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CELLULAR AND EXTRACELLULAR LEVELS OF RETROVIRUS—HOST INTERACTIONS ON THE EXAMPLE OF THE BOVINE LEUKOSE VIRUS. 2. CRITICAL STAGES — MULTIPLICITY AND VERSATILITY

(review)

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Abstract

The wide spread of viral infections and the ease of overcoming the species-specific barriers require the identification of critical stages in the virus interaction with multicellular organisms of mammals and the analysis of key molecular genetic systems involved. To date, a large amount of data has already been accumulated on the diversity and complexity of such systems, as well as the involvement in them the wide range of metabolic pathways. In this regard, attempts to identify some common elements that are implemented in different infectious processes are of particular relevance. This paper is such attempt made on the example of the analysis of the main events of cattle infection by bovine leukemia virus (BLV). Systems involved in the entry of BLV genetic material into the cytoplasm of host cells, the suppression of innate and adaptive immunity, as well as interactions between the genomes of the BLV provirus and the host genome are the identified critical stages. The direct participants in the reception of viral proteins are parts of some host tansmembrane systems (G.Yu. Kosovsky et al., 2017; V.I. Glazko et al., 2018; L. Bai et al., 2019; H. Sato et al., 2020). During virus reproduction in host cells, host enzymes modify virus envelope proteins by (A. De Brogniez et al., 2016; W. Assi et al., 2020). Importantly, modifications of SARS-CoV-2 spike proteins, as well as BLV envelope proteins, have a significant impact on their pathogenicity (M. Hoffmann et al., 2020). Pathogenicity and depressing effect of both BLV and SARS-CoV-2 on innate and adaptive immunity is realized in part through the activation of T regulatory cells and an increase in the expression of the growth transforming factor TGF-β (L.Y. Chang et al., 2015; G.Yu. Kosovsky et al., 2017; W. Chen et al., 2020). Intracellular mechanisms of protection against retrotranspositions, recombinations between viruses and host retrotransposons, the formation of new elements of host regulatory networks such as microRNAs, and the integration of proviral DNA into the host genome are closely related and controlled by interfering RNA (RNAi) systems with the key gene *dicer1* (P.V. Maillard et al., 2019; E.Z. Poirier et al., 2021; G.Y. Kosovsky et al., 2020). These systems can provide a certain «resistance» of the host genome both to the integration of exogenous genetic material and to transpositions of own mobile genetic elements. Apparently, it is the polygenicity of the control of these critical stages of viral infection that leads to difficulties in predicting their development and developing methods for their prevention.

Keywords: bovine leukemia virus, SARS-CoV-2, HIV-1, transmembrane systems, innate and adaptive immunity, interfering RNA systems, transpositions, mobile genetic elements

In recent years, data have been accumulating that consistently destroy simplified ideas about the interaction of retroviruses with host cells. Traditionally, each event of this interaction is considered separately, which does not allow assessing the polyvariance of its implementation from a holistic point of view. Moreover, interactions of retroviruses with host cell populations are mostly studied in vitro which often leads to contradictory results and complicates the development of methods for predicting the pathogenesis and spread of the infection.

There are several key stages in the interactions of a virus with a multicellular host organism. The first thing a virus encounters when it enters the body is the need to bind viral envelope proteins to receptor proteins on host cell membranes. As a rule, several domains of viral proteins and a number of host cell receptors most of which are associated with transmembrane transport systems participate in the binging. The second stage is the interaction of the virus with the host's immune defense, namely innate and adaptive immunity, and the third key stage is the integration of proviral DNA into the genome of the host cells.

In this review, we consider the polyvariance of molecular genetic systems involved in these events on an example of bovine leukemia virus (BLV, *Retroviridae*, *Deltaretrovirus*) as one of the most studied retroviruses.

BLV belongs to the *Retroviridae* family along with human T-leukemia viruse type 1 and 2 (HTLV-1 and HTLV-2). BLV infection in about 70% of cows is asymptomatic (aleukemic stage). In 25-30% of animals, persistent lymphocytosis develops; B-cell lymphoma occurs in 1-5% of animals after a 4-5-year latent period [1)].

Vaccination against BLV is still ineffective, so by far the most common way to improve the health of the dairy herd is to prevent infected animals from breeding. This approach is costly and, in addition, leads to a decrease in the productive potential of the herd, since a relatively increased susceptibility to BLV infection is often associated with high milk production. The combination of two circumstances (the low incidence of leukemia in infected animals and the loss of a part of the highly productive gene pool in the course of herd health improvement) actualizes the issues of predicting individual risks of oncogenesis and infectious danger of BLV carriers [2]. In this regard, of particular importance is the study of the molecular mechanisms of the processes occurring at each of the three stages of BLV-induced pathogenesis listed above.

