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Review Article

SLAMF receptors on normal and malignant B cells

Idit Shachar*, Avital Barak, Hadas Lewinsky, Lital Sever, Lihi Radomir

Department of Immunology, Weizmann Institute of Science, Israel

ABSTRACT

The Signaling Lymphocyte Activation Molecule family (SLAMF) is a collection of nine surface receptors expressed mainly on hematopoietic cells, and was found to modulate the behavior of immune cells. SLAMF receptors are expressed on B cells in health and disease. Each SLAM receptor has a unique differential expression pattern during the development and activation of B cells. Furthermore, recent findings have revealed a principal role for this family of receptors in B cell malignancies, emphasizing their importance in the control of malignant cell survival, cell to cell communication within the tumor microenvironment, retention in the supporting niches and regulation of T cell anti-tumor response. This review summarizes the latest studies regarding SLAMF expression and behavior in B cells and in B cell pathologies, and discusses the therapeutic potential of these receptors.

1. SLAM receptors

Adaptive and innate immune responses are orchestrated by dynamic interactions between cell-surface molecules and their respective ligands, including antigen receptors, cytokine and chemokine receptors, and co-stimulatory molecules. The Signaling Lymphocyte Activation Molecule (SLAM) family is a collection of nine surface receptors expressed mainly on hematopoietic cells, that modulate the behavior of immune cells. While most SLAMF receptors are homophilic, SLAMF2 and SLAMF4 serve as ligands for each other [1]. SLAMF receptors have been shown to function as co-stimulatory molecules and to regulate the activation and differentiation of a wide array of immune cell types involved in both innate and adaptive immune responses [1–3]. Receptors of the SLAM family share a common ectodomain organization: a membrane-proximal immunoglobulin (Ig)-like constant domain, and a membrane-distal Ig variable domain responsible for ligand recognition. Six SLAMF receptors (SLAMF1, SLAMF3, SLAMF4, SLAMF5, SLAMF6, and SLAMF7) carry one or more copies of an immunoreceptor tyrosine-based switch motif (ITSM) in their cytoplasmic tails, while SLAMF8 and SLAMF9 lack most of their cytosolic tail region [1]. SLAMF8 (BLAME) and SLAMF9 (CD84H) genes are located outside of the SLAM locus and their ligands are still unknown and contain a relatively shorter cytoplasmic tail and do not include the tyrosine based switch motif [4–6].

SLAMF receptors interact with intracellular SLAM-associated protein (SAP)-related molecules, a group of SH2-domain containing adaptor proteins that link SLAM receptors to downstream intracellular signaling pathways. In T, NK and NKT cells, SLAMF receptors interact with SAP; in contrast, in mature B cells, SLAMF receptors induce a downstream cascade through the SAP homologue, Ewing's sarcoma-associated transcript-2 (EAT2) [7–9]. The rodent genome also encodes an EAT2-related transducer (*Ert*) [10,11]; however, in humans, *ERT* has evolved into a non-functional pseudo-gene.

Monocytes, macrophages, T cells, NK and NKT cells have been the focus of the majority of studies on SLAMF receptors [1,12]. However, in recent years the role of SLAMFs in regulation of B cell signaling both in health and disease has been elucidated. In this review, we aim to summarize the latest studies describing SLAMF expression and behavior in B cells and in B cell pathologies.

2. The SLAM family of receptors in healthy B cells

SLAMF receptors are expressed on B cells. Each SLAM receptor has a unique differential expression pattern during the development and activation of B cells (Table 1), as was demonstrated in human and murine B cells by Da Salort et al. [13]. These unique expression patterns suggest an important role for SLAMF receptors in regulation of differentiation and function of B cells.

2.1. SLAMs in humoral and germinal center responses

Generating long-term humoral immunity is crucial for protection against pathogens, and for successful vaccinations. The humoral response requires interactions between T and B cells; antigen-specific T cells interact with their cognate B cells, which help them mature into T_{FH} cells, a subset of $CD4^+$ helper T cells that specialize in supporting germinal center (GC) B cells. When follicular B cells encounter an antigen, they differentiate into either extrafollicular plasmablasts or early memory B cells, or return to the follicle and undergo rapid proliferation to form a GC. In the GCs, T_{FH} help B cells to initiate the humoral response and regulate its magnitude and quality. Stable T:B interactions

* Corresponding author at: Department of Immunology, Weizmann Institute of Science, Rehovot 76100, Israel.
E-mail address: idit.shachar@weizmann.ac.il (I. Shachar).

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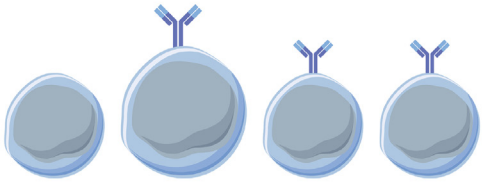
Table 1
Expression of SLAMF receptors on BM and splenic B cells.

BM

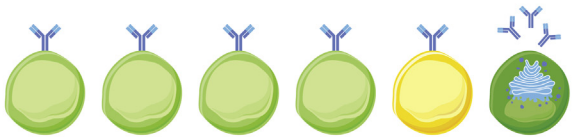


	PRO B	LARGE PRE B	IMMATURE B	MATURE B
SLAMF1 (CD150)	++	+	+	+
SLAMF2 (CD48)	++++	++++	++++	+++++
SLAMF3 (CD229)	+	+	+	+
SLAMF4 (CD224)	-*	-*	-*	-*
SLAMF5 (CD84)	++	++	+	+
SLAMF6 (CD352)	+	++	+	+
SLAMF7 (CD319)	++++	++	+	+
SLAMF8	-**	-**	-**	-**
SLAMF9	-**	-**	-**	-**

* – NOT EXPRESSED

** – UNCHARACTERIZED

Spleen



	T1/T2	NAÏVE	MZ	GC	MEMORY	PLASMA
SLAMF1 (CD150)	++++	+	++	+	+	+
SLAMF2 (CD48)	++++++	++++	++++	+++++	+++	+++++
SLAMF3 (CD229)	+++	+	++	+	++	++
SLAMF4 (CD224)	-*	-*	-*	-*	-*	-*
SLAMF5 (CD84)	+++++	+	+	++	++	+
SLAMF6 (CD352)	++++++	++	+++++	++	++	++
SLAMF7 (CD319)	+	-	-	+	-*	++++
SLAMF8	-**	-**	-**	-**	-**	-**
SLAMF9	-**	-**	-**	-**	-**	-**

* – NOT EXPRESSED

** – UNCHARACTERIZED

must occur for optimal B cell help [14,15].

The SAP/SLAM family of adhesion molecules was shown to be essential for such lengthy interactions in the GC. T_{FH} cells in the GC express high levels of SAP [16]. Both T_{FH} and GC B cells express SLAMF1, SLAMF5 and SLAMF6 [17,18]. SAP was shown to play a crucial role in the long-term humoral response at the GC [19]. In its absence, T cells are unable to form stable long-term conjugates with cognate B cells [20–22]. However, although SAP transmits the SLAMF-induced cascades, deletion of a single SLAMF member, SLAMF1 or SLAMF3, does not affect GC development and anti-viral antibody production in response to lymphocytic choriomeningitis virus [23]. SLAMF5 and SLAMF6 were shown *in vitro* to mediate the adhesive interactions required for prolonged T:B contact in a SAP-dependent manner, yet, both SLAMF5 and SLAMF6 deficient mice show a grossly normal GC formation and exhibit only a slight defect in GC responses to NP-ova immunization [22]. These studies raised the possibility of redundancy in this receptor family. However, in contrast to SAP deficient mice, GC responses were almost normal in SLAMF1, SLAMF5 and SLAMF6 triple knockout (ko) mice, with no decrease, and even a slight elevation in antibody response [24–26]. These results contrast the suggestion that the lack of antibody is SLAM dependent.

