirus SARS-CoV-1 is involved not only in the T cell infection, but also in the direct inhibition of the TCR-dependent signaling. Analysis of its primary sequence showed that the fusogenic domain of the SARS-CoV-1 S protein mimics the transmembrane domain of the TCR α-chain and can disrupt interactions between the chains of the TCR complex, thus preventing the antigen-dependent signaling. Its specific immunosuppressive activity was confirmed in the experiment *in vivo*, in a model of collagen-induced arthritis in mice [48]. Given a close similarity of the amino acid sequence of the SARS-CoV-2 fusogen with the corresponding SARS-CoV-1 protein, as well as with the transmembrane domain of the TCR α-chain, it is highly probable that such mechanism also exists for the new coronavirus, although this still needs to be shown [49].

T LYMPHOCYTE INFECTION WITH SARS-CoV-2 AND COVID-19 PATHOGENESIS

SARS-CoV-2 infection is accompanied by significant changes in the functioning of immune system, and potential ability of SARS-CoV-2 to infect T lymphocytes may be directly related to manifestations associated with the disease. The first and the most obvious one is lymphopenia, which is found in most COVID-19 patients [50, 51] and is associated with the disease severity [50, 51]. T cell infection with the virus and induction of apoptosis in these cells appear to contribute significantly to the development of lymphopenia in COVID-19; moreover, the infection may be its main cause.

The functional exhaustion of T lymphocytes is also commonly reported in COVID-19 patients [52, 53]. This is a variant of T cell dysfunction, in which a short-term T lymphocyte hyperactivation in response to an antigen is replaced by a progressive decrease in the proliferative activity, loss of effector functions, expression of inhibitory receptors such as PD-1 and CTLA, and epigenetic and transcriptional reprogramming [52, 53]. The decrease

in the T cell functions in COVID-19 may be partly due to their non-productive infection with SARS-CoV-2, as well as non-infectious T lymphocyte regulation associated with the direct interaction of the viral S protein with the TCR, which causes the blockade or disruption of the antigen-dependent signaling.

The third phenomenon associated with the novel coronavirus infection is an uncontrolled excessive inflammatory response (cytokine storm), which is one of the most common causes of death in COVID-19 [50, 51]. Generally, hyperinflammation in this pathology is attributed to inappropriate activation of nonspecific defense cells − the main producers of pro-inflammatory factors [50, 51]. However, the cells of adaptive immunity, in particular, T lymphocytes, should play a direct role in this process. First of all, we are talking about a subpopulation of regulatory T cells (Tregs), which deserve a separate discussion in the context of this work.

SARS-CoV-2 and regulatory T lymphocytes. Treg subpopulation plays a key role in maintaining the self-tolerance and immune homeostasis. Natural Tregs (nTregs) mature in the thymus and their main task is to suppress the immune response to autoantigens, while inducible Tregs (iTregs) are formed at the late stages of any immune response and are designed to limit excessive

inflammation, thereby preventing tissue damage by the products of activated immune cells.

A number of data point to Tregs as a possible target for SARS-CoV-2. The CD147 molecule, an alternative entry receptor for the virus that mediates infection of primary T lymphocytes [5], has an increased expression on the Treg membrane and marks activated cells (CD45R0$^+$ Tregs) with a high suppressive activity [54]. The content of CD147 on the Treg membrane correlates with the expression of FoxP3, the main transcription factor and marker of this subpopulation [54]. Moreover, in order to maintain the stable expression of FoxP3, regulatory cells need a signal that they receive through CD147 when it binds to the physiological ligand CD98 expressed by the non-immune environment [55]. It has been shown that inducible Tregs with a high expression of CD147 (CD147high iTregs) effectively suppress inflammatory response in a model of experimental colitis in humanized mice, in contrast to similar cells with low CD147 content (CD147-low iTregs) [55].