The complexity of the interaction of the envelope proteins of the virus with the proteins of the plasma membrane of the host cells. Previously, we considered the basics and implications of the binding of the BLV envelope protein, encoded by the *env* gene, to the cellular receptor of the adapter-related protein complex-3 (AP-3) which is involved in the transport of proteins into lysosomes [3]. We found that in BLV-infected cows, the expression of the gene encoding the AP3D1 receptor is higher, but it does not correlate with an increase in the number of lymphocytes, which is usually considered as a preleukemic condition [4]. Another target for the reception of BLV *env* gene products which promotes the fusion of infected and infection-free cells is the transmembrane transporter of cationic amino acids SLC7A1/CAT1 [5, 6].

The *env* genes of BLV and human T-cell leukemia virus type I (HTLV-1) are 36% identical in amino acid sequences [7]. Entry of these retroviruses into target cells is initiated by interaction between Env and host cell receptors. Glucose transporter 1 (GLUT1) [8], neuropilin 1 (NRP-1) [9] and heparan sulfate proteoglycan (HSPG) [10] have been identified as cellular receptors for HTLV-1 attachment and cell infection.

The structure of GLUT1 has 12 hydrophobic transmembrane domains, six extracellular loops, and seven intracellular domains [11]. Like GLUT1, cationic amino acid transporter 1 (CAT1)/SLC7A1 has 14 membrane domains and has been identified in mouse cells as a membrane receptor for ecotropic murine leukemia viruses (eMuLV) [12]. CAT1 is a 622 amino acid protein with pronounced hydrophobic characteristics and is involved in sodium-independent transport of arginine, lysine, and histidine [13, 14]. Two different motifs in the third extracellular loop of CAT1 bind to the N-terminus of the *env* gene product subunit (SU) which is a determinant for eMuLV infection [15, 16]. Human CAT1 cells do not

confer susceptibility to human immunodeficiency virus infection. However, expression of mouse CAT1 in human cells can lead to acquired susceptibility [17]. Like human cells, hamster cells are completely resistant to eMuLV infection [18], and in many other animals, CAT1 proteins are also not involved in eMuLV infection, indicating that CAT1 may be species-specific for eMuLV infection. Importantly, both AP-3 and CAT1 expression occurs in various mammalian tissues. Therefore, retroviruses have no preferential target cells. It is obvious that other host proteins can also ensure the success of virus contacts with differentiated host cell populations.

According to Matsuura et al. [19], proteins carrying an immunoreceptor tyrosine-based activation motif (ITAM) which is present in the cytoplasmic tails of several protein components of antigen receptors on T- and B-cells, may be a key element for BLV reception together with the Fc receptor of immunoglobulin E. This motif is designated as Yxx(L/I)-x6-8-Yxx(L/I) where x corresponds to a variable amino acid residue.

Proteins of several viruses (e.g., BLV which causes B-cell lymphomas or leukemia in cattle, Epstein-Barr virus which causes Burkitt B-cell lymphomas in humans, and human herpesvirus 8 which causes sarcomas and primary effusion B-cell lymphomas in humans) contain ITAMs. The targets of these viruses are, in particular, B-lymphocytes, as well as non-hematopoietic cells, such as epithelial and endothelial cells. The BLV envelope glycoprotein (Env) contains two overlapping copies of the sequence (YXXL/I)2 (ITAM) in the C-terminal domain of the transmembrane (TM) protein. The Env BLV protein is synthesized as the Pr72 precursor peptide which is glycosylated in the rough endoplasmic reticulum and Golgi apparatus. Pr72 is cleaved by the cellular protease into two mature proteins, the gp51 surface subunit and the gp30 subunit with transmembrane localization. Due to disulfide bonds, gp51 and gp30 proteins form a stable complex and are included in the emerging viral particles. The gp51 protein binds to the cationic amino acid transporter 1 (CAT1)/SLC7A1 which acts as a cellular receptor for BLV and is responsible, as mentioned above [17], for its broad host specificity. The gp30 protein contains three different domains. These are an extracellular domain that interacts with gp51 and contains at the N-terminus a region of about 12 hydrophobic amino acids, the so-called fusion peptide [20], a transmembrane domain that anchors the gp51-gp30 complex in the plasma membrane of infected cells and in the virion [21], and a 58 amino acid cytoplasmic tail containing three YXXL sequences which were originally identified as two sets of ITAMs [22].

