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Review Article

SLAMF1/CD150 in hematologic malignancies: Silent marker or active player?

Inna Gordiienko*, Larysa Shlapatska, Larysa Kovalevska, Svetlana P. Sidorenko

Department of Molecular and Cellular Pathobiology, R.E. Kavetsky Institute of Experimental Pathology, Oncology and Radiobiology National Academy of Sciences of Ukraine, Kyiv, Ukraine

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ABSTRACT

SLAMF1/CD150 receptor is a founder of signaling lymphocyte activation molecule (SLAM) family of cell-surface receptors. It is widely expressed on cells within hematopoietic system. In hematologic malignancies CD150 cell surface expression is restricted to cutaneous T-cell lymphomas, few types of B-cell non-Hodgkin's lymphoma, near half of cases of chronic lymphocytic leukemia, Hodgkin's lymphoma, and multiple myeloma. Differential expression among various types of hematological malignancies allows considering CD150 as diagnostical and potential prognostic marker. Moreover, CD150 may be a target for antibody-based or measles virus oncolytic therapy. Due to CD150 signaling properties it is involved in regulation of malignant cell fate decision and tumor microenvironment in Hodgkin's lymphoma and chronic lymphocytic leukemia. This review summarizes evidence for the important role of CD150 in pathogenesis of hematologic malignancies.

1. Introduction

SLAMF1/CD150 receptor is a founder of signaling lymphocyte activation molecule (SLAM) family of cell-surface receptors. Initially, CD150 was identified as a marker of activated B cells by monoclonal antibody (mAb) IPO-3 [1,2]. Lately it was detected on the majority of cells within hematopoietic system, especially those that have the activated phenotype [3]. In 1995 cDNA encoding signaling lymphocyte activation molecule (SLAM) was isolated from T cell cDNA library by expression cloning using mAb A12 [4]. The antigen recognized by both IPO-3 and A12 mAbs received cluster designation CDw150 (6th HLDA, 1996, Kobe, Japan) and CD150 (7th HLDA, 1997, Harrogate, GB) [5,6]. For these 30 years CD150 expression, molecular structure, signal transduction and functions were extensively studied in physiological conditions, immunodeficiencies and autoimmune disorders. It was shown that CD150 is actively involved in the regulation of innate and adaptive immunity, and in maintaining tissue microenvironment. It is also a bacterial sensor and a receptor for *Morbilliviruses*. However, our knowledge about CD150 engagement in malignancies of hematopoietic system is rather limited. This review is focused on CD150 expression, signaling properties and functions in hematological malignancies.

2. The pattern of CD150 expression in normal and malignant hematopoietic cells

Within T-cell lineage CD150 is expressed starting on immature $CD4^-CD8^-$ thymocytes and strongly increased on $CD4^+CD8^+$ thymocytes. The level of CD150 expression is drastically dropping on naïve T cells with subsequent upregulation on central memory and effector T cells [7,8]. Weak expression of CD150 is observed in natural killer cells (NKT) [9]. While CD150 is not present on the cell surface of monocytes, it is upregulated on activated cells of monocytes/macrophages lineage. At the same time, CD150 is detected in the cytoplasm of human monocytes and macrophages with preferential localization to early recycling compartments [10]. CD150 is also expressed at very low level on immature dendritic cells (DCs) with strong upregulation following maturation stimuli [7,11,12]. Moreover, in unstimulated DCs CD150 was found in the cytoplasm where it was colocalized with cis-Golgi marker GM-130 and lysosomal marker LAMP-1 [13]. Resting platelets express CD150 at low level that are not regulated by TRAP activation [14]. CD150 is scarcely expressed on basophils and bone marrow derived mast cells, while natural killer cells, neutrophils, eosinophils and erythrocytes are CD150 negative [7].

There is a noticeable heterogeneity in CD150 cell surface expression on the subpopulations of normal B cells. In ontogenesis early CD150 expression is detected on nearly half of B-cell progenitors in bone

* Corresponding author at: Department of Molecular and Cellular Pathobiology, R.E. Kavetsky Institute of Experimental Pathology, Oncology and Radiobiology of NAS of Ukraine, 45 Vasylkivska str., Kyiv 03022, Ukraine.
E-mail address: gordiienko@nas.gov.ua (I. Gordiienko).

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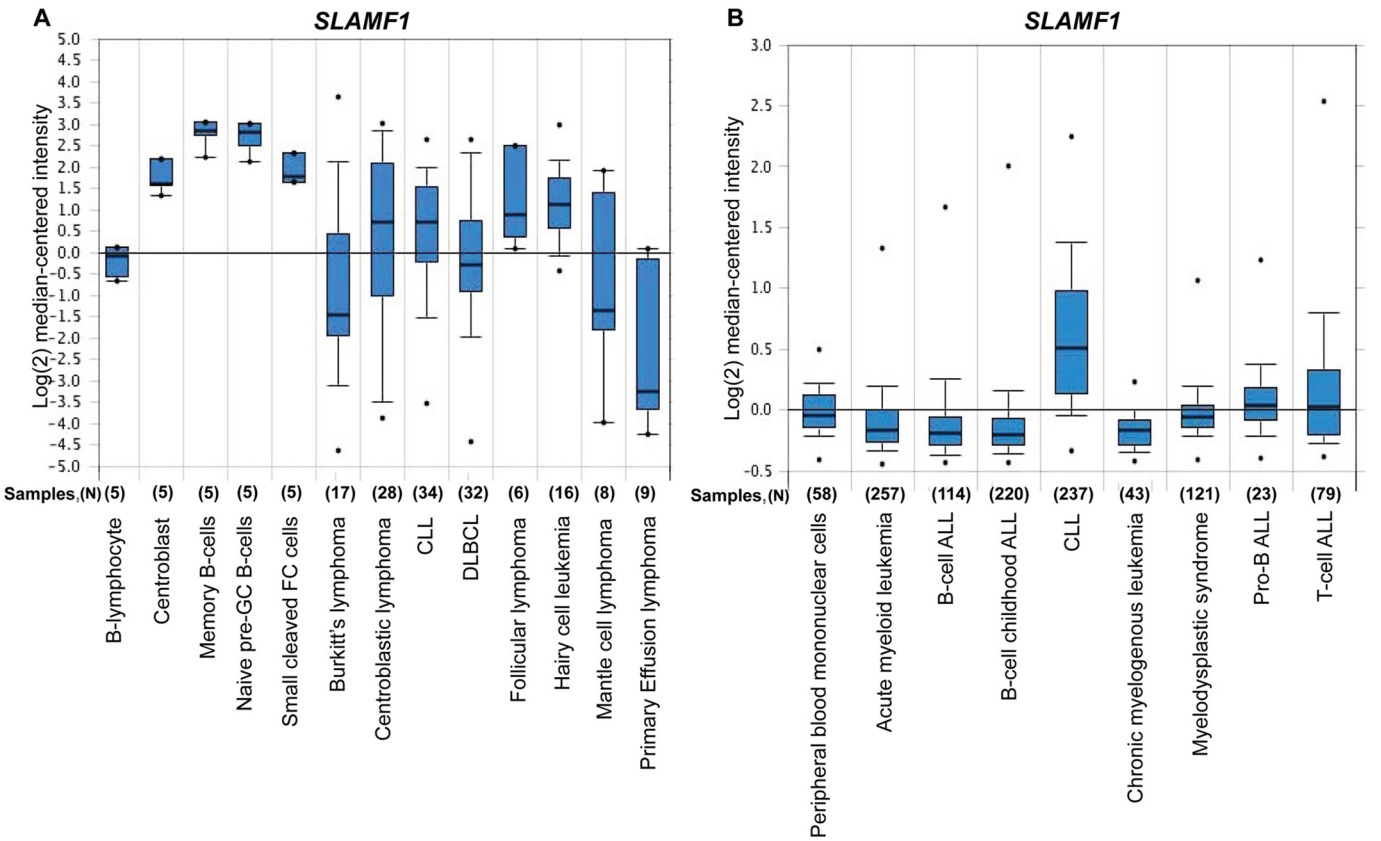