Expression of two other SARS-CoV-2 receptors, transmembrane protein KREMEN1 and receptor tyrosine kinase AXL, has also been found in the Treg subpopulation [9, 56], with AXL apparently playing the same role as CD147 in the functioning of these cells.
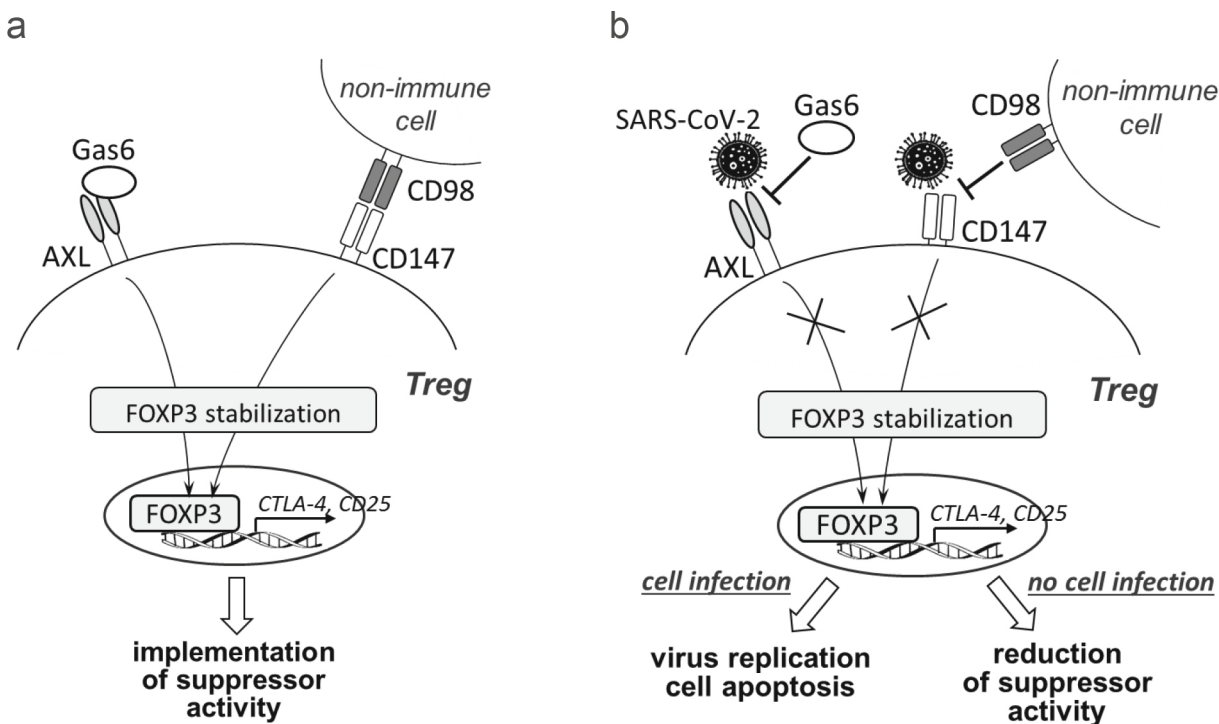
Possible mechanisms of SARS-CoV-2 interaction with regulatory T lymphocytes. CD147 and AXL molecules are highly expressed on the Treg membrane and are involved in Treg functioning: the signals received by the cells when these molecules bind to endogenous ligands (CD98/Gas6) are necessary to maintain stable expression of the key transcription factor FoxP3 (a). Alternatively, CD147 and AXL serve as entry receptors for SARS-CoV-2, and the encounter of Treg with the virus can lead to the cell infection or its non-infectious regulation (b). In the first case, the target cell usually undergoes apoptosis, while in the case of non-infectious regulation, the virus can bind to CD147/AXL and competitively inhibit the interaction of these receptors with endogenous ligands (CD98/Gas6), thus preventing cell stabilization and implementation of their suppressor activity. See the text for details.

Its endogenous ligand Gas6 (Growth arrest-specific) stimulates in a dose-dependent manner both *in vivo* and *in vitro* expression of the transcription factor FoxP3 in $CD4^+CD25^+$ Tregs and enhances Treg suppressive activity against effector $CD4^+$ T lymphocytes, the action of Gas6 *in vitro* being abolished completely or partially by the AXL gene knockdown or functional blockade of this receptor [56].