The three YXXL sequences in the cytoplasmic tail of gp30 BLV also correspond to the YXXφ tyrosine-based motif, where X is a variable residue and φ is an amino acid with a hydrophobic side chain (23). The YXXφ motif functions as an endocytic sorting motif and binds directly to the μ2 subunit of adapter protein-2 (AP2) [24]. The AP2 complex plays an essential role in initiating clathrin-mediated endocytosis [25]. The Env protein of most retroviruses (e.g., human immunodeficiency virus HIV, simian immunodeficiency virus SIV, and HTLV-1) contains only one YXXφ motif [26-28]. For HIV, the YSPL sequence contained in the Env protein is important for viral endocytosis and is required for virus replication and infectivity [29]. In vivo, YXXL gp30 sequences mediated high proviral loads in sheep experimentally infected with BLV [30]. It was found that a mutation in the second YXXL sequence, which leads to the replacement of tyrosine at position 498 by alanine, significantly reduces viral infectivity by reducing both the frequency of virus entry into the cell and the incorporation of the viral envelope protein into virions [23]. Thus, two of the three YXXL sequences in gp30 seem to play a crucial role in the development of a viral infection, namely, in binding to

cell membrane proteins, in particular, to T- and B-lymphocytes.

Posttranslational modification of viral proteins, such as glycosylation and methylation of arginine, can significantly contribute to their reception by host cells. For example, gp51 contains eight asparagine (N) residues; they presumably serve as sites for N-glycosylation [31], which can significantly affect viral replication, antigen conformation, the ability to form syncytium in vitro [32, 33], and infectivity in vivo [32]. Glycosylation of Env occurs both when virions attach to cell membranes and when cells merge with cells to form syncytium [34-36]. Env-associated glycans can protect surface viral proteins from neutralizing antibodies [36, 37]. A family of protein-specific arginine-N-methyltransferases (PRMT) catalyzes arginine methylation [38]. PRMT5 is a type II arginine methyl transferase. Arginine methylation plays a critical role in the biology of several viruses, in particular of hepatitis delta virus, hepatitis B virus, human immunodeficiency virus 1, Epstein-Barr virus and Kaposi's sarcoma-associated herpesvirus, and also, as followed from the data presented [38], of BLV. The authors of this study report that high expression of PRMT5 occurred in BLV-infected cattle only at high but not low proviral loads [38]. As it turned out, this is also true for artificial BLV infection (from the earliest stages of BLV infection to the stage of lymphoma).

Note that the multicomponent nature of molecular systems ensuring interaction with the host cell is not unique to BLV. Due to the pandemic, SARS-CoV-2 (*Coronaviridae*, *Alphacoronavirus*) seems to be the virus in which the molecular genetic systems involved in such interactions are the most studied. In contacts of SARS-CoV-2 with mammalian cells, as in the case of BLV, it is possible to isolate host proteins that are directly involved in the binding of the SARS-CoV-2 envelope protein (spike), as well as a number of systems that are indirectly involved in this. SARS-CoV-2 is an enveloped virus with single-strand positive viral RNA (ssRNA). Its entry into human cells is initiated through the binding of a spike protein (S protein) of the viral envelope to the angiotensin-converting enzyme 2 (ACE2) receptor on host cells. The type 2 transmembrane serine protease (TMPRSS2) and the endosomal cysteine proteases cathepsin B and L (CatB/L) cleave the S protein is into S1 and S2 fragmens. TMPRSS2 is believed to be of paramount importance for the entry of SARS-CoV-2 into host cells. ACE2 and TMPRSS2 are expressed in different cell types, including not only capillary endothelial cells, but also pneumocytes, macrophages, and other cells [39]. The C-terminal domain of the S1 subunit is responsible for the binding of SARS-CoV-2 to ACE2, and the S2 subunit undergoes conformational changes that lead to the fusion of the virus envelope with the cell membrane and the penetration of the virus content into the target cell. In the cytoplasm, the RNA of the virus is released, and the viral RNA polymerase necessary for virus replication is synthesized. The innate immune response is the host's first line of defense against SARS-CoV-2 infection. Toll-like receptors recognize viral RNA, i.e., double-stranded (dsRNA) (TLR3 receptor) and single-stranded (ssRNA) (TLR7 and TLR8), and serve as triggers for innate immune responses, including the expression of type I interferon genes and a number of cytokines [40]. In addition to the direct reception of the virus by host cell proteins, other metabolic modifications initiated by cellular enzymes occur. For example, glycosylation or methylation of argenins at the S proteolysis site of the spike protein, resulting in its cleavage into S1 and S2 subunits, can play a certain role at this stage [39].