An additional role of SLAMFs is in the regulation of the T-independent antibody response. SLAMF2 stimulation in C57BL/6 mice enhances the B cell IgG response to T-independent antigens [27]. An increase in T-independent antibody production was also reported in SLAMF3 deficient mice. These mice exhibit increased levels of marignal zone (MZ) and B1A B cells and elevated levels of T-independent type II Abs [28]. Furthermore, aged SLAMF3−/− mice develop systemic autoimmunity characterized by elevated GC, MZ T1 and plasma cell populations [29].

2.2. SLAMFs in B cell maintenance

SLAMF receptors are involved in regulation of naïve B cell survival [30].

SLAMF2 is the receptor for SLAMF4, which modulates T cell function [31,32]. SLAMF2 is expressed on B and T cells, NK cells, DCs, monocytes, neutrophils, mast cells and eosinophils [31]. Interaction of soluble SLAMF2 (CD48) with CD2 on murine B cells was shown to confer protection from cell death [33] and in human B cells, cross linking of CD48 resulted in augmented B cells activation in the presence of CD40-CD40 ligands interactions [34].

SLAMF8 is mainly expressed on myeloid cells such as dendritic cells and peripheral blood mononuclear cells, and its expression in monocytes was shown to increase in response to IFNγ stimulation. Interestingly, a significant expansion of B1b cell population was detected mainly in the peritoneal cavity, when bone marrow cells were artificially transduced with retroviral SLAMF8 and transplanted into irradiated mice [6]. The increase in B1b cells has raised speculation regarding the role of SLAMF8 in the lineage commitment or maintenance of B cells.

SLAMF6 is expressed by T and B cells, NK cells, monocytes and platelets [22,35]. This receptor has various functions such as modulation of T cell function, affecting NKT cell development and regulation of cytokine secretion by innate immune cells [22,32,36,37].

It was recently shown that interaction of B cells with T cells in a SLAMF6 dependent manner regulates the maintenance/survival of the mature naïve peripheral B cell population. Naïve mature B survival is supported by naïve T cells in a non-antigen specific manner. Following interaction between B and T cells *via* SLAMF6, a downstream signaling cascade in T cells, which is mediated by the SAP adaptor, leads to the upregulation of the cytokine, macrophage migration inhibitory factor

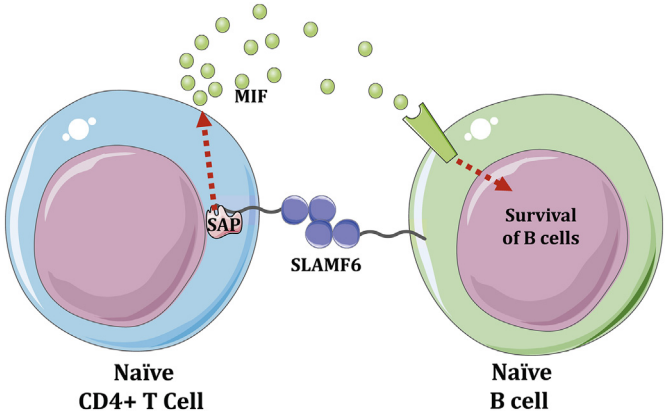


Fig. 1. Interaction of B cells with T cells in a SLAMF6 dependent manner regulates the maintenance/survival of the mature B cell population.

(MIF). In the B-cell partner, this interaction results in an augmented expression of the MIF receptor, CD74, a process that is mediated by EAT-2. Consequently, this interaction induces survival of naive B cells. Furthermore, in X-linked lymphoproliferative syndrome.

XLP patients, SAP deficiency reduces CD74 expression on B cell populations resulting in perturbation of the of B cell survival from the naïve stage [9] (Fig. 1).

3. SLAMFs in B cell malignancies

Members of the SLAM family were shown to play a role in hematological malignancies. Here, we focus on two B cell neoplasms, chronic lymphocytic leukemia and multiple myeloma (Table 2).

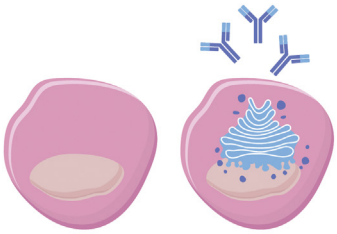
3.1. SLAMFs in CLL

3.1.1. CLL

Chronic lymphocytic leukemia (CLL) is the most common leukemia in the Western world. It is characterized by an ongoing accumulation of mature CD19 + CD5+ B lymphocytes in the peripheral blood, lymphoid organs and bone marrow (BM). This accumulation has been predominantly attributed to decreased apoptosis; however, cell proliferation and clonal evolution have also been described [38]. The origin of the CLL cell is still unknown. While CLL cells carrying unmutated immunoglobulin heavy chain variable region (IGHV) genes (U-CLL) likely derive from unmutated mature CD5+ B cells, the CLL cells carrying mutated IGHV genes (M-CLL) are derived from a CD5 + CD27+ post-germinal center B-cell subset [39]. Currently, CLL remains an incurable disease, and despite significant progress in the last few years in the understanding of the biology and pathophysiology of CLL, as well as the development of improved forms of treatment, patients require lifelong chemotherapeutic treatment with significant side effects.

In recent studies, the contribution of signals from the tumor microenvironmental to the progression of malignancies has been recognized, and heavily studied [40,41]. CLL cells are resistant to apoptosis *in vivo* and are known to overexpress anti-apoptotic proteins including BCL2 and MCL1 [42,43]. This phenomenon is not recapitulated *in vitro*, where CLL cells undergo spontaneous apoptosis under common conditions that normally support the culture of human B-cell lines [44]. Therefore, it was proposed that factors necessary for CLL survival, or resistance to apoptosis, are deficient in *ex vivo* cultures and enhanced cell survival is not entirely intrinsic to the leukemic cell. The complex cellular and molecular contexts created in the surrounding tissues, jointly termed the CLL microenvironment, provide both signals for the increased CLL accumulation, and promote primary drug resistance [45,46]. This drug resistance, and is mostly dependent on

Table 2
Expression of SLAMF receptors on CLL and MM cells, as described in [58,90].



	CLL	MM
SLAMF1 (CD150)	+	++
SLAMF2 (CD48)	++++	+++++
SLAMF3 (CD229)	+++	+++
SLAMF4 (CD224)	-	-
SLAMF5 (CD84)	+++	-
SLAMF6 (CD352)	+++++	+++
SLAMF7 (CD319)	+	+++
SLAMF8	-	-
SLAMF9	-	-

direct contact between the CLL and stromal cells [46,47]. Stromal cells secrete chemokines leading to attraction and retention of CLL cells in tissues, with corresponding chemokine receptors and adhesion molecules found on the leukemic cells [48]. The CLL microenvironment provides signals which regulate CLL survival. Further, CLL cells induce changes in their microenvironment, both *in vitro* and *in vivo*, by inducing an inflammatory cytokine milieu, an exhaustion phenotype in T cells, and the differentiation of myeloid cells with immunosuppressive activity [49–52]. Some of these interactions are dependent on cell-cell contact, while others are mediated through chemokines, growth factors, and possibly through extracellular matrix components. Several studies demonstrated that accessory cells, such as mesenchymal marrow stromal cells [46,53], follicular dendritic cells (FDC) [54], monocyte-derived nurse like cells (NLC) [51] and endothelial cells [55] support CLL cell survival and the expression of anti-apoptotic proteins. The connection between CLL cells and their microenvironment is established and continuously maintained by chemokines and chemokine receptors (such as CXCL12 and CXCR4) and adhesion molecules (including VLA-4 and the receptor VCAM-1) [48].

