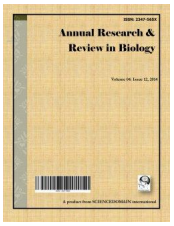

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The Search for a Receptor for Cell Infection by Bovine Leukemia Virus: Data Mining and Signaling Pathways Analysis

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Authors' contributions

This work was carried out in collaboration between all authors. All authors read and approved the final manuscript.

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ABSTRACT

The bovine leukaemia virus (BLV) is widely spread all over the world. Currently, treatment of leukaemia-infected animals is not carried out. Not all virus carriers become ill with leukaemia. The existing genetic resistance to the disease is due to the presence of alleles of resistance of the main histocompatibility complex. However, another mechanism of resistance is possible, which is associated with the penetration of the virus into the cell. The work aimed to analyse the currently available data on possible receptors of the virus. Four potential molecules were found. The results suggest that the potential BLV receptor is a CD209 protein.

Keywords: Bovine leukaemia virus; receptor; CD209 protein.

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1. INTRODUCTION

Bovine leukaemia is a chronic proliferative disease caused by a retrovirus, bovine leukaemia virus (BLV), of the *Retroviridae* family, *Deltaretrovirus* genus. The first report of this disease was made by Leisering in 1871, and three years later Bollinger described bovine leukaemia as a clearly defined disease entity. The virus itself was first isolated in 1969 [1]. No natural reservoir of BLV has been found [2]. The genome of the virus was completely sequenced in 1985 [3]. Most animals infected with BLV (approximately 70%) are asymptomatic, and approximately one-third of them develop a mild disease form, persistent lymphocytosis [4]. Lethal lymphosarcoma occurs in less than 0.6–5% of infected animals, primarily in adult ones (over 4–5 years of age). The main approaches to control BLV include identification and elimination or isolation of BLV-infected animals.

In general, human cells are highly unlikely to be infected with BLV. However, its similarity (58%) to human T-lymphotropic virus (HTLV), which belongs to the same genus, still leaves room for negative effects of infection with the virus [5]. Consequences may be particularly negative following recombination between BLV and HTLV, as it has been shown that replacement of the BLV RNA region containing the primary and secondary encapsidation signals with a similar region from HTLV produces a recombinant virus able to replicate in a cell culture [6]. These findings require more serious study of the BLV prevalence and biology, as well as the mechanisms that make cattle resistant to the virus.

Resistance to BLV is primarily determined by the presence of resistance alleles of the BoLA-DRB3 gene encoding one of the antibody chains, which also bind the viral capsid proteins [7]. The frequencies of alleles associated with BLV resistance, susceptibility, and neutrality significantly vary between breeds [8-10]. There are cattle breeds that have a minimum amount of BoLA-DRB3 alleles, are never affected by leukaemia, and show low virus carrier state levels, such as Yakutian and Kostroma breeds, zebu and zebu hybrids (*Bos indicus*). We assume that other mechanisms apart from immune response definitely play a role in the resistance of these breeds to BLV. We hypothesise that a polymorphism of the gene encoding the BLV receptor required for cell infection may be involved in this case. The goal of this study was to identify a potential viral receptor through analysis of literature data and described intermolecular interactions.

2. METHODOLOGY

We utilised the following information search resources in this study: PubMed (https://www.ncbi.nlm.nih.gov/pubmed) and TargetInsights (https://demo.elseviertextmining.com). Intermolecular interactions were analysed using the Pathway Studio® 9 software and the ResNet® 13 reference database (Elsevier) containing mammalian data. The ResNet database contains brief descriptions of biological objects (in particular, proteins, cell processes, diseases, etc.), as well as functional links between them obtained by processing Medline-indexed full-text articles and abstracts.

3. RESULTS AND DISCUSSION

The literature analysis revealed that the virus requires its SU protein (glycosylated) to penetrate the cell [10]. The SU virus protein is a subunit of the BLV envelope complex, which includes 2 proteins - SU and TM. Both proteins are encoded by the *env* gene. SU contains a signal peptide, a proline-rich region and two Zn2+ binding domains. The amino acid sequence of the SU protein contains seven immunogenic sites. Also processed SU protein is glycosylated, which greatly reduces its immunogenicity. The structure and functions of the proteins of the envelope complex are described in detail in the review [11]. The secondary structure of the C-terminal surface portion of the SU viral protein has been shown to be highly similar to human ERVW-1 protein (endogenous retrovirus group W member 1 or syncytin 1) [10 and our observation by Psi-Blast], and the similarity of these amino acid sequences is 33%. This protein has a structure similar to that of retrovirus proteins and plays an important role in the formation of placental syncytium by promoting cell fusion [12]. The intermolecular interaction analysis with the ResNet13 database identified several proteins bound to ERVW-1 (Fig. 1).

Toll-like receptor 4 (TLR4) is involved in recognition of pathogens and activation of innate immunity. Presumably, ERVW-1 can bind to TLR4 and inhibit lipoprotein secretion during the immune response [13], but this is only an assumption. L-serine transporter (SLC1A4) and

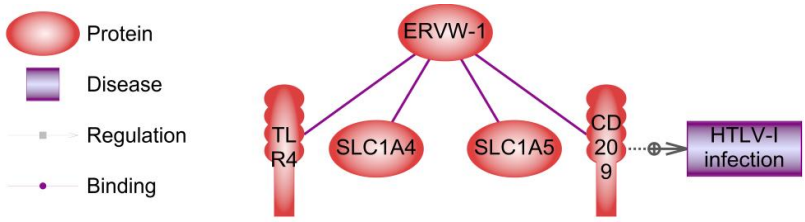

Fig. 1. Interaction between ERVW-1 and other proteins. Prepared with PathwayStudio9 (Elsevier)

sodium-dependent neutral amino acid transporter (SLC1A5) serve as ERVW-1 receptors [14]. These three proteins are expressed in most cell types, including blood cells, and thus cannot be viewed as potential BLV receptors as the virus affects only blood cells (B-cells).

CD209 (dendritic cell-specific intracellular adhesion molecule (ICAM)-3 grabbing non-integrin) is of particular interest, as it is the only molecule related to human T-cell leukaemia virus infection among all identified molecules [15,16]. Polymorphism of the CD209 promoter has been shown to be associated with human T-cell leukaemia virus infection [17]. Experiments have demonstrated that ERVW-1 binds to CD209 [18]. Besides, CD209 is expressed in a limited number of cells, most notably B-cells. This evidence suggests CD209 as a potential receptor for BLV.

4. CONCLUSION

Therefore, having analysed currently available data, we assume that CD209 is a candidate receptor for BLV. This assumption requires experimental confirmation, analysis of interactions of viral particles with CD209 and a search for polymorphic variants of the *CD209* gene in different cattle breeds and *Bos taurus* subspecies.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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