If we generalize these data for taxonomically unrelated DNA- and RNA-containing viruses from groups with different types of replication, we can draw an obvious conclusion. At the first contact of the virus with the cell and at the stage

of virion maturation in the cytoplasm, there are two complex events which can significantly affect the subsequent spread of the pathogen. These are the interaction of the envelope protein virus with several host cell plasma membrane proteins and post-translational modifications performed by host enzymes during the synthesis of viral proteins.

Virus pathogenicity and adaptive immunity. The next key step in the interaction of a virus with a multicellular host organism is the activation of an adaptive response. It begins with antigen presentation in which class II gene products of the major histocompatibility complex (MHC) play a decisive role. The major histocompatibility complex is controlled by a highly polymorphic set of genes responsible for peptide antigen presentation and immune response, thereof it is associated with disease susceptibility. BoLA is the major histocompatibility gene complex in cattle. In particular, BoLA-DRB3 is a highly polymorphic class II BoLA locus with 365 alleles registered in the immunopolymorphism database (IPD database) of the MHC (https://www.ebi.ac.uk/ipd/mhc/group/BoLA/). Its polymorphism is associated with many infectious diseases in cattle [41-43]. Associations of BoLA-DRB3 polymorphisms with BLV proviral load (PVL) and associated symptoms are well documented [44-46].

An association between some BoLA-DRB3 allelic variants and BLV resistance was first described over 30 years ago [47, 48]. BoLA-DRB3 polymorphisms have been shown to influence the regulation of PVL by BLV during experimental infection in cattle [49, 50]. However, in recent years, it has become clear that in Holstein cows, PVL BLV and the development of lymphoma may be associated with different allelic variants of BoLA-DRB3 [51].

BVL-induced lymphoma develops as a result of the interaction of elements of the viral genome and products of the host genome in addition to BoLA-DRB3. For example, the integration of the provirus BLV in the region of the host genes involved in oncogenesis affects their expression [52-55]. In a number of studies, it is noted that quite often the integration of the BLV provirus is detected in the areas of localization of retroviruses [56-60].

The interaction of viral genes with host genes is of particular importance. For example, products of a number of host lymphocytic genes (transcription factors, cell cycle regulators, protein kinases, phosphatases), which affect apoptosis, proliferation, promote cell immortalization and ultimately lead to oncogenesis, transactivate the viral Tax protein, an activator of transcription of proviral DNA integrated into the host genome [53, 58, 61-63]. In turn, activation of BLV proviral DNA is to some extent due to the fact that Tax reduces the methylation activity of the BLV promoter region [64].

Tax mediates the activation of gene expression via the nuclear factor kappa-light-chain-enhancer of activated B cells (NF-kB) pathway [61]. Tax reduces the stability of various inhibitors of NF-kB in the cytoplasm (such as IkBa and oxidoreductase containing the WW domain) and induces nuclear translocation of NF-kB [65]. Tax interacts with the RelA subunit of the NF-kB complex [65, 66]. It is known that Tax induces an increase in the expression of many host genes, in particular tumor necrosis factor alpha TNFα [67, 68]. Our studies revealed that in BLV-infected cows, regardless of their origin and farms where they were kept, one of the most common changes, along with differences in platelet counts [69], is a decreased expression of NK-lysine, one of the main proteins in cytotoxic granules of T-killers and NK cells, which indicates inhibition of innate immunity factors [4]. Summarizing these research data, we proposed a scheme explaining the inhibition of not only innate immunity, but also antibody genesis. In brief, the essence of this scheme is as follows. Tax induces an increase in the expression of

TNFα which activates Treg cells, the producers of transforming growth factor beta TGF-β [70]. The TGF-β inhibits the proliferation and activity of T-killers and NK-cells, the producers of NK-lysines and increases the number and activity of platelets, in particular platelet antiapoptotic activity that was also described by other researchers [71-73].

The data accumulated to date generally do not contradict our earlier hypothesis about the mechanism of the host's innate and adaptive immunity suppression by the BLV through activation of TNF, being one of the leading immune response regulators, by BLV proteins [4]. It should be noted that, in our opinion, the key factor of the pathogenicity (aggressiveness) of the virus is the ability of the virus proteins to suppress various links of the host's immunity.

Based on accumulating evidence, expression of microRNAs (miRNAs) and long non-coding RNA sequences may be another source of influence of BLV viral genome elements on host immune responses [74-77].