The question of Treg infection with coronavirus has not yet been raised anywhere, but this infection is highly probable and needs to be tested. Additionally, even in the absence of infection, SARS-CoV-2 can bind to the CD147/AXL membrane receptors on these cells and competitively inhibit their interaction with endogenous ligands (CD98/Gas6), thus preventing cell stabilization and implementation of their suppressor activity (figure). It is the direct effect of the virus on regulatory T cells that may be responsible for a significant decrease in the number of Tregs in the circulation in patients with severe COVID-19 [50, 57]. And since Treg subpopulation plays a key role in limiting excessive immune response, a decrease in the number and/or activity of these cells should contribute to the uncontrollable inflammatory response (cytokine storm) associated with severe COVID-19 and might even play a key role in this process. In addition, the virus-dependent impairment of Tregs may be related to the functional exhaustion of T lymphocytes, which prevents an effective antiviral response [52]. It is the violation of Treg control that can be responsible for the hyperactivation of effector T lymphocytes preceding their functional depletion [53].

Finally, speaking of CD147 as a functional receptor for SARS-CoV-2, it should be noted that this molecule is relevant not only for Tregs. It is closely associated with the development and functioning of T lymphocytes in general. Thus, CD147 is highly expressed on double-negative thymocytes and is involved in their expansion [58]. In the peripheral regions, CD147 regulates migration of activated T lymphocytes [59], as well as their proliferative response to polyclonal stimulation [60]. As a result, CD147-dependent infection can regulate T cell population both at the stage of antigen-independent differentiation and during the response of T cells to an antigen.

CONCLUSIONS

The first studies of SARS-CoV-2 interaction with T lymphocytes showed that the virus can infect T cells and that its main functional receptor in non-immune tissues, ACE2, either does not participate in this process [40] or is not detected on the virus-positive T cells [5, 43]. In the case of T cell infection, alternative SARS-CoV-2 receptors come to the fore, primarily CD147 and AXL molecules [5, 40]. Nevertheless, the issue of ACE2 expression

appears relevant. Firstly, despite a convincing demonstration of the presence of viral RNA, viral proteins, and virions in the infected T lymphocytes, the level of T cells infection is not comparable to that in traditional virus target tissues [40] with stable ACE2 expression. Secondly, the fact that ACE2 is absent or poorly presented on the general T cell population does not exclude its expression by individual subpopulations of T lymphocytes. In this regard, the most interesting cells are regulatory T lymphocytes, pro-inflammatory T helper subpopulations, as well as virus-specific activated $CD4^+/CD8^+$ T cells that infiltrate virus-infected tissues. It is no coincidence that T cells infected by SARS-CoV-2 are stably detected in lung tissues and bronchoalveolar lavage of COVID-19 patients, as the repertoire of viral receptors and the level of their expression can change in the lesions.

Furthermore, it should be noted that T lymphocytes can receive SARS-CoV-2 receptors, specifically, ACE2, from other cells via extracellular microvesicles that traditionally contain this molecule [36]. Hence, it is conceivable that resident T cells of barrier organs or virus-specific T lymphocytes infiltrating affected tissues receive the main functional SARS-CoV-2 receptor through such $ACE2^+$-microvesicles from the traditional virus targets with high levels of ACE2 expression (e.g., lung epithelium, vascular endothelium), thus becoming susceptible to the virus. This is the case if the microvesicles are released by the non-infected cells. If, however, the cell secreting $ACE2^+$-microvesicles is infected by the virus, which is very likely for the lesion site, the microvesicles might contain viral material in addition to the viral receptors. It was shown that microvesicles formed by SARS-CoV-2-infected cells contain viral RNA [61] and may be involved in the spread of the infection.

Therewith, it is important to note that in the case of infection, T lymphocytes themselves can participate in the spread of the virus. Pontelli et al. assign the role of the "Trojan horse" to the infected T lymphocytes in this situation [42]. Indeed, based on the current data, the level of T cell infection with SARS-CoV-2 is low and the productivity of infection has not yet been confirmed. It is possible that the virus binds to T cells with a focus on regulating their activity and/or on their transport functions.

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