3.1.2. CLL and SLAMS

Several SLAM family members were shown to be expressed on CLL cells; SLAMF1/CD150 [56]; SLAMF2/CD48 [57]; SLAMF3/LY9 [58]; SLAMF5/CD84 [59] and SLAMF7/CRACC [60]. SLAMF2, SLAMF3, SLAMF5, and SLAMF6 are expressed at medium to high levels, while SLAMF1 and SLAM7 are only weakly expressed. Six out of seven SLAMF receptors analyzed showed discrepancy in the expression between normal mature polyclonal B cells and pathological CLL B cells. SLAMF1, SLAMF2 and SLAMF7 were found to be downregulated, while SLAMF3,

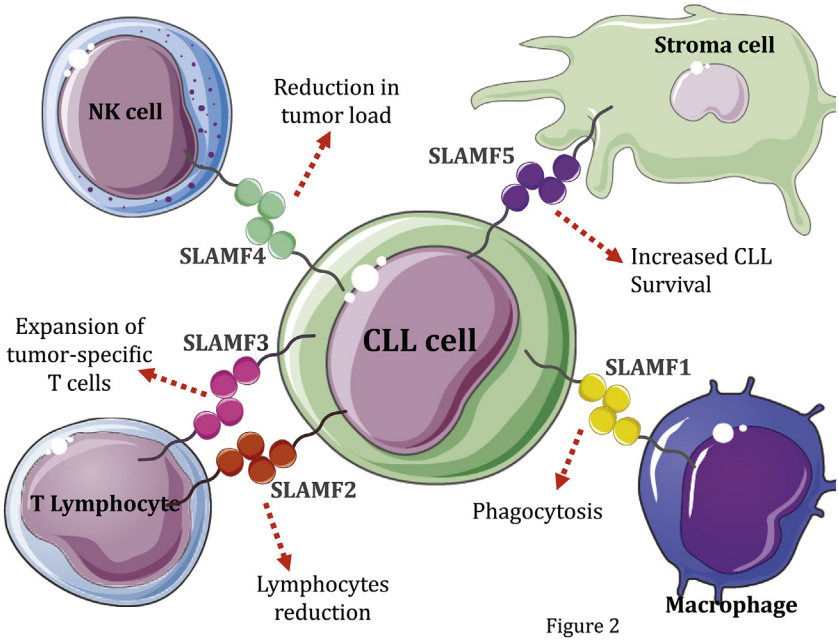


Fig. 2. The different functions of SLAMF receptors in CLL.

SLAMF5, and SLAMF6 were overexpressed in CLL B cells [61]. Different function is attributed to each of the following SLAMF member (Fig. 2).

3.1.2.1. SLAMF1/CD150. SLAMF1 has been associated with many functions in diverse cell types, including migration of dendritic cells and macrophages, enhancing phagocytosis by macrophages, and Treg and T cell functionality [26,62,63]. In human CLL, SLAMF1 was shown to be highly expressed in mutated CLL compared to unmutated IgHV CLL which is associated with a worse prognosis [56,64–66]. Silencing SLAMF1 in a human CLL cell line modulates migration and autophagic vesicle formation, making the cells resistant to specific therapies. In patients, SLAMF1 expression is lost on a subset of aggressive CLL cells. Low SLAMF1 expressing CLL cells are more resistant to therapies. These studies confirm that low or loss of SLAMF1 expression underlie unfavorable clinical outcome experienced by patients [67].

3.1.2.2. SLAMF2/CD48. SLAMF2 is highly expressed on both murine and human CLL cells [68]. A pilot study utilizing anti-CD48 antibodies in CLL patients demonstrated a transient reduction in lymphocyte numbers in response to treatment [69].

3.1.2.3. SLAMF3/LY9/CD229. CD229 is also overexpressed on CLL. CD229 is naturally processed and presented as a tumor associated antigen in primary human CLL cells, enabling the expansion of autologous tumor-specific T cells [58].

3.1.2.4. SLAMF4/2B4/CD244. SLAMF4 is expressed on diverse immune cells. Unlike the other members of the family, it is not a homophilic receptor in human, mice, or rats, but serves as a counter-receptor for SLAMF2/CD48 [2].

SLAMF4 is most famously known as regulator of both NK and T cell function and has been described as a dual function receptor on both these cells. Accordingly, activation by CD48 of SLAMF4 can induce both inhibitory and activating signals to T and NK cells [70].

T cells acquire an exhausted state in CLL. This exhausted state is associated with increased expression of inhibitory receptors including programmed death-1 (PD1, CD279), CD160 (BY55), and CD244 (SLAMF4) [50] on $CD3^+CD8^+CCR7^-$ cells [71]. Blocking PD-L1 in the murine CLL model downregulates CD244 expression levels on T cells, restoring T cell activity [72]. SLAMF4 is also expressed on NK cells. Ligation of the FcγRIIIA/CD16 receptor by the anti-CD20 mAb Rituximab stably impairs the spontaneous cytotoxic response attributable to several NK-activating receptors, including SLAMF4 [73]. These studies suggest that SLAMF4 expressed on both T and NK cells might serve as an attractive target in CLL, activating T and NK cell anti-tumor activity.

3.1.2.5. SLAMF5/CD84. SLAMF5 is expressed on human CLL cells, and cells in the CLL microenvironment. Activation of cell surface SLAMF5 initiates a signaling cascade that enhances CLL cell survival. Both decreased expression of SLAMF5 and its immune-mediated blockade induce the death of CLL cells [59]. SLAMF5 expressed on CLL cells interact with SLAMF5 receptors on cells in their microenvironment, inducing cell survival of both interacting partners. Blocking SLAMF5 *in vitro* and *in vivo* disrupts the interaction of CLL cells with their microenvironment, resulting in induced cell death [74]. This cross-linking leads to elevated expression and secretion of CCL3 in CLL cells, which leads to the expression of Bcl-2 in the stroma as well as stromal secretion of cytokines including IL-6 and IL-8, thereby contributing to CLL survival [59,75,76], in an autocrine loop [74].

Recently, SLAMF5 was found to regulate PD-L1 expression, on both human and mouse CLL cells and their supportive microenvironment and PD-1, and other known exhaustion markers, on T cells [77]. The PD-L1-PD-1 axis is an important pathway known to play role in failed T cell mediated anti-tumor response, by PD-L1 on tumor cells binding PD-1 on T cells [78]. In the absence of SLAMF5, there is a reduction in PD-L1 expression on CLL cells and PD-1 on T cells, resulting in reduced exhaustion and induced activity of T cells [77]. These results demonstrated a role for SLAMF5 in regulation of immune checkpoints by leukemia cells, and suggested that SLAMF5 blockade as a therapeutic strategy to reverse tumor-induced immune suppression [77].

Thus, the importance of SLAMF5 lies in its triple role in CLL. SLAMF5 regulates the survival of both CLL cells [59] and of cells comprising the microenvironment. In addition, SLAMF5 bridges between the CLL and the stroma, supporting retention of CLL cells in their niche. Finally, SLAMF5 regulates anti-tumor T cell activity in the tumor microenvironment. Thus, blocking SLAMF5 induces death of both CLL and stromal cells, the release of malignant cells from their niches in the BM to the periphery, and restores T cell anti-tumor response, suggesting it can serve as a therapeutic target.

3.1.2.6. SLAMF6/LY108/NTB-A/CD352. SLAMF6 is highly expressed by both murine and human CLL cells [35,68]. Anti-SLAMF6 mAbs can effectively eliminate B cells from CLL patient samples, while not affecting the cellular composition of blood samples from healthy patients [35]. In addition, blocking SLAMF6 in SCID mice transplanted with mouse CLL cells (TCL-1), or $RAG^{-/-}$ mice transplanted with the human MEC-1 CLL cell line, reduced tumor burden [68]. Thus, SLAMF6 is an attractive target in CLL.