Retroviral miRNAs actively influence various metabolic pathways of the host not only through the suppression of translation of the host mRNA, but also through interactions with its miRNA profile [78] or by interfering with the processes by which microRNAs are involved in the regulation of cell division and innate immunity functions [79, 80]. In recent years, microRNAs have attracted increasing attention as evidence is accumulating that these small RNA molecules (18-23 nucleotides), being one of the leading components in the epigenome formation, significantly contribute to the regulation of gene expression profiles [81].

To date, the studies performed reveals a spectrum of genes and gene networks the regulation of which in modern highly productive cattle breeds fundamentally differ from that of ancient ancestral forms in targets for miRNA of more than 1600 structural genes. These genes are involved in various metabolic pathways, including those associated with immunity [82]. The expression profiles of miRNAs involved in the regulation of transcription of structural genes the products of which are active in various metabolic pathways, and in particular in the key functions of the immune system at different stages of cow lactation, have been revealed [83, 84].

In recent years, special attention has been paid to the study of the organization, expression, and targets of BLV miRNAs due to the known similarity of this retrovirus with human T-cell leukemia virus types I and II (HTLV-1 and HTLV-2) [52, 85-87]. Sequencing of a collection of small RNAs obtained from B-lymphomas of BLV-infected sheep made it possible to isolate 10 regions of 20-23 nucleotide sequences of five BLV microRNAs that were transcribed from proviral DNA between the *env* gene and exon 2 R3 with coordinates of BLV proviral DNA positions 6398-6906 [88]. It was found that BLV microRNA transcripts in lymphoma cells account for approximately 40% of all microRNAs in these cells, and that transcription occurs with the participation of RNA polymerase III. Revealed suppression of the whole genome proviral DNA expression is due to epigenetic modification of 5′LTR which prevents transcription while no suppression occurs at the region of localization of microRNA genes [86]. The authors believe that activation of BLV miRNA transcription in pre-leukemic and leukemic cell clones is due to the host immune system-mediated selection against cell clones expressing BLV proteins. Moreover, it turned out that one of the BLV miRNAs, the BLV-miR-B4 identical in the nucleotide sequence of the "grain" region (nucleotides 2-7) to miR-29 of the bovine genome, exceeds miR-29 which is a member of the family miR-17-92 (oncomir-1) in terms of expression [79, 89]. Overexpression of miR-29 is found in BLV-infected tumor cells, as well as in human and mouse B-lymphomas [90]. The available data also indicate that BLV

miRNA plays a significant role in BLV-induced oncogenesis, and its antagonist is an antisense transcript from the 3'-end of BLV proviral DNA [76]. Note that the relationship between the expression of BLV proviral DNA, BLV microRNA, and leukocytosis has not been sufficiently studied. In addition, study of BLV-infected cell cultures suggests some antagonism between expression of full-length BLV proviral DNA and microRNA due to selection against BLV-expressing cell clones performed by the host's immune system.

An additional factor of the aggressiveness of retroviruses is their mutagenic activity against various host genes that control the processes of cell division, apoptosis, and cell differentiation. Thus, mutations in the host *p53* gene and polymorphisms of tumor necrosis factor α (TNFα) are directly associated with the development of lymphoma [91-93]. It also turned out that the expression levels of DNA repair proteins MSH2 (DNA Mismatch Repair Protein Msh2) and EXO1 (Exonuclease 1) are associated with the development of BLV-induced lymphomas. This suggests that one of the mechanisms causing the onset of the disease is the accumulation of mutations in a number of host genes [94]. In addition, the expression of the arginine-N-methyltransferase (PRMT5) gene involved in virus reception by host cells positively correlates with a high BLV proviral load and the development of the lymphoma stage. It was shown that changes in BLV pathogenicity is associated with downregulation of PRMT5 expression [95].

Thus, as at the BLV reception stage, a set of BLV genomic elements actively influence a large number of links in the innate and adaptive immunity of the host and inhibit them. It can be expected that proteins such as Tax serve as the key effector of suppression; in addition, microRNAs encoded by BLV have a significant effect on lymphogenesis in BLV-infected cows [77, 96]. Apparently, this can explain the many years of unsuccessful vaccination of cattle with BLV proteins.

The complexity of variability in the integration of BLV proviral DNA into the host genome. Integration of proviral DNA into the host genome is the critical point of the multiple ways to control the penetration of the BLV genetic material into host cells and the interaction of the virus with factors of the innate and adaptive immunity of the host. This process is also complex and is ensured by different molecular genetic systems [3]. There also are two fundamental points essential for the appearance of aggressive cell clones which are precursors of lymphomas. These are the extent of integration itself and the predisposition to mutagenesis of proviral DNA integrated into the genome.

