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REVIEW

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SLAMF receptors: key regulators of tumor progression and emerging targets for cancer immunotherapy

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Abstract

The signaling lymphocytic activation molecule family (SLAMF) consists of nine distinct cell surface receptors predominantly expressed on immune cells, each characterized by unique structural features, expression patterns, downstream signaling pathways, and biological functions. These receptors play critical roles in modulating various immune cell activities within the tumor microenvironment, thereby shaping immune responses in cancer. Although accumulating evidence demonstrates their value as therapeutic targets for developing cancer immunotherapies, the full spectrum of SLAMF receptors in cancer remains incompletely understood. This review aims to provide a comprehensive overview of the molecular characteristics and immunomodulatory functions of each SLAMF receptor, underscoring their pivotal contributions to cancer progression. Furthermore, we also highlight their potential as promising targets for advancing cancer immunotherapeutic strategies. Finally, we discuss clinical trials evaluating the efficacy and safety of SLAMF receptor-based immunotherapies, emphasizing their translational relevance in the development of cancer treatments.

Keywords Signaling lymphocytic activation molecule, Immunity, Cancer, Immunotherapy

Introduction

Between 1992 and 2002, scientists discovered a group of membrane receptors that play crucial roles in transmitting signals to immune cells (Fig. 1) [1–9]. These observations provided initial insights into the signaling lymphocytic activation molecule family (SLAMF) receptors, which are also closely related to X-linked lymphoproliferative (XLP) disease [6, 10–12].

SLAMF receptors, comprising nine members, SLAMF1 (SLAM, CD150) [7, 13], SLAMF2 (CD48, BALST-1) [4], SLAMF3 (CD229, Ly9) [8, 14, 15], SLAMF4 (CD244, 2B4) [3, 16, 17], SLAMF5 (CD84) [2], SLAMF6 (CD352, NTB-A/SF2000 in human, Ly108 in mouse) [1, 9, 18], SLAMF7 (CD319, CRACC, CS1) [19], SLAMF8 (CD353, BLAME) [20], and SLAMF9 (CD84H, SF2001) [9], are widely expressed on various hematopoietic cells. Despite their similarities, these receptors have distinct structures, ligands, expression profiles, and intracellular signaling networks.

Downstream signaling components of SLAMF receptors involve intracellular adaptor proteins and protein tyrosine kinase (PTK), in which SLAMF-associated protein (SAP) families including SAP, EWS/Fli 1-activated transcript-2 (EAT-2), and EAT-2 related transducer (ERT) play important roles [6, 21–26]. Of note, variations in SLAMF receptor expression and associated proteins

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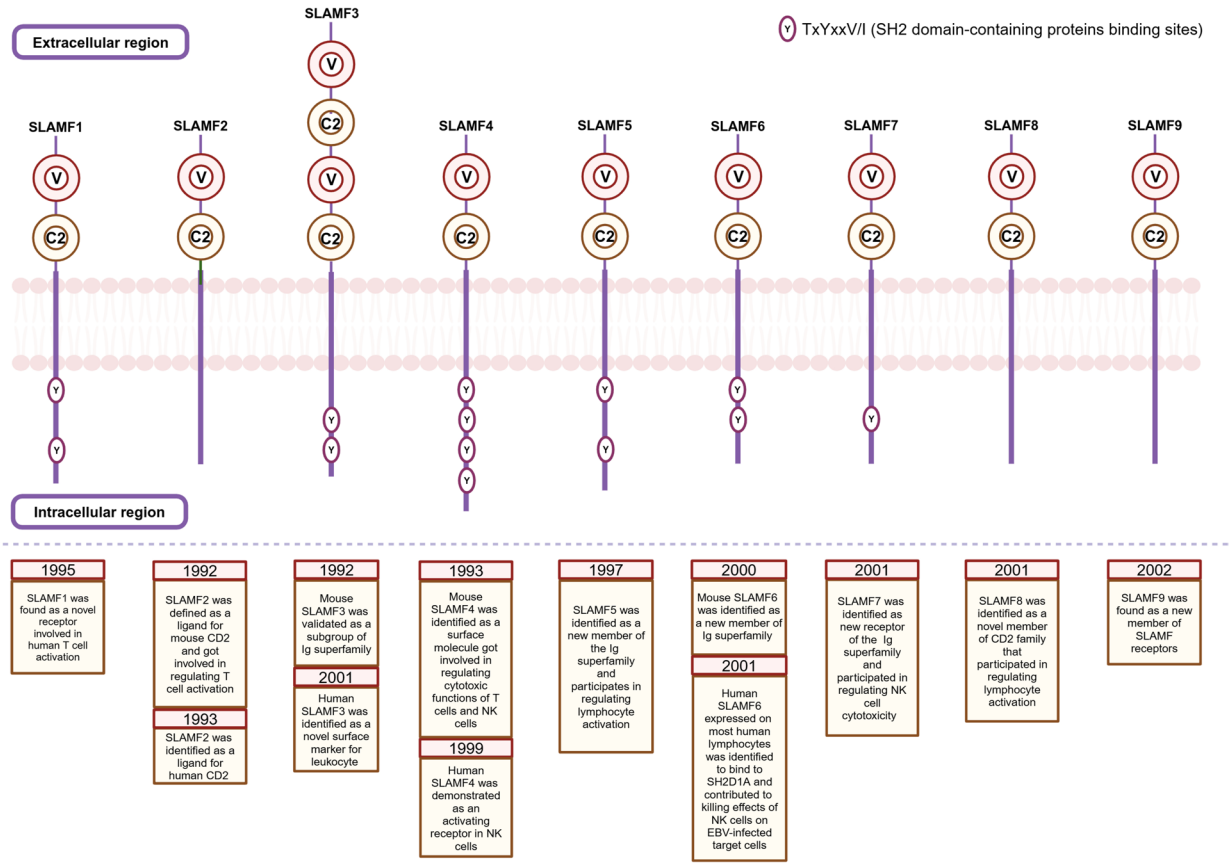