3.2. SLAMs in Multiple myeloma

3.2.1. MM

Multiple myeloma (MM) is a malignant disease created by accumulation of monoclonal plasma cells in the BM [79,80]. It is the second most common hematological cancer [81]. MM evolves from healthy plasma cells in a multistep process, first turning into a non-malignant benign stage called Monoclonal Gammapathy of Undetermined Significance (MGUS) [82], which then either advances directly into MM or continues into Smoldering Multiple Myeloma (SMM), which progresses into Multiple Myeloma at a rate of 10% per year. In the final stage of the disease, MM can also transform into Plasma Cell Leukemia (PCL), a stage at which the plasma cells become independent of the bone marrow microenvironment and are found in the circulation or manifest as extramedullary myeloma [83]. The MM population has been reported to contain different types of MM cells. The CD138low/neg population has been described as MM stem cells, also called Pre-PC. This population has been reported to be less sensitive to drugs, less mature and can induce MM in xenograft-transplanted immunodeficient mice. Patients with more than 20% of these cells have significantly reduced overall survival, in comparison to patients with fewer such cells [84,85].

Despite progress in the development of current therapeutics, MM is still considered an incurable disease not only because of its intrinsic tumor characteristics but also due to the protective microenvironment [81]. MM cells are strongly dependent on the bone marrow microenvironment, comprised of myeloid cells, BM stromal cells, T cells, osteoclasts, osteoblasts and others [86–89]. These cells play important roles in the regulation of MM cell growth, survival and drug resistance by producing supportive growth factors (*e.g.,* IL-6, IL-8, and VEGF) and contacts through integrins (*e.g.*, CD44, CD74, CD48, ICAM-1) [90–93].

3.2.2. sMM and SLAMF receptors

Several SLAMF receptors have been studied as possible targets in MM, most notably SLAMF7. The expression of SLAMF1, SLAMF2, SLAMF3, SLAMF6, SLAMF7 has previously been reported on primary human MM patient cells [94,95].

3.2.2.1. SLAMF1/CD150. Studies on SLAMF1 in MM are limited and are currently not conclusive. Muccio et al. found that human MM cells do express SLAMF1, albeit at a lower level than healthy plasma cells, but with high expression on plasma cell leukemia cells [95]. The expression on human derived MM cells was supported by a different study, although this study showed a higher expression of SLAMF1 on MM compared to healthy plasma cells [96]. A different study using the human cell line RPMI 8226 showed no expression of SLAMF1 on MM cells, [97]. These contradicting results do not provide conclusive evidence to demonstrate expression of SLAMF1 on MM cells and thus do not support its use as a therapeutic target.

3.2.2.2. SLAMF2/CD48. Studies have shown high expression of SLAMF2 on both malignant and healthy human plasma cells [95]. Furthermore, a different study found that blocking SLAMF2 (CD48) with anti-CD48 antibody within the microenvironment induces killing of these cells *in vitro* as well as *in vivo* [98], suggesting SLAMF2 as an attractive target in MM.

3.2.2.3. SLAMF3/LY9/CD229. SLAMF3 is expressed on both malignant and healthy plasma cells. Within the malignant cells, it has been shown to be expressed on human MGUS, SMM and MM cells, in newly diagnosed, refractory and plasma cell leukemia patients. Expression was also observed on human pre-PCs, however to a lower extent than on CD138high MM cells [95,99–101]. The high cell surface expression of SLAMF3 on MM warrants its further evaluation for treatment.

3.2.2.4. SLAMF4/2B4/CD244. Several studies have confirmed a significant increase in SLAMF4 expression on human MM patient derived T cells [102,103]. SLAMF4 expression on T cells was found to be correlated with tumor burden in mice [102]. Interestingly, treating MM mice with an anti-PD-L1 blocking antibody, an anti immunological checkpoint PD-1 antibody, does not reduce T cell expression of SLAMF4 or any other exhaustion markers. Co-administration of anti-PD-L1 and anti-SLAMF2 does not further enhance the survival of the mice beyond administration of anti-PD-L1 alone [102].

SLAMF4 expression on NK cells derived from MM patients is reduced relative to its levels on NK cells from healthy controls [104]. Furthermore, NK cells from the bone marrow display lower expression of SLAMF4 compared to blood. Thus, the high expression of SLAMF2 on MM cells and changes in SLAMF4 expression on MM derived T and NK cells makes it an attractive target for inducing anti-tumor immunity of T and NK cells.

3.2.2.5. SLAMF6/LY108/NTB-A/CD352. Similarly to SLAMF1, studies on SLAMF6 in MM are rather limited. Reports have shown high expression on human healthy plasma cells as well as on MM cells, was shown in patients with refractory disease, newly diagnosed patients, as well as in plasma cell leukemia patients [95].

3.2.2.6. SLAMF7/CD319/CRACC/CS1. SLAMF7 is highly expressed on human healthy and malignant plasma cells, regardless of the disease stage, but not on healthy or primary tumor environment [95,105–107]. The anti-SLAMF7 antibody, Elutozumab, is currently used for Multiple Myeloma treatment. Its mechanism of action is mostly attributed to ADCC of the MM cells. The antibody coats the cells and is then recognized by FC receptors on NK cells [94,105–107]. Moreover, it was shown that adhesion of MM cells to their BM stroma is decreased in the presence of the antibody [106].

A phase III trial in 646 patients showed that the addition of Elutozumab to lenaolamide and dexamethasone increased the overall response rate to 79%, compared to 66% in its absence. Consequently, in 2015 the FDA approved the antibody for the treatment of MM [105].

4. Concluding remarks

SLAMF members play important roles in B cell differentiation, and function both in health and pathogenesis. Recent findings have demonstrated an important role for this family of receptors in B cell malignancies, suggesting a pivotal role for these receptors in the control of malignant cell survival, interaction with cells in their tumor microenvironment, and retention in the supporting niches. The expression of SLAMF receptors on cells in the microenvironment of B cell malignancies can be an advantage. Their expression on normal tissues is low and is upregulated in the tumor microenvironment. Therefore, blocking this receptor activity can be specific mostly to the tumor cells and cells in the tumor microenvironment, leaving healthy cells untouched. Further studies exploring the functions of these receptors can pave the way towards better understanding these immune cell malignancies, and the development of new potential therapies.

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References

[1] J.L. Cannons, S.G. Tangye, P.L. Schwartzberg, SLAM family receptors and SAP adaptors in immunity, Annu. Rev. Immunol. 29 (2011) 665–705.

[2] S. Calpe, N.H. Wang, X. Romero, S.B. Berger, A. Lanyi, P. Engel, C. Terhorst, The SLAM and SAP gene families control innate and adaptive immune responses, Adv. Immunol. 97 (97) (2008) 177–250.

[3] C. Detre, M. Keszei, N. Garrido-Mesa, K. Kis-Toth, W. Castro, A.F. Agyemang, N. Veerapen, G.S. Besra, M.C. Carroll, G.C. Tsokos, N. Wang, E.A. Leadbetter, C. Terhorst, SAP expression in invariant NKT cells is required for cognate help to support B-cell responses, Blood 120 (2012) 122–129.

[4] W. Zhang, T. Wan, N. Li, Z. Yuan, L. He, M. Yu X Zhu, X. Cao, Genetic approach to insight into the immunobiology of human dendritic cells and identification of CD84-H1, a novel CD84 homologue, Clin. Cancer Res. 7 (2001) 822s–829s.

[5] C.C. Fraser, D. Howie, M. Morra, Y. Qiu, C. Murphy, Q. Shen, J.C. Gutierrez-Ramos, A. Coyle, G.A. Kingsbury, C. Terhorst, Identification and characterization of SF2000 and SF2001, two new members of the immune receptor SLAM/CD2 family, Immunogenetics 53 (2002) 843–850.

[6] G.A. Kingsbury, L.A. Feeney, Y. Nong, S.A. Calandra, C.J. Murphy, J.M. Corcoran, Y. Wang, M.R. Prabhu Das, S.J. Busfield, C.C. Fraser, J.L. Villeval, Cloning, expression, and function of BLAME, a novel member of the CD2 family, J. Immunol. 166 (2001) 5675–5680.