Fig. 1. The CD150 mRNA expression level in lymphomas and leukemias. (A) Downregulated CD150 mRNA expression level in different types of B-cell lymphomas and leukemia compared to normal B-cell subpopulations [110] (8603 measured genes; top 5%, p-value $1{\cdot}e^{-4}$). (B) CD150 is expressed at low level in leukemias with the exception of CLL (1152 measured genes; top 5%, p-value $1{\cdot}e^{-4}$) [111]. CD150 mRNA was assessed by microarray technology. Represented data were obtained from a publically available database Oncomine. This data base contains published data that have been collected, standardized, annotated and analysed by Compendia Bioscience (http://www.oncomine.com, May 2018, Termo Fisher Scientific, Ann-Arbor, MI, USA).

marrow (pro-B and pre-B cells) [15]. The cell surface CD150 expression is absent on immature B cells but is noticeable from the stage of naïve B cells, slightly downregulated on memory B cells followed by increasing toward plasma cells differentiation (Fig. 1A) [8,15–17]. The pattern of CD150 expression on cells within hematopoietic system is similar in human and mice with several exceptions. In contrast to humans, CD150 was found on mouse hematopoietic stem cells, megakaryocyte-biased bipotential progenitors and megakaryocyte precursors [18–20]. Nevertheless, human-induced pluripotent stem cells (hiPSCs) express CD150 and can be infected by measles virus [21].

According to the 2016 revisions to the World Health Organization classifications of tumors of hematopoietic and lymphoid tissues and of myeloid neoplasms and acute leukemia, the frequency of T cell malignancies is in minority. More prevalent are disorders of myeloid origin, and predominant are B cell leukemias and lymphomas [22,23]. This is linked to the complicated process of B cell differentiation involving rearrangement of immunoglobulin variable region genes at different check-points [24]. As a rule, leukemic cells retain key phenotypic features of their normal cell analogues. So, a wide CD150 expression range on leukemic/lymphoma cells could be expected. Surprisingly, only malignant T cells at cutaneous T-cell lymphoma (CTCL) and Sezary syndrome demonstrate substantially high CD150 cell surface expression [25]. There is no evidence for CD150 expression either on mRNA or protein level in other immature or mature T cell malignancies except of half cases of T-cell acute leukemia [2,3,7] (Fig. 1B). T cell lines also demonstrated similarly very limited profile of CD150 expression [2,3,7], while neoplasms of myeloid origin are CD150 negative (Fig. 1B). Meanwhile, cell line THP-1 that is derived from acute monocytic leukemia expressed CD150 on the cell surface of 40% of cells [10].

CD150 is ubiquitously expressed on normal lymphocytes of B cell lineage. However, numerous data indicate that the CD150 is rather aberrantly expressed on the surface of malignant B cells. Neoplastic B cells that reflect $CD150^+$ normal B cell counterparts do not always express CD150 on the cell surface. CD150 negative B-cell malignancies include pre-B acute lymphoblastic leukemia, small lymphocytic lymphoma, sporadic Burkitt lymphoma, germinal center subtype of diffuse large B-cell lymphoma (DLBCL), lymphoplasmacytic lymphoma, and primary cutaneous marginal zone B cell lymphoma [1,26–28]. In several types of B-cell malignancies CD150 cell surface expression level is much lower than that in developmentally related normal B-cell subsets (Fig. 1A). For example, primary mantle cell lymphoma has low CD150 expression level [26]. Despite the highest level of CD150 cell surface expression on normal plasma cells, primary multiple myeloma (MM) cases are characterized by weak CD150 expression level. Moreover, the number of $CD150^+$ neoplastic B cells dramatically decreases in relapse MM cases in comparison to newly diagnosed cases [29]. Chronic lymphocytic leukemia (CLL) B cells demonstrate heterogeneity in cell surface CD150 expression [30] while activated B-cell type of (ABC) DLBCL, hairy cell leukemia, follicular lymphoma are mainly CD150 positive [2]. In addition, Hodgkin's and Reed-Shternberg cells in Hodgkin's lymphoma (HL), which also are of B-cell origin, express CD150 both on the surface and cytoplasm [16]. These data obtained on primary neoplastic B cells correlate with studies on malignant B-cell lines in vitro where the CD150 protein expression was limited and not always correlates with CD150 mRNA level. While different levels of CD150 mRNA expression were detected in majority of cell lines of B cell origin (only pre-B cell line REH was negative), CD150 protein expression was found