A number of works [52-53, 55, 77, 97] consider massive integration of BLV into the genomes of B-lymphocytes followed by elimination of most cell clones and the frequency of mutational events in the key BLV genes for oncogenesis which occur in these clones. Some of publications mention that quite often the BLV proviral DNA integrates in the sites of retrotransposon localization.

Whole genome sequencing of the bovine genome revealed that the frequency of occurrence of the trinucleotide microsatellite (AGC)n in the bovine genome is 90, being 142 times higher than in the human and dog genomes. It also turned out that 39% of microsatellite loci with the AGC core in the bovine genome are associated with the evolutionarily young and Bov-A2 SINE retrotransposon species-specific for cattle [98]. Bov-A2 in its origin is closely related in origin to the long dispersed nuclear element (LINE) BovB [99]. BovB is an autonomous retrotransposon for which horizontal transfer is known in a number of species [100].

We have previously obtained evidence of a close relationship between microsatellites and retrotransposons [101]. We then compared the frequency of

occurrence of genomic DNA fragments of different lengths flanked by inverted repeats of microsatellites (AGC)6G, (GAG)6C, and (AG)9C in Black-and-White Holstain cows differing in BLV infection, as detected by the presence of in BLV proviral DNA genomes, and milk production. It turned out that the polymorphism of such fragments in the (AGC)6G and (GAG)6C spectra coincides in animals infected with BLV and distinguishes them from infection-free individuals regardless of their milk production. On other hand, the (AG)9C spectra differentiate cows by milk production but not by the presence of proviral BLV DNA in the genomes [102, 103]. Sequencing DNA fragments flanked by the (AGC)6G inverted repeat turned out that in animals infected with BLV there is an "overrepresentation" of homology regions with retrotransposons and their recombination products compared to cows free from the BLV infection [104]. Analysis of the associations of sequences localized between the inverted repeat (GAG)6C in the genomes of Black-and-White Holsteini cattle with structural genes showed that in most cases such sequences are associated with the genes of the immune and cell signaling systems or with their 5'-flanks in the intergenic space. In cows infected with bovine leukemia virus, in contrast to infection-free cows, such a sequence was found in the NK-lysine gene [105]. In addition, the NonLTR/SINE/SINE2 superfamily were detected in genomic DNA fragments flanked by an inverted repeat of the Helitron transposon at a frequency that was 5 times higher in the BLV-infected animals than in infection-free cows. In general, in the sequenced fragments, the density of transposable genetic elements (in particular, retrotransposons) in BLV-infected animals was higher than in infection-free ones [106-108].

Based on these data, we put forward a hypothesis that there are certain intracellular mechanisms the weakening of which promotes the BLV proviral DNA integration into the host genome while in the animals resistant to the infection it does not occur [104]. To designate the phenomenon of increased resistance to retrotranspositions and integration of DNA copies of retroviral sequences into the genome we suggest the term "genomic resistance to retrotranspositions".

Interestingly, the genomic resistance to retrotranspositions that we noted is confirmed by data on the consequences of the coronavirus infection COVID-19 caused by SARS-CoV-2, a virus with a different type of genome replication than in BLV. This may testify in favor of the universality of the mechanism of genomic resistance to retrotranspositions. Thus, infection of human lung and intestinal cells with SARS-CoV-2 induced increased expression of retrotransposons [109, 110]. It is assumed that the activation of retrotransposons leads to an increase in the amount of reverse transcriptase they encode, and the resulting higher intracellular level of this enzyme further increases the risk of retrotranspositions [109, 110]. Thus, chimeric transcripts (recombination products) of a retrotransposon and SARS-CoV-2 RNA have been found, which suggests the potential insertion of proviral fragments into the human genome [109, 110]. Note that the leading and terminating parts of the SARS-CoV-2 genome often form chimeric RNA. Therefore, SARS-CoV-2 can enter human cells and interact with retrotransposons in the host genome, causing more severe symptoms in patients with underlying diseases [109, 110].