[7] S.G. Tangye, B.C.M. van de Weerdt, D.T. Avery, P.D. Hodgkin, CD84 is up-regulated on a major population of human memory B cells and recruits the SH2 domain containing proteins SAP and EAT-2, Eur. J. Immunol. 32 (2002) 1640–1649.

[8] A. Veillette, Immune regulation by SLAM family receptors and SAP-related adaptors, Nat. Rev. Immunol. 6 (2006) 56–66.

[9] L. Radomir, S. Cohen, M.P. Kramer, E. Bakos, H. Lewinsky, A. Barak, Z. Porat, R. Bucala, P. Stepensky, S. Becker-Herman, I. Shachar, T cells regulate peripheral naive mature B cell survival by cell-cell contact mediated through SLAMF6 and SAP, J. Immunol. 199 (2017) 2745–2757.

[10] P. Engel, M.J. Eck, C. Terhorst, The SAP and SLAM families in immune responses and X-linked lymphoproliferative disease, Nat. Rev. Immunol. 3 (2003) 813–821.

[11] S. Latour, A. Veillette, The SAP family of adaptors in immune regulation, Semin. Immunol. 16 (2004) 409–419.

[12] N. Wu, A. Veillette, SLAM family receptors in normal immunity and immune pathologies, Curr. Opin. Immunol. 38 (2016) 45–51.

[13] J. De Salort, J. Sintes, L. Llinas, J. Matesanz-Isabel, P. Engel, Expression of SLAM (CD150) cell-surface receptors on human B-cell subsets: from pro-B to plasma cells, Immunol. Lett. 134 (2011) 129–136.

[14] K. Rajewsky, Clonal selection and learning in the antibody system, Nature 381 (1996) 751–758.

[15] J. Hu, C. Havenar-Daughton, S. Crotty, Modulation of SAP dependent T:B cell interactions as a strategy to improve vaccination, Curr. Opin. Virol. 3 (2013) 363–370.

[16] C.S. Ma, S. Suryani, D.T. Avery, A. Chan, R. Nanan, B. Santner-Nanan, E.K. Deenick, S.G. Tangye, Early commitment of naive human CD4(+) T cells to the T follicular helper (T(FH)) cell lineage is induced by IL-12, Immunol. Cell Biol. 87 (2009) 590–600.

[17] H. Qi, From SAP-less T cells to helpless B cells and back: dynamic T-B cell interactions underlie germinal center development and function, Immunol. Rev. 247 (2012) 24–35.

[18] I. Yusuf, R. Kageyama, L. Monticelli, R.J. Johnston, D. Ditoro, K. Hansen, B. Barnett, S. Crotty, Germinal center T follicular helper cell IL-4 production is dependent on signaling lymphocytic activation molecule receptor (CD150), J. Immunol. 185 (2010) 190–202.

[19] C.S. Ma, S. Pittaluga, D.T. Avery, N.J. Hare, I. Maric, A.D. Klion, K.E. Nichols, S.G. Tangye, Selective generation of functional somatically mutated IgM (+)CD27(+), but not Ig isotype-switched, memory B cells in X-linked lymphoproliferative disease, J. Clin. Investig. 116 (2006) 322–333.

[20] H. Qi, J.L. Cannons, F. Klauschen, P.L. Schwartzberg, R.N. Germain, SAP-controlled T-B cell interactions underlie germinal centre formation, Nature 455 (2008) 764–769.

[21] J.L. Cannons, L.J. Yu, D. Jankovic, S. Crotty, R. Horai, M. Kirby, S. Anderson, A.W. Cheever, A. Sher, P.L. Schwartzberg, SAP regulates T cell-mediated help for humoral immunity by a mechanism distinct from cytokine regulation, J. Exp. Med. 203 (2006) 1551–1565.

[22] J.L. Cannons, H. Qi, K.T. Lu, M. Dutta, J. Gomez-Rodriguez, J. Cheng, E.K. Wakeland, R.N. Germain, P.L. Schwartzberg, Optimal germinal center responses require a multistage T Cell:B Cell adhesion process involving integrins, SLAM-associated protein, and CD84, Immunity 32 (2010) 253–265.

[23] F. Zhao, J.L. Cannons, M. Dutta, G.M. Griffiths, P.L. Schwartzberg, Positive and negative signaling through SLAM receptors regulate synapse organization and thresholds of cytolysis, Immunity 36 (2012) 1003–1016.

[24] B. Huang, J. Gomez-Rodriguez, S. Preite, L.J. Garrett, U.L. Harper, P.L. Schwartzberg, CRISPR-mediated triple knockout of SLAMF1, SLAMF5 and SLAMF6 supports positive signaling roles in NKT Cell Development, PLoS One 11 (2016) e0156072.

[25] J.K. Hu, J.C. Crampton, M. Locci, S. Crotty, CRISPR-Mediated Slamf1Delta/Delta Slamf5Delta/Delta Slamf6Delta/Delta Triple Gene Disruption Reveals NKT Cell Defects but Not T Follicular Helper Cell Defects, PLoS One 11 (2016) e0156074.

[26] N. Wang, P.J. Halibozek, B. Yigit, H. Zhao, M.S. O'Keeffe, P. Sage, A. Sharpe, C. Terhorst, Negative regulation of humoral immunity due to interplay between the SLAMF1, SLAMF5, and SLAMF6 receptors, Front. Immunol. 6 (2015) 158.

[27] D. Yuan, Y. Guo, S. Thet, Enhancement of antigen-specific immunoglobulin G responses by anti-CD48, J. Innate Immun. 5 (2013) 174–184.

[28] M. Cuenca, X. Romero, J. Sintes, C. Terhorst, P. Engel, Targeting of Ly9 (CD229) disrupts marginal zone and B1 B Cell homeostasis and antibody responses, J. Immunol. 196 (2016) 726–737.

[29] J. de Salort, M. Cuenca, C. Terhorst, P. Engel, X. Romero, Ly9 (CD229) Cell-surface receptor is crucial for the development of spontaneous autoantibody production to nuclear antigens, Front. Immunol. 4 (2013) 225.

[30] J. Punnonen, B.G. Cocks, J.M. Carballido, B. Bennett, D. Peterson, G. Aversa, J.E. de Vries, Soluble and membrane-bound forms of signaling lymphocytic activation molecule (SLAM) induce proliferation and Ig synthesis by activated human B lymphocytes, J. Exp. Med. 185 (1997) 993–1004.

[31] M. Elishmereni, F. Levi-Schaffer, CD48: a co-stimulatory receptor of immunity, Int. J. Biochem. Cell Biol. 43 (2011) 25–28.

[32] C. Detre, M. Keszei, X. Romero, G.C. Tsokos, C. Terhorst, SLAM family receptors and the SLAM-associated protein (SAP) modulate T cell functions, Semin. Immunopathol. 32 (2010) 157–171.

[33] A.M. Genaro, J.A. Gonzalo, L. Bosca, C. Martinez, CD2-CD48 interaction prevents apoptosis in murine B lymphocytes by up-regulating bcl-2 expression, Eur. J. Immunol. 24 (1994) 2515–2521.

[34] E.N. Klyushnenkova, L. Li, R.J. Armitage, Y.S. Choi, CD48 delivers an accessory signal for CD40-mediated activation of human B cells, Cell. Immunol. 174 (1996) 90–98.

[35] W. Korver, S. Singh, S. Liu, X. Zhao, S. Yonkovich, A. Sweeney, K. Anton, R. We Lomas III, A. Smith Greenwood, D.H. Tran, P. Shinkawa, M. Jimenez, P. Yeung, G. Aguilar, S. Palencia, P. Vatta, M. Mueller, X. Zhan, Y. Em Newton, J. Liu, P. Emtage Zhao, M.D. Levy, E.D. Hsi, W.D. Funk, A. Abo, The lymphoid cell surface receptor NTB-A: a novel monoclonal antibody target for leukaemia and lymphoma therapeutics, Br. J. Haematol. 137 (2007) 307–318.