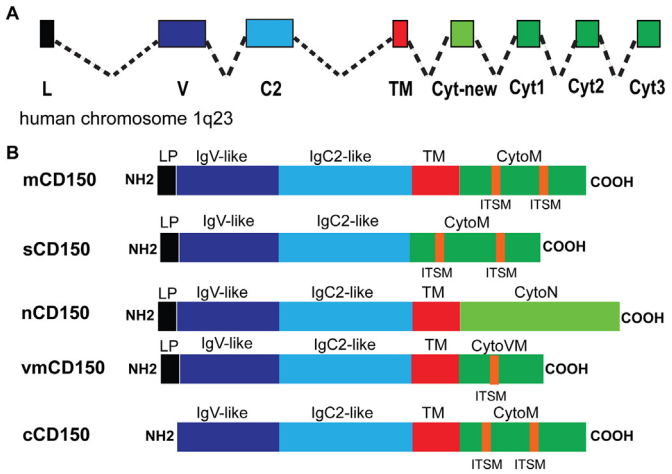

Fig. 2. Structure of *SLAMF1* gene and alternatively spliced CD150 isoforms. (A) Structural organization of human *SLAMF1* gene. It is located on human chromosome 1q23 forming a cluster in genomic segment of 359 bp together with genes of six other SLAM family members. Boxes show eight exons that encode human *SLAMF1* gene. L – exon of leader sequence; V – exon of Ig variable (V)-like extracellular domain; C2 – exon of Ig constant (C2)-like extracellular domain; TM – exon of transmembrane region; transcription from Cyt-new exon leads to shift in reading frame and generation of alternative cytoplasmic tail of CD150; Cyt1-3 – exons encode the canonical cytoplasmic tail. Dotted lines represent introns. (B) Structure of CD150 isoforms. mCD150 – a canonical transmembrane CD150 isoform with two immunoreceptor tyrosine-based switch motifs (ITSM) in cytoplasmic tail; sCD150 – secreted or soluble CD150 form without transmembrane region; nCD150 – novel CD150 isoform that has alternative cytoplasmic tail without ITSMs or any known signaling motifs. vmCD150 – variable membrane CD150 form has truncated cytoplasmic tail with one ITSM; cCD150 – cytoplasmic isoform without leader peptide. All described CD150 isoforms have the same extracellular part. Cytoplasmic tail with two ITSMs is common for mCD150, sCD150 and cCD150.

only in pre-B cell line BLIN-1, Burkitt's lymphoma cell lines BJAB and Raji, and also HL cell lines [31]. All these suggests that malignant B cells try to escape CD150 expression. This can be achieved by differential expression of distinct CD150 isoforms, which cannot be expressed on cell surface, but also may depend on regulation of CD150 expression.

3. Molecular framework of CD150

CD150 is a single chain type I transmembrane phosphoglycoprotein with molecular mass in range from 70 kDa to 95 kDa. The core protein of CD150 has molecular mass around 42 kDa [3,4]. The gene *SLAMF1* that encodes CD150 is localised at the genomic segment of human chromosome 1q23 and consists of eight exons that are separated by seven introns. First exon encodes leader peptide of CD150 protein, second – N-terminal variable (V) Ig-like domain, third – N-terminal constant (C2) domain, fourth – transmembrane domain and recently identified new exon (Cyt-new) followed by Cyt1-3 exons encode cytoplasmic part of CD150 (Fig. 2A) [32,33]. As a result of alternative splicing several structurally different CD150 isoforms are generated: canonical transmembrane CD150 isoform with two immunoreceptor tyrosine-based switch motifs (ITSM) in cytoplasmic tail (mCD150), secreted isoform without transmembrane region (sCD150), novel CD150 isoform (nCD150) with alternative cytoplasmic tail, variable membrane CD150 (vmCD150) isoform, which have truncated cytoplasmic tail, and cytoplasmic CD150 (cCD150) isoform lacking leader sequence (Fig. 2B) [4,33].

The mCD150 isoform possesses signaling properties due to presence of two ITSMs (TxYxxL/I) motifs in cytoplasmic tail that serve as docking sites for different SH2 containing molecules including tyrosine and/or serine/threonine kinases as well as tyrosine and inositol phosphatises [34,35]. All available data about CD150-mediated signaling and function in normal and malignant hematopoietic cells are concerning mCD150 isoform.

Secreted or soluble sCD150 isoform lacks 30 amino acids that encompass entire 22 amino acid transmembrane region [4]. Expression of sCD150 was detected at mRNA level in activated normal B and T cells, mature DCs, primary cases of classical HL, HL cell lines, B-lymphoblastoid cell lines as well as in blood serum of healthy individuals and patients with rheumatoid arthritis [4,36–38]. In CLL B cells expressed sCD150 mRNA on significantly higher level than normal peripheral blood $CD19^+/CD19^+CD5^+$ B cells. CD150 was detected in culture supernatant of CLL B cells independently of cell surface CD150 expression and in blood serum of CLL patients and healthy donors [39]. Recombinant sCD150 induce B cells proliferation only at high concentration around 20 μg/ml that is far from physiological [36]. So, whether sCD150 may act as natural ligand for transmembrane CD150 in tissue microenvironment is still a controversial question.

Recently a novel CD150 isoform (nCD150) was found in tumors of central nervous system (CNS). Transcription from Cyt-new exon leads to shift in reading frame and formation of nCD150 isoform with 94 aa cytoplasmic tail lacking classical ITSMs or any another known signaling motifs [33].Besides tumors of CNS nCD150 expression at mRNA level was detected in subpopulation of human tonsillar B cells, normal T cells ($CD3^+$), primary DCs, macrophages from peripheral blood, B-lymphoblastoid cell lines, Burkitt's lymphoma cell lines, pre-B acute lymphoblastic leukemia cell lines, HL cell lines, cells of human acute monocytic leukemia cell line THP-1 and MM, primary cases of CLL. It should be noted that nCD150 isoform is predominant in CNS tumors in contrast to normal and malignant B cells where mCD150 is prevailed [31,33,39].

Taken together, the presence of several structurally different CD150 isoforms and their differential expression in normal and malignant hematopoietic cells may underline functional diversity of CD150.

4. CD150 signaling properties and functions in hematopoietic cells

CD150 on the surface of hematopoietic cells is linked to different signaling pathways depending on cell type, their stage of differentiation, CD150 ligands, combinations of signals from other receptors, and also availability of key components of signaling network.