One of the mechanisms of intracellular defense against retroviruses is the activity of the endogenous nuclease Dicer [111, 112]. The internal cellular antiviral mechanisms are part of the innate immune response and include RNA interference (RNAi) and the interferon system (IFN). The two systems operate quite differently, although both can be induced by viral long double-stranded RNA (dsRNA) or high base-pair single-stranded RNA (ssRNA). The source of dsRNA can be the virus itself (in the case of a virus with a dsRNA genome) or two complementary RNA strands formed as viral RNA replication intermediates

or convergent viral DNA transcripts. Paired regions of ssRNA, also commonly referred to as dsRNA, are localized at high density in hairpins in viral genomes or in viral transcripts. Both types of dsRNA (viral genomic double-stranded RNA or hairpin structures in viruses with single-stranded genomic RNAs) are absent in appreciable amounts in uninfected cells and act as signs of viral infection, inducing innate antiviral immune responses. Long dsRNA is cleaved by type III endoribonuclease Dicer into small interfering RNAs (siRNAs), the RNA duplexes 21-24 nucleotides long. One strand of each siRNA duplex binds to the Argonaute (Ago) protein which, together with available proteins, forms an RNA-induced silencing complex (RISC) and mediates endonucleolytic cleavage (slicing) of complementary target RNAs. Ago is involved in an RNAi- and miRNA-mediated process that leads to mRNA degradation and/or inhibits translation [111].

Available data indicate that the interferon and RNAi systems are antagonistic as different components of antiviral defense in mammals [112]. Our own studies have shown that cows with high leukocytosis tend to have lower expression of the *ifn-α* gene compared to animals free from BLV infection and those with moderate leukocytosis [4]. Note that the first group exhibits a statistically significant increase ($p < 0.5$) in the expression of the Dicer1 (*dc1*) and *ago2* genes compared to the second of these three groups [113]. Interestingly, we also found statistically significant ($p < 0.5$) positive correlations between the expression of these two genes in cows free of BLV infection [113]. In case animals with insertions of BLV proviral DNA into the genome and the expression of BLV reverse transcriptase (*pol*) are treated together as one group, regardless of the level of leukocytosis, then a statistically significant correlation between the expression of *dc1* and *ago* is also observed. The expression of both genes correlates positively ($p < 0.5$) with an increase in the number of leukocytes and lymphocytes and with the pol expression. If we conditionally divide the group of animals with proviral DNA insertion and *pol* expression into subgroups of individuals with moderate (less than 20×10^9/l) and high (more than 20×10^9/l) leukocytosis, it turned out that in cows with moderate leukocytosis, correlations between *dc* and *ago2* disappear while negative correlation appears between *ago2* expression and thrombocytosis. At that, in animals with high leukocytosis, a correlation between *dc1* and *pol* expression is preserved ($p < 0.5$) and correlations of *dc1* and *pol* expression with the number of eosinophils is detercted [113]. In the group of BLV-infected cows with microRNA expression, there are correlations between the number of leukocytes, lymphocytes, monocytes, *pol* and *dc1* expression, but there is no correlation between *dc1* and *ago2* expression [113].

The complexity and variability of the correlation relationships between the expression of the studied genes and the leukocyte blood count that we revealed are obviously due to high quantitative dynamics of cells of different differentiation types and various maturation levels in the peripheral blood in vivo, especially at various stages of the infectious process. Gene expression available for analysis changes in a significantly smaller number of cells, from which total mRNA is isolated at the first stages of the study. This problem becomes especially clear for the dynamics of the *dc1* gene product (aviDicer1) isoform with deletions of exons 7 and 8 in embryonic stem and differentiated somatic cells [112]. In our studies [113], the activity of *dc1* expression was assessed for the terminal region of the transcript (exon 29). Therefore, it is obvious that in the blood cell population we could type the expression of both the full transcript and the aviDicer1 isoform.

Thus, intracellular protection against the integration of the sequence of DNA copies of retroviruses and, apparently, retrotranspositions in the host genome also depends on the set of genes. The end result may turn out to be similar

with the contribution of the activity of different genes, depending on the network relationships between them.