[36] B. van Driel, G. Wang, G. Liao, P.J. Halibozek, M. Keszei, M.S. O'Keeffe, A.K. Bhan, N. Wang, C. Terhorst, The cell surface receptor Slamf6 modulates innate immune responses during Citrobacter rodentium-induced colitis, Int. Immunol. 27 (2015) 447–457.

[37] N. Wang, M. Keszei, P. Halibozek, B. Yigit, P. Engel, C. Terhorst, Slamf6 negatively regulates autoimmunity, Clin. Immunol. 173 (2016) 19–26.

[38] F. Caligaris-Cappio, P. Ghia, Novel insights in chronic lymphocytic leukemia: are we getting closer to understanding the pathogenesis of the disease? J. Clin. Oncol. 26 (2008) 4497–4503.

[39] M. Seifert, L. Sellmann, J. Bloehdorn, F. Wein, S. Stilgenbauer, J. Durig, R. Kuppers, Cellular origin and pathophysiology of chronic lymphocytic leukemia, J. Exp. Med. 209 (2012) 2183–2198.

[40] J.A. Burger, No cell is an island unto itself: the stromal microenvironment in chronic lymphocytic leukemia, Leuk. Res. 31 (2007) 887–888.

[41] A.D. Ramsay, M. Rodriguez-Justo, Chronic lymphocytic leukaemia—the role of the microenvironment pathogenesis and therapy, Br. J. Haematol. 162 (2013) 15–24.

[42] S. Kitada, J. Andersen, S. Akar, J.M. Zapata, S. Takayama, S. Krajewski, H.G. Wang, X. Zhang, F. Bullrich, C.M. Croce, K. Rai, J. Hines, J.C. Reed, Expression of apoptosis-regulating proteins in chronic lymphocytic leukemia: correlations with in vitro and in vivo chemoresponses, Blood 91 (1998) 3379–3389.

[43] G. Packham, F.K. Stevenson, Bodyguards and assassins: Bcl-2 family proteins and apoptosis control in chronic lymphocytic leukaemia, Immunology 114 (2005) 441–449.

[44] R.J. Collins, L.A. Verschuer, B.V. Harmon, R.L. Prentice, J.H. Pope, J.F. Kerr, Spontaneous programmed death (apoptosis) of B-chronic lymphocytic leukaemia cells following their culture in vitro, Br. J. Haematol. 71 (1989) 343–350.

[45] J.A. Burger, P. Ghia, A. Rosenwald, F. Caligaris-Cappio, The microenvironment in mature B-cell malignancies: a target for new treatment strategies, Blood 114 (2009) 3367–3375.

[46] L. Lagneaux, A. Delforge, D. Bron, C. De Bruyn, P. Stryckmans, Chronic lymphocytic leukemic B cells but not normal B cells are rescued from apoptosis by contact with normal bone marrow stromal cells, Blood 91 (1998) 2387–2396.

[47] J.S. Damiano, A.E. Cress, L.A. Hazlehurst, A.A. Shtil, W.S. Dalton, Cell adhesion mediated drug resistance (CAM-DR): role of integrins and resistance to apoptosis in human myeloma cell lines, Blood 93 (1999) 1658–1667.

[48] E. ten Hacken, J.A. Burger, Microenvironment dependency in chronic lymphocytic leukemia: the basis for new targeted therapies, Pharmacol. Ther. 144 (2014) 338–348.

[49] A. Schulz, G. Toedt, T. Zenz, S. Stilgenbauer, P. Lichter, M. Seiffert, Inflammatory cytokines and signaling pathways are associated with survival of primary chronic lymphocytic leukemia cells in vitro: a dominant role of CCL2, Haematologica 96 (2011) 408–416.

[50] J.C. Riches, J.K. Davies, F. McClanahan, R. Fatah, S. Iqbal, S. Agrawal, A.G. Ramsay, J.G. Gribben, T cells from CLL patients exhibit features of T-cell exhaustion but retain capacity for cytokine production, Blood 121 (2013) 1612–1621.

[51] J.A. Burger, N. Tsukada, M. Burger, N.J. Zvaifler, M. Dell'Aquila, T.J. Kipps, Blood-derived nurse-like cells protect chronic lymphocytic leukemia B cells from spontaneous apoptosis through stromal cell-derived factor-1, Blood 96 (2000) 2655–2663.