Similarly, to other member of SLAM family, with the exception of receptor-ligand pair CD48 (SLAMF2) and CD244/2B4 (SLAMF4), CD150 is a self-ligand receptor. Low affinity ($Kd \geq 200$ μM) self-association is mediated by the N-terminal IgV-like domain, which enables head-to-head contact between two monomers [40–42]. The binding avidity may increase due to the redistribution or clustering after cell activation mediated by other receptor–ligand interactions [40,43]. CD150 is localised to ceramide enriched lipid rafts in T cells, DCs and malignant CLL B cells [13,39,44].

CD150 was found to be the major receptor for several *Morbilliviruses*, in particular measles virus (MV) [45]. In case of MV the role of attachment protein is played by hemagglutinin, which directly binds the IgV-like domain of cellular receptor, mediating virus entry into the cell [46,47]. It should be noted that the human CD150 serves as a cellular receptor for wild type as well as vaccine strains of MV [45]. These findings gave a boost for development new approaches in MV oncolytic therapy [48]. CD150 is not only a self-ligand and a receptor for Morbilliviruses, but also a bacterial sensor in the elimination of Gram-negative bacteria [41,49,50].

Mostly due to the presence of paired ITSM motifs in CD150 tail, it serves as a signaling receptor. ITSMs are docking sites for SH2-containing molecules like adaptor proteins, protein tyrosine kinases, as well as protein tyrosine and inositol phosphatases. CD150 was shown to interact with several components of signaling machinery that directly or indirectly link this receptor to different signaling pathways. Since mouse monoclonal antibodies IPO-3 and A12 against human CD150

block CD150 self-self interaction or MV hemagglutinin binding [40,45] these antibodies are used in the model systems for signaling and functional studies.

In human T cells CD150 via its ITSMs directly binds SH2-containing molecules: adaptor protein SAP/SH2D1A, protein tyrosine phosphatases SHP1 and SHP-2, and also inositol phosphatase SHIP [51,52]. SAP/SH2D1A SH2-domain has strong affinity to tyrosine phosphorylated ITSMs, and even is able to bind non-phosphorylated membrane-proximal ITSM in CD150. Due to high degree of structural homology of SH2-domains, SAP/SH2D1A blocks binding to phosphorylated ITSMs tyrosine-phosphatases SHP-1 and SHP-2, which are negative regulators of T cell functions [51,53]. SAP SH2 domain has a second binding surface that interacts directly with the SH3 domain of T-cell specific Src-kinase FynT in its active configuration and does not involve canonical SH3 or SH2 binding interactions. This way SAP promotes CD150 tyrosine phosphorylation [53–55] and the recruitment of downstream signaling intermediates. In addition, SAP was shown to interact in T cells with Dok1 adaptor protein [56]. In mouse thymocytes and model cell lines SAP is linked to adaptor proteins Dok1, Dok2 and Shc, inositol phosphatase SHIP, and the Ras-GTPase-activating protein RasGAP [52]. SAP also interacts with PKCθ in mouse T cells. This constitutive SAP-PKCθ association is Fyn independent. Moreover, CD150 engagement increases TCR-induced PKCθ recruitment to the site of T cell stimulation [57]. As PKCθ is detected as a part of the CD150-SAP complex following TCR ligation, CD150 engagement facilitates PKCθ and Bcl-10 recruitment, NF-κB1 activation, and IL-4 production via a ternary CD150-SAP–PKCθ complex [57–59]. In mouse $CD4^+$ T cells CD150 ligation with antibodies induce Akt phosphorylation that presumably leads to activation of Akt pathway [60]. These CD150-mediated signal transduction pathways are involved in regulation of several T cell functions, including IL-4, IL-13 and INF-γ production, TCR-independent proliferation of previously activated human $CD4^+$ T cells and human Th1 clones, cytotoxic activity of $CD8^+$ T cells, T cell-mediated help for germinal center formation [4,44,58,61–63]. At the same time, CD150 associated molecules, signal transduction pathways and their functions in malignant T cells were not reported.

Direct and indirect evidence suggests that in mouse NKT cells CD150 is linked with SAP and Fyn. CD150-SAP-Fyn pathway is involved in promotion of positive selection and proliferation, and/or prevention of negative selection of immature NKT cells [42,64,65]. Information about CD150 expression in NKT-derived neoplasms is not available.

In normal human B cells adaptor protein SAP is found only in minor subpopulation of germinal center B cells, however it is expressed in Epstein-Barr virus (EBV)-transformed B-lymphoblastoid cell lines, Burkitt's and Hodgkin's lymphoma cell lines, tumor cells in primary diffuse large B cell lymphoma and Hodgkin's disease [27,34,66–68]. In human B cells CD150 via ITSMs directly binds SH2-containing proteins SAP, SHP-2, SHIP, and regulatory subunit of PI3-kinase [34,66,69]. CD150 cytoplasmic domain also directly binds serine/threonine kinase HPK1 in phospho-tyrosine independent manner [16]. In addition, it coprecipitates with receptor tyrosine phosphatase CD45 and Srk-family kinases Lyn and Fgr, moreover, Lyn uses ITSMs in CD150 cytoplasmic tail as substrates [27,66]. These molecules may connect CD150 with Akt-mTOR axis and also SAP-independent MAPK pathways (ERK1/2, p38 MAPK and JNK1/2) in normal B lymphocytes and in malignant cells of B cell origin [16,27,39,66,69]. In the model of DT40 chicken knockout cell sublines transfected with SAP and/or CD150, CD150-mediated Akt phosphorylation requires Syk and SAP, is negatively regulated by Lyn and Btk, but is SHIP independent. However, in B cells CD150-induced ERK phosphorylation requires SHIP and Syk but not SH2D1A [27]. In addition, in CLL malignant B cells CD150 directly binds beclin-1, Vsp34 and UVRAG that are involved in autophagosome generation [30]. These signaling events support several CD150 functional properties in B cells, for example augmentation of proliferation induced by CD40 mAb and IL-4, induction of proliferation and Ig synthesis by activated B cells [35,36]. On the other hand, CD150-induced signals can synergize with CD95-mediated apoptosis [66].