Another reason for the variability in the relationship between the virus and the host is the increased mutability of the nucleotide sequences of the virus. In some studies, the estimated mutation rate in retroviruses was on average about 10^{-3}-10^{-5}per nucleotide in one transcription cycle [114]. Such variability is primarily due to the predisposition of some parts of the nucleotide sequence of the viral RNA itself to the formation of secondary structures. In particular, these motifs include sequences with increased ability to form G4 quadruplexes [115]. We assessed [116, 117] the distribution of nucleotide motifs predisposed to the formation of secondary structures (G4 quadruplexes, triplexes, inverted repeats) both in RNA and in BLV proviral DNA. Our findings showed that the number and density of sequences capable of forming G4 quadruplexes increased in the BLV *env* gene compared to the *pol* gene. We found [116, 117] that the *pol* gene contains sequences with G4 quadruplex motifs on the flanks, which have a certain homology (> 70%) with regions of retroviruses belonging to other groups of retroviruses and found in other species, which coincides to some extent with reported data [118]. We also revealed an increased density of nucleotide motifs with a predisposition to the formation of secondary structures in the long terminal repeats (LTR) of the BLV genome when comparing the results of their sequencing presented in GenBank (National Center for Biotechnology Information, https://www.ncbi.nlm.nih. gov/). Analysis of polymorphic regions in the sequenced LTR BLV from GenBank performed separately for primary infected animals and for lymphomas [119] found only partial matches. This may indicate different clonal selection in populations of BLV-infected cells and in lymphomas undergoing stages of tumor progression. The greatest polymorphism appears in both cases in the regions where the regulatory sequences are located. Of the three sequences of potential G4 quadruplexes, the first one (positions 49-68 bp of LTR BLV) coincides with the most polymorphic region in sequences both in different isolates and in lymphomas, as well as with the TxRE regulatory region [117]. The other two are characterized by a relatively increased polymorphism in lymphomas and are located at positions 469-508 bp, i.e., on the 5′-flank of the site of homology to the primate endogenous retrovirus (positions 505-531 bp). This is consistent with our previous assumption of a relationship between the localization of potential G4 quadruplexes and recombination events, in particular, in the *pol* BLV gene [117].

In addition, two non-overlapping inverted repeats were identified which differed in complexity and unequal polymorphism of localization sites [117]. In sequences from GenBank and from lymphomas [119], the first inverted repeat is localized in the regulatory sequences in the U3 region with relatively low polymorphism, the second inverted repeat found in the U5 region in sequences with high polymorphism overlaps with purine-pyrimidine tracks predisposed to formation of intramolecular triplexes. Another purine-pyrimidine sequence predisposed to the formation of DNA-RNA triplexes, is localized in a relatively conserved region and overlaps with the second regulatory region of TxRE [117].

It can be expected that the detected genetic heterogeneity of LTR regulatory motifs is associated with an increased density of noncanonical nucleic acid structures localized in them (in particular, G4 quadruplexes), which contributes to the interaction of viral proteins with various host defense systems. It should be noted that G4 quadruplexes are present in the genomes of both DNA and RNA viruses and control the critical stages of their replication. For example, G4 quadruplexes in the HIV-1 genome regulate reverse transcription and proviral DNA transcription steps, which require their interaction with cellular proteins

and/or RNA [120]. A search is under way for ligands for G4 quadruplexes that could provide antiviral protection, and some encouraging results have been obtained [121].

The significance of G4 quadruplexes in mutagenesis and regulation of viral gene expression together with the preferential localization of G4 quadruplexes in certain regions of the genome of both viruses and their hosts, suggest close coevolution of the virus with the host and mutual "mimicry" in the genomic distribution of such noncanonical sequences [122].

It is important to note that in viruses of different origins, all three critical stages of interaction with host cells have certain similarities. The penetration in all cases is associated with host proteins that provide transport across the cell membrane (and, consequently, with glycosylation of viral proteins and modifications of host protease targets on these proteins). Suppression of innate immunity is associated with an increase in the production of growth-transforming factor TGF-β by regulatory T-cells of mammals [123, 124]. The interaction of virus and host genome involves molecular genetic systems for recombination, including reverse transcription, with influence on the host's regulatory networks.

Thus, in the interaction of retroviruses with mammalian cells, as exemplified by the processes during infection of cattle with the bovine leukemia virus (BLV), virus reception by host cell proteins, protective reaction of the host's innate and adaptive immunity, and integration of proviral DNA into the host genome can be distinguished as critical events. Many host genes are involved in the processes occurring at all stages of the interaction between the virus and the host cell, and such polygenicity is characteristic of various viral infections. For the first stage, two levels of sources of variability can be distinguished, i.e., the interaction itself with host proteins (reception, membrane fusion) and modification of viral proteins during its reproduction in host cells (glycosylation, methylation). The interaction with the host immune system involves viral proteins and microRNAs in the metabolic pathways that provide innate and adaptive immunity. Post-translational modifications of viral proteins can contribute to and modulate the processes occurring at this stage. The third stage is also characterized by the interaction of virus and host gene products, apparently involved in metabolic pathways that are directly related to the proviral DNA integration and retrotranspositions in the host genome. All these processes are accompanied by a high rate of mutation and even recombination between viral sequences. The polygenicity of the relationship between the pathogen and the host (in fact, the formation of networks of their interacting genes) leads to the severity of individual manifestations of the disease. The effective prediction of its development can be based on the simultaneous assessment of the expression of a set of genes that are critical for the pathogen—host relationships at different stages of this process.

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