[52] M. Plander, P. Ugocsai, S. Seegers, E. Orso, A. Reichle, G. Schmitz, F. Hofstadter, G. Brockhoff, Chronic lymphocytic leukemia cells induce anti-apoptotic effects of bone marrow stroma, Ann. Hematol. 90 (2011) 1381–1390.
[53] P. Panayiotidis, D. Jones, K. Ganeshaguru, L. Foroni, A.V. Hoffbrand, Human bone marrow stromal cells prevent apoptosis and support the survival of chronic lymphocytic leukaemia cells in vitro, Br. J. Haematol. 92 (1996) 97–103.
[54] I.M. Pedersen, S. Kitada, L.M. Leoni, J.M. Zapata, J.G. Karras, N. Tsukada, T.J. Kipps, Y.S. Choi, F. Bennett, J.C. Reed, Protection of CLL B cells by a follicular dendritic cell line is dependent on induction of Mcl-1, Blood 100 (2002) 1795–1801.
[55] X. Badoux, C. Bueso-Ramos, D. Harris, P. Li, Z. Liu, J. Burger, S. O'Brien, A. Ferrajoli, M.J. Keating, Z. Estrov, Cross-talk between chronic lymphocytic leukemia cells and bone marrow endothelial cells: role of signal transducer and activator of transcription 3, Hum. Pathol. 42 (2011) 1989–2000.
[56] C.D. Schweighofer, K.R. Coombes, L.L. Barron, L. Diao, R.J. Newman, A. Ferrajoli, S. O'Brien, W.G. Wierda, R. Luthra, L.J. Medeiros, M.J. Keating, L.V. Abruzzo, A two-gene signature, SKI and SLAMF1, predicts time-to-treatment in previously untreated patients with chronic lymphocytic leukemia, PLoS One 6 (2011) e28277.
[57] S. Sembries, H. Pahl, S. Stilgenbauer, H. Dohner, F. Schriever, Reduced expression of adhesion molecules and cell signaling receptors by chronic lymphocytic leukemia cells with 11q deletion, Blood 93 (1999) 624–631.
[58] D. Bund, C. Mayr, D.M. Kofler, M. Hallek, C.M. Wendtner, Human Ly9 (CD229) as novel tumor-associated antigen (TAA) in chronic lymphocytic leukemia (B-CLL) recognized by autologous CD8+ T cells, Exp. Hematol. 34 (2006) 860–869.
[59] I. Binsky-Ehrenreich, A. Marom, M.C. Sobotta, L. Shvidel, A. Berrebi, I. Hazan-Halevy, S. Kay, A. Aloshin, I. Sagi, D.M. Goldenberg, L. Leng, R. Bucala, Y. Herishanu, M. Haran, I. Shachar, **CD84** is a survival receptor for CLL cells, Oncogene 33 (2014) 1006–1016.
[60] V. Moinet-Hedin, T. Tabka, L. Poulain, T. Godard, M. Lechevrel, C. Saturnino, J.C. Lancelot, J.Y. Le Talaer, P. Gauduchon, Biological properties of 5,11-dimethyl-6H-pyrido[3,2-b]carbazoles: a new class of potent antitumour drugs, Anticancer Drug Des. 15 (2000) 109–118.
[61] M. Coma, E. Tothova, T. Guman, M. Hajikova, M. Giertlova, M. Sarissky, Altered expression pattern of SLAM family receptors on pathological B cells of patients with chronic lymphocytic leukemia, Leuk. Lymphoma 58 (2017) 1726–1729.
[62] D. Howie, M. Simarro, J. Sayos, M. Guirado, J. Sancho, C. Terhorst, Molecular dissection of the signaling and costimulatory functions of CD150 (SLAM): CD150/SAP binding and CD150-mediated costimulation, Blood 99 (2002) 957–965.
[63] S.B. Berger, X. Romero, C. Ma, G. Wang, W.A. Faubion, G. Liao, E. Compeer, M. Keszei, L. Rameh, N. Wang, M. Boes, J.R. Regueiro, H.C. Reinecker, C. Terhorst, SLAM is a microbial sensor that regulates bacterial phagosome functions in macrophages, Nat. Immunol. 11 (2010) 920–927.
[64] A. Zucchetto, I. Cattarossi, P. Nanni, E. Zaina, G. Prato, M. Gilestro, D. Marconi, P. Bulian, F.M. Rossi, L. Del Vecchio, P. Omede, M. Geuna, G. Del Poeta, V. Gattei, Cluster analysis of immunophenotypic data: the example of chronic lymphocytic leukemia, Immunol. Lett. 134 (2011) 137–144.
[65] L.V. Abruzzo, L.L. Barron, K. Anderson, R.J. Newman, W.G. Wierda, S. O'Brien, A. Ferrajoli, M. Luthra, S. Talwalkar, R. Luthra, D. Jones, M.J. Keating, K.R. Coombes, Identification and validation of biomarkers of IgV(H) mutation status in chronic lymphocytic leukemia using microfluidics quantitative real-time polymerase chain reaction technology, J. Mol. Diagn. 9 (2007) 546–555.
[66] F. Caligaris-Cappio, T.J. Hamblin, B-cell chronic lymphocytic leukemia: a bird of a different feather, J. Clin. Oncol. 17 (1999) 399–408.
[67] C. Bologna, R. Buonincontri, S. Serra, T. Vaisitti, V. Audrito, D. Brusa, A. Pagnani, M. Coscia, G. D'Arena, E. Mereu, R. Piva, R.R. Furman, D. Rossi, G. Gaidano, C. Terhorst, S. Deaglio, SLAMF1 regulation of chemotaxis and autophagy determines CLL patient response, J. Clin. Invest. 126 (2016) 181–194.
[68] B. Yigit, P.J. Halibozek, S.S. Chen, M.S. O'Keeffe, J. Arnason, D. Avigan, V. Gattei, A. Bhan, O. Cen, R. Longnecker, N. Chiorazzi, N. Wang, P. Engel, C. Terhorst, A combination of an anti-SLAMF6 antibody and ibrutinib efficiently abrogates expansion of chronic lymphocytic leukemia cells, Oncotarget 7 (2016) 26346–26360.
[69] S. Greenaway, A.J. Henniker, M. Walsh, K.F. Bradstock, A pilot clinical trial of two murine monoclonal antibodies fixing human complement in patients with chronic lymphatic leukaemia, Leuk. Lymphoma 13 (1994) 323–331.
[70] S.N. Waggoner, V. Kumar, Evolving role of 2B4/CD244 in T and NK cell responses during virus infection, Front. Immunol. 3 (2012) 377.
[71] G.D. te Raa, M.F. Pascutti, J.J. Garcia-Vallejo, E. Reinen, E.B. Remmerswaal, I.J. ten Berge, R.A. van Lier, E. Eldering, M.H. van Oers, S.H. Tonino, A.P. Kater, CMV-specific CD8+ T-cell function is not impaired in chronic lymphocytic leukemia, Blood 123 (2014) 717–724.
[72] F. McClanahan, J.C. Riches, S. Miller, W.P. Day, E. Kotsiou, D. Neuberg, C.M. Croce, M. Capasso, J.G. Gribben, Mechanisms of PD-L1/PD-1-mediated CD8 T-cell dysfunction in the context of aging-related immune defects in the Emicro-TCL1 CLL mouse model, Blood 126 (2015) 212–221.
[73] C. Capuano, M. Romanelli, C. Pighi, G. Cimino, A. Rago, R. Molfetta, R. Paolini, A. Santoni, R. Galandrini, Anti-CD20 therapy acts via FcgammaRIIIA to diminish responsiveness of human natural killer cells, Cancer Res. 75 (2015) 4097–4108.
[74] A. Marom, A.F. Barak, M.P. Kramer, H. Lewinsky, I. Binsky-Ehrenreich, S. Cohen, A. Tsitsou-Kampeli, V. Kalchenko, Y. Kuznetsov, V. Mirkin, N. Dezorella, M. Shapiro, P.L. Schwartzberg, Y. Cohen, L. Shvidel, M. Haran, S. Becker-Herman, Y. Herishanu, I. Shachar, CD84 mediates CLL-microenvironment interactions, Oncogene 36 (2017) 628–638.
[75] J.E. Reittie, K.L. Yong, P. Panayiotidis, A.V. Hoffbrand, Interleukin-6 inhibits apoptosis and tumour necrosis factor induced proliferation of B-chronic lymphocytic leukaemia, Leuk. Lymphoma 22 (1996) 83–90 (follow 186, color plate VI).
[76] A. Moreno, M.L. Villar, C. Camara, R. Luque, C. Cespon, P. Gonzalez-Porque, G. Roy, J. Lopez-Jimenez, A. Bootello, E.R. Santiago, Interleukin-6 dimers produced by endothelial cells inhibit apoptosis of B-chronic lymphocytic leukemia cells, Blood 97 (2001) 242–249.
[77] H. Lewinsky, A.F. Barak, V. Huber, M.P. Kramer, L. Radomir, L. Sever, I. Orr, V. Mirkin, N. Dezorella, M. Shapiro, Y. Cohen, L. Shvidel, M. Seiffert, Y. Herishanu, S. Becker-Herman, I. Shachar, CD84 regulates PD-1/PD-L1 expression and function in chronic lymphocytic leukemia, J. Clin. Invest. (2018), https://doi.org/10.1172/JCI96610 [Epub ahead of print].
[78] P. Greaves, J.G. Gribben, The role of B7 family molecules in hematologic malignancy, Blood 121 (2013) 734–744.
[79] R. Fonseca, J. San Miguel, Prognostic factors and staging in multiple myeloma, Hematol. Oncol. Clin. North Am. 21 (2007) 1115–1140.
[80] R. Fonseca, P.L. Bergsagel, J. Drach, J. Shaughnessy, N. Gutierrez, A.K. Stewart, G. Morgan, B. Van Ness, M. Chesi, S. Minvielle, A. Neri, B. Barlogie, W.M. Kuehl, P. Liebisch, F. Davies, S. Chen-Kiang, B.G. Durie, R. Carrasco, O. Sezer, T. Reiman, L. Pilarski, H. Avet-Loiseau, G International Myeloma Working, International Myeloma Working Group molecular classification of multiple myeloma: spotlight review, Leukemia 23 (2009) 2210–2221.
[81] S. Singhal, J. Mehta, Multiple myeloma, Clin. J. Am. Soc. Nephrol. 1 (2006) 1322–1330.
[82] B.M. Weiss, J. Abadie, P. Verma, R.S. Howard, W.M. Kuehl, A monoclonal gammopathy precedes multiple myeloma in most patients, Blood 113 (2009) 5418–5422.
[83] R.E. Walker, M.A. Lawson, C.H. Buckle, J.A. Snowden, A.D. Chantry, Myeloma bone disease: pathogenesis, current treatments and future targets, Br. Med. Bull. 111 (2014) 117–138.
[84] Y. Kawano, S. Fujiwara, N. Wada, M. Izaki, H. Yuki, Y. Okuno, K. Iyama, H. Yamasaki, A. Sakai, H. Mitsuya, H. Hata, Multiple myeloma cells expressing low levels of CD138 have an immature phenotype and reduced sensitivity to lenalidomide, Int. J. Oncol. 41 (2012) 876–884.
[85] A. Chaidos, C.P. Barnes, G. Cowan, P.C. May, V. Melo, E. Hatjiharissi, M. Papaioannou, H. Harrington, H. Doolittle, E. Terpos, M. Dimopoulos, S. Abdalla, H. Yarranton, K. Naresh, L. Foroni, A. Reid, A. Rahemtulla, M. Stumpf, I. Roberts, A. Karadimitris, Clinical drug resistance linked to interconvertible phenotypic and functional states of tumor-propagating cells in multiple myeloma, Blood 121 (2013) 318–328.
[86] M.R. Reagan, I.M. Ghobrial, Multiple myeloma mesenchymal stem cells: characterization, origin, and tumor-promoting effects, Clin. Cancer Res. 18 (2012) 342–349.
[87] A.M. Roccaro, A. Sacco, P. Maiso, A.K. Azab, Y.T. Tai, M. Reagan, F. Azab, L.M. Flores, F. Campigotto, E. Weller, K.C. Anderson, D.T. Scadden, I.M. Ghobrial, BM mesenchymal stromal cell-derived exosomes facilitate multiple myeloma progression, J. Clin. Invest. 123 (2013) 1542–1555.
[88] A. Vacca, D. Ribatti, A.M. Roccaro, A. Frigeri, F. Dammacco, Bone marrow angiogenesis in patients with active multiple myeloma, Semin. Oncol. 28 (2001) 543–550.
[89] A. Mahindra, T. Hideshima, K.C. Anderson, Multiple myeloma: biology of the disease, Blood Rev. 24 (Suppl. 1) (2010) S5–11.
[90] T. Hideshima, D. Chauhan, R. Schlossman, P. Richardson, K.C. Anderson, The role of tumor necrosis factor alpha in the pathophysiology of human multiple myeloma: therapeutic applications, Oncogene 20 (2001) 4519–4527.
[91] T. Hideshima, N. Nakamura, D. Chauhan, K.C. Anderson, Biologic sequelae of interleukin-6 induced PI3-K/Akt signaling in multiple myeloma, Oncogene 20 (2001) 5991–6000.
[92] K. Noborio-Hatano, J. Kikuchi, M. Takatoku, R. Shimizu, T. Wada, M. Ueda, M. Nobuyoshi, Oh. I, K. Sato, T. Suzuki, K. Ozaki, M. Mori, T. Nagai, K. Muroi, Y. Kano, Y. Furukawa, K. Ozawa, Bortezomib overcomes cell-adhesion-mediated drug resistance through downregulation of VLA-4 expression in multiple myeloma, Oncogene 28 (2009) 231–242.
[93] K. Bommert, R.C. Bargou, T. Stuhmer, Signalling and survival pathways in multiple myeloma, Eur. J. Cancer 42 (2006) 1574–1580.
[94] S.V. Radhakrishnan, N. Bhardwaj, T. Luetkens, D. Atanackovic, Novel anti-myeloma immunotherapies targeting the SLAM family of receptors, Oncoimmunology 6 (2017) e1308618.
[95] V.E. Muccio, E. Saraci, M. Gilestro, V. Gattei, A. Zucchetto, M. Astolfi, M. Ruggeri, E. Marzanati, R. Passera, A. Palumbo, M. Boccadoro, P. Omede, Multiple myeloma: new surface antigens for the characterization of plasma cells in the era of novel agents, Cytometry B Clin. Cytom. 90 (2016) 81–90.
[96] M. Schoenhals, C. Frecha, A. Bruyer, A. Caraux, J.L. Veyrune, M. Jourdan, J. Moreaux, F.L. Cosset, E. Verhoeyen, B. Klein, Efficient transduction of healthy and malignant plasma cells by lentiviral vectors pseudotyped with measles virus glycoproteins, Leukemia 26 (2012) 1663–1670.
[97] I.M. Gordiienko, L.M. Shlapatska, L.M. Kovalevska, S.P. Sidorenko, Differential expression of CD150/SLAMF1 in normal and malignant B cells on the different stages of maturation, Exp. Oncol. 38 (2016) 101–107.
[98] N. Hosen, H. Ichihara, A. Mugitani, Y. Aoyama, Y. Fukuda, S. Kishida, Y. Matsuoka, H. Nakajima, M. Kawakami, T. Yamagami, S. Fuji, H. Tamaki, T. Nakao, S. Nishida, A. Tsuboi, S. Iida, M. Hino, Y. Oka, Y. Oji, H. Sugiyama, CD48 as a novel molecular target for antibody therapy in multiple myeloma, Br. J. Haematol. 156 (2012) 213–224.
[99] S. Yousef, J. Marvin, M. Steinbach, A. Langemo, T. Kovacsovics, M. Binder, N. Kroger, T. Luetkens, D. Atanackovic, Immunomodulatory molecule PD-L1 is expressed on malignant plasma cells and myeloma-propagating pre-plasma cells in