In mouse and human macrophages CD150 is linked to elimination of Gram-negative bacteria [10,49]. In mouse macrophages CD150 is expressed on the cell surface and is functioning as a bacterial sensor, recognizing outer membrane proteins of Gram-negative bacteria OmpC and OmpF [49,50]. Coupled with bacteria, CD150 undergoes internalization into the developing phagosomes where its cytoplasmic tail serves as a platform for association with Beclin-1/Vps34/UVRAG protein complex. Active Beclin-1/Vps34/UVRAG enzyme complex mediates generation of phosphatidylinositol-3-phosphate which in turn recruits EEA-1 for phagosome maturation and is essential for NOX2 activation followed by reactive oxygen species production [49,50,70]. Recruitment of Beclin-1/Vps34/UVRAG complex to CD150 is independent of SLAM adapter EAT2a/b or ITSM signaling motifs [70]. Thus, CD150 is required for Gram-negative bacteria killing in mouse macrophages by regulation of phagosomes maturation and ROS generation.

In human macrophages CD150 is expressed prevalently in cytoplasmic compartments and its interaction with outer bacterial membrane is not sufficient to elicit CD150-mediated effect in eliminating Gram-negative bacteria. CD150 enhances TLR4 signaling by recruitment of TRAM adapter in Rab11-dependent manner from early recycling compartments to *E. coli* containing phagosomes. TRAM delivery to phagosomes is crucial for TLR4-TRAM-TRIF complex formation that induces IRF3-mediated INF-β expression [10]. Our knowledge about CD150 associated molecules, signaling and function in malignant cells is limited only to THP-1 cell line derived from acute monocytic leukemia. These mechanisms are the same as in primary normal macrophages [10].

In DCs, CD150 ligation with different ligands exert opposite effects. Stimulation with anti-CD150 antibodies results in activation of inflammatory and adaptive T cell responses due to the increase of IL-12 and IL-8 production but has no effect on the production of IL-10 [11]. At the same time, CD150 self-ligation mediates inhibition of IL-12, TNF-α and IL-6 production by DCs, leading to the inhibition of naïve $CD4^+$ T cell differentiation toward Th1 phenotype [12]. However, little is known about CD150 downstream intermediates in DC. Since CD150 ligation on DC with hemagglutinin of wild type MV on the membrane of transfected CHO cells stimulate Akt and inhibit p38 MAPK phosphorylation, without concomitant ERK1/2 activation, it can be assumed that Akt and MAPK pathways are involved in CD150 signal transduction in DC [71]. There is no evidence of CD150 expression in DC neoplasms.

5. Regulation of CD150 expression

CD150 could be considered as a phenotypical marker of activated T cells, B cells, monocytes and DCs. It expression is strongly upregulated in T cells activated via CD3, CD28 and PHA [3,4,7]. LPS stimulation of primary macrophages causes an increase of cell surface CD150 expression level up to 50%. Moreover, different types of TLRs are positive regulators of CD150 expression since usage of various TLR agonists such as Pam3Cys (TLR1/2), FSL-1 (TLR2/6), R848 (TLR7 and -8), CL075 (TLR8) and *E. coli* efficiently elevates CD150 mRNA expression level in monocytes and macrophages [10]. Cell surface CD150 expression is upregulated on DCs upon numerous maturation stimuli (CD40L, Poly(I:C), LPS, IL-1β), but is not altered by TNF-α, IL-12, IL-18 or different types of lypoproteins (OspA, Tp47) [11,37]. Ligation of pattern recognition receptor DC-SIGN by antibody, mannan or MV on DCs promotes sphingomyelinases activation with following ceramide generation and CD150 translocation from intracellular compartments to ceramide enriched regions in plasma membrane [13]. The strongest positive regulators of CD150 expression on B cells are CD180, CD40, CD20, BCR, whereas PMA and IL-4 are less effective [3,7]. Epstein-Barr virus infection of B cells leads to elevation of CD150 expression through EBV-encoded proteins EBNA-2 and LMP1 [72,73]. A copy number gain

at 1q23.3 resulting in strong CD150 overexpression is observed in 30.8% of EBV positive DLBCLs case [74]. Moreover, cells with high level of CD150 and LMP1 expression from EBV positive DLBCL derived cell line Farage are characterized by increased resistance to CHOP therapy compared to $CD150^{low}$ cells [75].

LMP1-, CD40-, IL-1β- and TLRs-mediated upregulation of CD150 expression is probably effected by regulation of NF-kB or AP1 transcription factors [73]. Despite the absence of classical TATA-box region in *SLAMF1* promoter it has several binding sites for transcription factors such as SP1, STAT6, IRF4, EBF1, NF-kB, ELF1, TCF3, and PU.1 [76]. The EBF1 is the key regulator of *SLAMF1* promoter activity in mice and human B cells that affect dimethylation of H3K4 leading to the "open" state of chromatin [76,77]. In distinct cellular types at different stages of differentiation various combinations of transcription factors are involved in CD150 gene regulation.

The data about regulation of CD150 expression in malignant hematopoietic cells are limited. However, it is clear that signaling networks are deregulated in malignant cells. That is why signals mediated via cell surface receptors not always have similar effects in normal and malignant cells. CD180 receptor, but not CD40 or BCR could be involved in regulation of CD150 expression in CLL B cells. Ligation of CD180 on CLL B cells leads to increase of CD150 mRNA level that could be explained by CD180-mediated upregulation of EBF1 expression [78]. From the other hand, it was shown that CD40-CD40L interaction alone or together with leukotriene B_4 activates CLL B cells and results in an augmented CD150 cell surface expression [79].

Translation efficiency may depend on various *cis*-elements in 5′-UTR of mRNA that include secondary structure, protein binding sites, non-AUG initiation codons, upstream open reading frame (uORF) etc. [80]. The uORF is sequences franked by stop and start codons and localised upstream of the main ORF. It was shown the number of uORFs in 5′UTR of mRNA negatively correlates with protein expression level since uORFs inhibit translation initiation from the main ORF and trigger mRNA degradation [81]. At least two CD150 isoform based on the structure and length of 5′-UTR were identified in B-lymphoblastoid (MP-1) and Burkitt lymphoma (Raji) cell lines. The long isoform of CD150 mRNA has 5′UTR of 349 nt in length with four uORFs that is characterized by 5–6 fold decrease of its translation activity, in comparison to CD150 mRNA short isoform without uORF in 5′UTR [82]. These may suggest that regulation of CD150 expression is independent of cell stress or activation and take place at the transcriptional level. At the same time, to avoid CD150 protein synthesis malignant cells could use switching the transcription to the CD150 isoforms with long 5′UTR.

In summary, CD150 expression is regulated via numerous cell-type specific extracellular stimuli that lead to activation of key transcription factors essential for *SLAMF1* promoter activity. Data analysis indicates that malignant hematopoietic cells, especially B cells, have down-regulated CD150 mRNA and protein expression compared to normal cell analogues. Malignant cells may use several ways to decrease or avoid CD150 expression: inactivation of signaling pathway important for CD150 upregulation; low or absent expression level of key transcription factors that regulate *SLAMF1* promoter activity; differential expression of structurally distinct CD150 isoforms; switching transcription from CD150 isoform with short 5′UTR to long CD150 isoform; potential overexpression of miRNA that target CD150; retaining CD150 protein in cytoplasmic compartments of malignant cells.

In line with this evidence the main question arises: what is the role of CD150 in pathogenesis of hematologic malignancies?

6. CD150 is a candidate for therapeutic intervention in leukemias and lymphomas

In the 1970s the first case reports demonstrated leukemia, Hodgkin's and Burkitt's lymphoma remissions or even eradications after measles virus (MV) infection or vaccination [83–86]. At that time MV receptors were not identified yet, but now it is clear that the main target for MV on leukemia and lymphoma cells is CD150 receptor. Dramatic improvements that were reported in these patients after measles infection are due to viral oncolysis and/or virus-induced anti-tumor immune responses. This is supported by experiments in cell lines and animal models to treat various types of cancer such as human B-cell lymphoma [73,87], MM, ovarian cancer, and glioma xenografts [25,48]. The assumption that CD150 may be a direct target for MV oncolysys is reinforced by the ability of MV to induce anti-neoplastic activity causing tumor regression in $CD150^+$ CTCL patients [88], and lysis of $CD150^+$ CTCL cell lines [25]. Moreover, CD150-dependent MV entry mediates sustained efficient viral spread in mantle cell lymphoma patients followed by tumor regression and prolonged survival of patients after radiovirotherapy [89]. There are a number of reports showing the regression of Hodgkin's lymphoma after measles or measles vaccine treatment [90,91].

The hallmarks of HL are mononuclear Hodgkin's cells and multinuclear Reed-Sternberg (HRS) cells, which usually account for only about 1–2% of cells in the tumor tissue. The 95% of all HL belong to the classical type of HL [23]. Using wide arsenal of cell surface receptors and cytokines these tumor cells create a favorable microenvironment that supports tumor cell survival and mediates immunosuppression [92–94]. HRS cells in up to 40% of HL cases are EBV positive with type II infection pattern and express LMP-1 protein that is linked to CD150 upregulation [94]. On the other hand, tumor necrosis factor (TNF) receptor family receptors, such as CD30, CD40, CD95, TACI, BCMA, and RANK on the surface of HRS are acceptors of signals from tumor microenvironment that initiate different signaling pathways in tumor cells and regulate their phenotype. For example, MEK/ERK and PI3 kinase/Akt pathways are aberrantly active in Hodgkin disease. The canonical and noncanonical NF-kB and JAK/STAT signaling pathways are also activated in HL due to inactivation of the negative regulators and amplifications of positive regulators or components of these signaling pathways [92,93,95].

HRS cells attract various types of immune system cells into lymphoma tissue forming a results in typical inflammatory microenvironment. HRS cells escape immunological surveillance using different strategies, including secretion of soluble factors (for example, IL-10, galectin-1, transforming growth factor β1) that inhibit the activation or kill cytotoxic T lymphocytes and/or professional antigen-presenting cells, and recruitment of Tregs and myeloid-derived suppressor cells into the microenvironment. Moreover, HRS cells expressing the PD-1 ligands enhance PD-1 signaling in immune effectors that attenuates or shuts down of TCR-associated downstream pathways including PI3K/AKT and MEK/ERK axises and downregulates cytokine production by tumor-infiltrating immune cells [92,93,96].

HRS cells in primary tumors and cell lines express high level of CD150 both on the cell surface and cytoplasm [16,27,68]. It is represented mainly by mCD150 isoform with signaling properties and also by the secreted sCD150 isoform, which can account for cytoplasmic CD150 expression [31]. Indeed, similarly to normal B cells, CD150 ligation on HL cell lines results in Akt phosphorylation that leads to subsequent phosphorylation its downstream targets: transcription factor FOXO1 and GSK-3β kinase [69]. In HL cell lines CD150 receptor is also linked to MAPK kinase pathways. Contrary to normal B cells, CD150 ligation attenuates ERK1/2 and p38 MAPK phosphorylation. At the same time signaling via CD150 could play an important role in maintaining JNK activation in HRS cells as CD150 ligation was shown to induce prolonged JNK activation in all studied HL cell lines [16]. How signals via CD150 can be initiated in primary HRS cells? CD150 was shown to be a homophilic receptor. In HL tumors CD150 is expressed as transmembrane form on HRS cells and different cellular components of tumor microenvironment. Moreover, secreted soluble sCD150 isoform is also present in tissue matrix, surrounding CD150-expressing cells [95]. Both transmembrane mCD150 receptor and sCD150 may bind CD150 on HRS cells and cells in tumor microenvironment. The consequences of CD150 self-binding in vivo depend

on whether CD150 is either ligated or blocked. Thus, CD150 could target HRS cells as well as T cells (especially Treg and Tc), B cells, plasma cells, and macrophages surrounding HRS.

Biological consequences (outcome) of CD150-mediated signaling events in HRS cells and $CD150^+$ immune cells in HL microenvironment are not clarified yet. However, in vitro studies demonstrated inhibition of proliferation and even cell death of HL cell lines in response to CD150 ligation with antibodies that is not dependent on JNK1/2 activity [16]. Thus, CD150 can be regarded as one of the receptors that are involved in regulation of tumor cell maintenance in low-rate proliferating Hodgkin's lymphoma.