the bone marrow of multiple myeloma patients, Blood Cancer J. 5 (2015) e285.
[100] F. Pojero, J. Flores-Montero, L. Sanoja, J.J. Perez, N. Puig, B. Paiva, S. Bottcher, J.J. van Dongen, A. Orfao, g EuroFlow, Utility of CD54, CD229, and CD319 for the identification of plasma cells in patients with clonal plasma cell diseases, Cytometry B Clin. Cytom. 90 (2016) 91–100.
[101] G. Carulli, G. Buda, A. Azzara, E.M. Ciancia, P. Sammuri, C. Domenichini, V. Guerri, M. Petrini, CD229 expression on bone marrow plasma cells from patients with multiple myeloma and monoclonal gammopathies of uncertain significance, Acta Haematol. 135 (2016) 11–14.
[102] W. Jing, J.A. Gershan, J. Weber, D. Tlomak, L. McOlash, C. Sabatos-Peyton, B.D. Johnson, Combined immune checkpoint protein blockade and low dose whole body irradiation as immunotherapy for myeloma, J. Immunother. Cancer 3 (2) (2015).
[103] C. Zelle-Rieser, S. Thangavadivel, R. Biedermann, A. Brunner, P. Stoitzner, E. Willenbacher, R. Greil, K. Johrer, T cells in multiple myeloma display features of exhaustion and senescence at the tumor site, J. Hematol. Oncol. 9 (2016) 116.
[104] R.T. Costello, A. Boehrer, C. Sanchez, D. Mercier, C. Baier, T. Le Treut, G. Sebahoun, Differential expression of natural killer cell activating receptors in blood versus bone marrow in patients with monoclonal gammopathy, Immunology 139 (2013) 338–341.
[105] H. Magen, E. Muchtar, Elotuzumab: the first approved monoclonal antibody for multiple myeloma treatment, Ther. Adv. Hematol. 7 (2016) 187–195.
[106] Y.T. Tai, M. Dillon, W. Song, M. Leiba, X.F. Li, P. Burger, A.I. Lee, K. Podar, T. Hideshima, A.G. Rice, A. van Abbema, L. Jesaitis, I. Caras, D. Law, E. Weller, W. Xie, P. Richardson, N.C. Munshi, C. Mathiot, H. Avet-Loiseau, D.E. Afar, K.C. Anderson, Anti-CS1 humanized monoclonal antibody HuLuc63 inhibits myeloma cell adhesion and induces antibody-dependent cellular cytotoxicity in the bone marrow milieu, Blood 112 (2008) 1329–1337.
[107] R. Ed Hsi, B. Steinle, S. Balasa, A. Draksharapu Szmania, B.P. Shum, M. Huseni, D. Powers, A. Nanisetti, Y. Zhang, A.G. Rice, A. van Abbema, M. Wong, G. Liu, F. Zhan, M. Dillon, S. Chen, S. Rhodes, F. Fuh, N. Tsurushita, S. Kumar, V. Vexler, J.D. Shaughnessy Jr., B. Barlogie, F. van Rhee, M. Hussein, D.E. Afar, M.B. Williams, CS1, a potential new therapeutic antibody target for the treatment of multiple myeloma, Clin. Cancer Res. 14 (2008) 2775–2784.