CLL is the unique native model for studying CD150 function in malignant B cells since about half of CLL cases expressed CD150 on the cell surface of malignant B cells. Drawing parallels between the phenotype features and biological properties of $CD150^-$ and $CD150^+$ CLL B cells will help to understand the role of CD150 in CLL pathogenesis. In structure of hematological malignancies CLL is one of the most common form of neoplasms [23]. It is a disease of mature B cells with unique phenotype profile ($CD5^+$, $CD19^+$, $CD23^+$) that are accumulated in peripheral blood, bone marrow and second lymphoid organs [97,98]. Significant molecular heterogeneity of malignant B cells underlies variable clinical courses of CLL patients. Around 20–30% of CLL patients have aggressive form of the disease that requires immediate treatment. The rest of the patients are characterized by stable disease course for many years without intervention [98,99]. However, there is a possibility of indolent CLL transformation into aggressive form or DLBCL (Richter syndrome) [100]. Numerous clinical and molecular markers allow prediction of clinical outcome for CLL patients. BCR mutational status is one of the strongest predictors of disease outcome with unmutated immunoglobulin heavy chain variable region genes (*IGHV*) in CLL cases having a poorer prognosis [101]. At the same time, markers that are associated with progression of indolent CLL are still not identified. Differentially expressed cell surface receptors on CLL B cells are an attractive area for searching potential prognosticators because of at least two reasons. Firstly, evaluation of cell surface receptors expression is cheaper in laboratory diagnostics compared to assessment of genetic lesions or mutational status of *IGHV*. Secondly, studying functions of cell surface receptors with signaling properties will open new insights into understanding CLL molecular heterogeneity and may help to find a perspective targets for therapeutic applications.

There are several lines of evidence that CD150 could be considered a potential surrogate prognostic marker of favorable CLL outcome. CLL B cells with mutated *IGHV* are characterized by significantly higher CD150 mRNA and cell surface expression levels compared to CLL B cells with unmutated *IGHV* [30,102,103]. Treatment-free survival for CLL patients with > 6.0% of CD150 positive B cells is 5 year longer versus CD150 negative CLL patients. Similarly, 10 years rate survival reached 94.7% in $CD150^+$ compared to 77.5% in $CD150^-$ CLL cases [30]. What is the biological significance of CD150 expression on CLL B cells?

CD150 as costimulatory and adhesion molecule could affect CLL pathobiology by regulating biological properties of CLL B cells and local tumor microenvironment. Silencing of *SLAMF1* in CLL derived cell line Mec-1 caused changes in expression of numerous genes that are linked to processes of vesicle trafficking, endocytosis, apoptosis/cell death, immune response, adhesion, and motility [30]. Analysis of primary CLL B cells revealed differences in phenotype profile of $CD150^+$ and $CD150^-$ B cells. $CD150^+$ CLL B cells demonstrate elevated expression levels of cell surface markers CD95, CD180, CD20, CD22, CD62L, chemokine receptor CXCR3 and its ligand CXCL10 in comparison to $CD150^-$ CLL B cells [30,39]. In contrast, $CD150^-$ CLL B cells are characterized by upregulated markers that are associated with aggressive CLL outcome: CD38, CD49d, CD44, CXCR4 and CXCL12 (Fig. 3) [30].

CD150-mediated signaling in CLL B cells could partially explain favorable outcome in $CD150^+$ CLL patients. Since canonical transmembrane mCD150 isoform is predominant in CLL B cells, CD150 ligation promotes Akt and MAPK signaling pathways activation [39]. The Akt signaling pathway is engaged in maintain malignant cell survival and proliferation so CD150-mediated Akt activation is in disagreement with favorable CLL outcome. As coreceptor molecule CD150 in CLL B cells can function alone or in cooperation with others cell surface receptors. Among them is CD180 that also is associated with mutational *IGHV* status and is involved in Akt and MAPK kinases activation [104–106]. CD180 is coexpressed and colocalized with CD150 on the cell surface membrane in around 60% of CLL cases. Recent studies revealed cytoplasmic expression of CD150 and CD180 in the rest of cell surface double negative $CD150^-CD180^-$ CLL cases [39]. It is important to note that ligation of CD150 and CD180 together on CLL B cells blocks Akt kinase phosphorylation with more profound effect on inactivation of mTOR-p70S6K-RPS6/4E-BP1 signaling axis than on Akt-GSK3β/FOXO1/3a pathways (Fig. 3). In addition, CD150 + CD180-mediated cross-talk between Akt and ERK1/2-RSK pathways in targeting mTORC1 may also silence translational events. Given that Akt-mTORC1- signaling axis is a key regulator of mRNA translation, simultaneous crosslinking of CD150 and CD180 could reduce protein synthesis in malignant B cells and this way attenuates CLL B cells propagation [39]. Both CD150 and CD180 are also involved in regulation of transctiption factors expression in CLL B cells. Mediated by CD150 + CD180 PU.1 upregulation may underpin the elevated CD20 level in $CD150^+$ CLL B cells, which is very important for CD20-directed therapy (Fig. 3). On the other hand, downregulation of IRF4 after CD150 + CD180 ligation also could affect transcriptional programs in CLL B cells [78]. It appears that cell surface expression of CD150 and CD180 is not profitable for CLL B cells. This is supported by CD150 and CD180 differential expression on CLLs B cells with significantly decreased level compared to normal B-cell analogues. One of the scenarios for CLL B cells is to avoid cell surface expression of CD150 and CD180 by retaining these receptors in cytoplasmic compartments.

Connection of cell surface CD150 expression with favorable CLL outcome could be also explained by its involvement in autophagy regulation. CD150 ligation on CLL B cells leads to ROS generation by NOX2 complex and JNK1/2 pathway activation followed by BCL2 phosphorylation and Beclin1 dissociation that are essential for autophagosome formation (Fig. 3). Thus, CD150 induces autophagic flux in primary CLL cells and links to drug-initiated autophagic response that makes $CD150^+$ cells more sensitive to therapeutic agents like fludarabine or new BH3 mimetic ABT-737 [30]. Interestingly, the level of JNK1/2 phosphorylation does not significantly change after simultaneous CD150 and CD180 crosslinking indicating that authophagosome formation may not be affected under such conditions [39]. Decrease of chemokine receptor CXCR4 expression level in $CD150^+$ CLL B cells results in reduced chemotaxis of malignant B cells toward SDF-1 enriched regions like bone marrow or lymph nodes with a profitable conditions for malignant B cells survival and proliferation [30]. Expression and signaling properties of CD150 in CLL B cells are summarized in Fig. 3.

CLL progression is strongly dependent on combination of extracellular signals, which malignant B cells obtain in local tissue microenvironments [107–109]. It is clear that CD150 is an active player in CLL B cells signaling networks. $CD150^+$ CLL B cells are less aggressive than malignant B cells in $CD150^-$ CLL cases, probably due to reduced level of protein synthesis, migratory activities to second lymphoid organs and bone marrow, increased sensitivity to therapeutic drugs. All these facts let us to hypothesize that CD150 in CLL B cells could function as potential tumor suppressor. CD150 may be activated in vivo via several ways: (i) self-ligation on the cell surface of malignant B cells; (ii) elevating the level of sCD150 in CLL B cells may act as a factor of constitutive CD150 activation; (iii) common in CLL microbial and autoantigens create platforms for CD150 activation similar to a pattern recognizing receptors. At the same time, many aspects concerning CD150 signaling are open and need further investigation. Taking into consideration CD150-mediated signaling and association of high cell

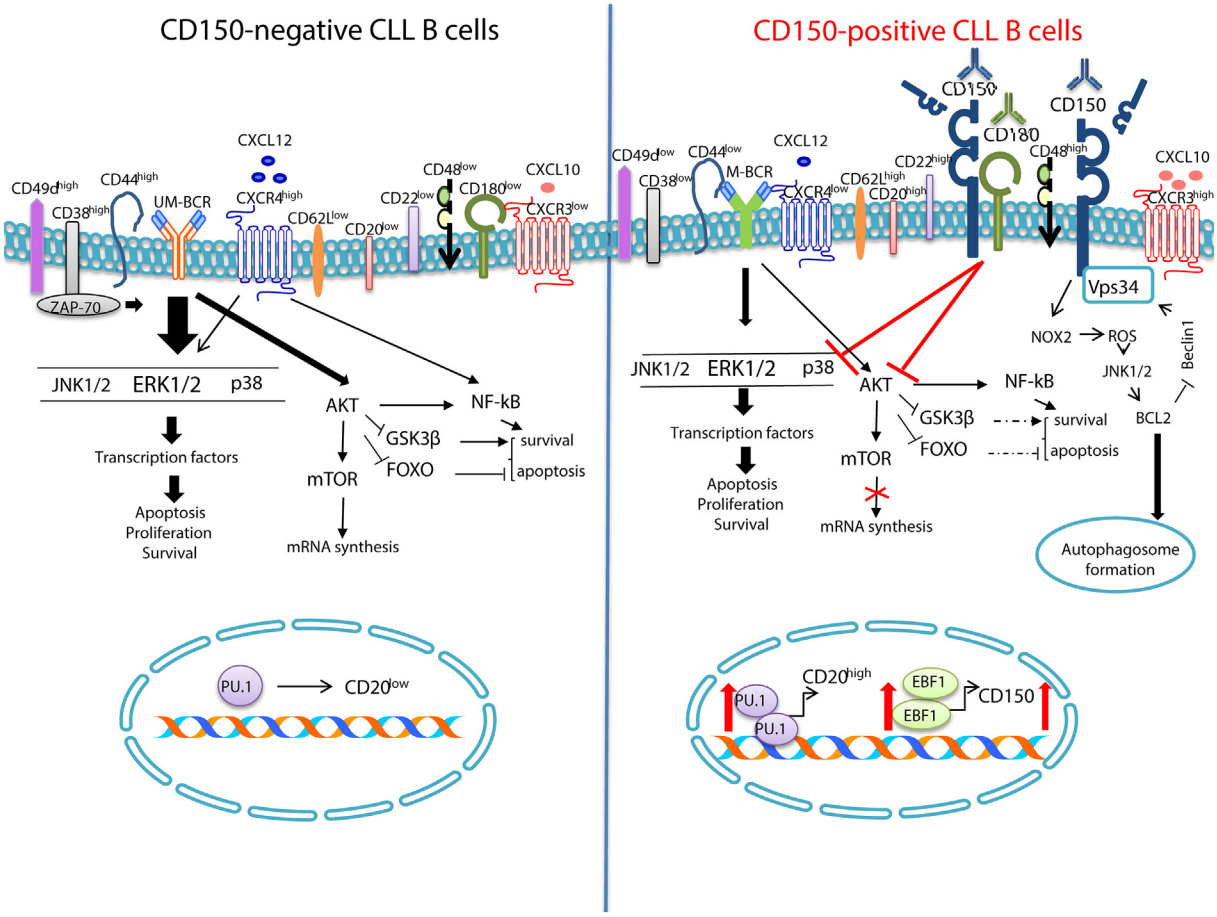

Fig. 3. Signaling pathways in CD150-negative and CD150-positive chronic lymphocytic leukemia B cells. Elevated level of CXCR4 in CD150-negative CLL B cells lead to more active malignant B cells migration toward supportive microenvironments of secondary lymphoid organs and bone marrow. High CD38, CD49d, CD44 expression levels enhance BCR-mediated signaling that results in aggressive behaviour of CD150-negative CLL B cells. Ligation of CD150 alone activates pro-survival Akt and MAPK signaling pathways in CLL B cells. When CD150 and CD180 are coexpressed, simultaneous ligation mutually inhibits Akt and MAPK signaling pathways leading to attenuation of protein synthesis in malignant B cells. By upregulation of EBF1 transcription factor CD180 positively regulates CD150 expression. CD180 or/and CD150 contribute to high PU.1 expression level in CD150^{+} CLL B cells that may result in upregulation of CD20 expression. CD150 ligation on CLL B cells leads to autophagosome formation that makes CD150-positive malignant B cells more sensitive to autophagy-inducing drugs e.g. fludarabine.

surface CD150 expression level on CLL B cells with more favorable outcome in CLL patients finding ways to upregulate cell surface CD150 expression in CLL B cells is a perspective direction that will allow modulating biological properties of malignant B cells.

7. Conclusions and perspectives

In hematopoietic malignancies CD150 cell surface expression is restricted to cutaneous T-cell lymphomas, few types of B-cell non-Hodgkin's lymphoma, and near half of the cases of CLL, HL, and MM. On the surface of malignant cells this receptor may serve as a target for MV-mediated oncolysis and, presumably, for antibody-based therapy. On the other hand, CD150 is an active player in pathogenesis of HL and CLL because of its involvement in the regulation of tumor cell biology and maintaining tumor microenvironment. This makes it an attractive candidate for new approaches in malignant cell fate modulation in HL and CLL.

Our knowledge about CD150 expression and functions outside hematopoietic system is very limited. Protein and mRNA CD150 expression was found in > 70% tumors of CNS, including glioblastoma, astrocytoma, ependymoma and others [33]. Earlier immuhistochemical studies revealed CD150 in squamous cell carcinomas of uterine cervix, esophagus, rectum and oral cavity [26]. However, the normal analogues do not express CD150. Broadening the studies of CD150 expression and function in tumor of different histogenesis will open new perspectives for differential diagnostics and improvement of therapeutic strategy.

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Declaration of interest

none.

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