Fig. 1 The molecular structures of SLAMF receptors and their respective initial discoveries. Abbreviation: Ig, immunoglobulin; NK, natural killer; ITSM, immunoreceptor tyrosine-based switch motif; SH2, Src homology 2; EBV, Epstein-Barr virus; SLAMF, signaling lymphocytic activation molecule family; IgV, immunoglobulin variable; IgC2, immunoglobulin constant 2; CD, cluster of differentiation. The figure is created with BioRender.com

across different immune cells lead to a broad spectrum of signaling outcomes.

The abnormal expression or activation of SLAMF receptors will disrupt the immune homeostasis, influencing the progression of cancer and other immune diseases, such as genetic diseases, infectious diseases, and autoimmune diseases [27–29]. Mechanistically, dysregulated SLAMF receptor activity profoundly affects immune responses by altering cell activation, differentiation, adhesion, and responses against antigens [30–33].

The tumor microenvironment (TME) is a complex ecosystem, consisting of multiple cells, extracellular matrix components, and signaling mediators [34]. Signal transduction is indispensable for regulating tumor progression and immune responses, partially relying on the ligand-receptor interactions during cell-to-cell contact [35]. Membrane receptors play essential roles in transmitting signals to cells, thereby regulating their development, maintenance, and diverse functions [15].

Given their important immunoregulatory functions, SLAMF receptors are critically involved in regulating immune responses within the TME, where they contribute to both immune evasion and anti-tumor immunity. Studies investigating the regulatory roles of SLAMF receptors in solid tumor progression have emerged, not as the previous studies that mainly focus on hematological malignancies.

Cancer immunotherapies, such as engineered lymphocyte therapy and immune checkpoint inhibitor (ICI) therapy, have achieved success in treating many cancer patients, yet some individuals remain unresponsive [36]. Therefore, it is urgent to discover novel therapeutic targets. Significant progression has been made in developing immunotherapies targeting SLAMF receptors, with some already under clinical evaluation. Delving into the underlying mechanisms of immune cell development, their functional processes, and their involvement in cancer pathogenesis helps identify key stages at which SLAMF receptors exert critical effects, providing a solid foundation for validating their therapeutic potential.

While considerable advancements have been made, a comprehensive review that integrates the extensive

involvements of SLAMF receptors in regulating cancer-associated immune cell functions and cancer progression is lacking. Our study aims to consolidate current insights on SLAMF receptors, offering an in-depth elucidation of their structural features, signaling networks, and their influence on immune cell behaviors. Additionally, we underscore the significant contributions of SLAMF receptors in regulating tumor progression. Ultimately, we propose that SLAMF receptors have considerable promise not only as biomarkers for cancer patient prognosis but also as viable immunotherapeutic targets.

SLAMF receptors and their downstream signaling pathway

Molecular structures of SLAMF receptors

SLAMF receptors comprise nine distinct members, all of which are encoded by genes located on human chromosome 1q23 and mouse chromosome 1H2 [37]. The canonical structure of SLAMF receptors includes three domains: an extracellular domain, a transmembrane domain, and an intracellular domain. However, the specific structural features vary among the different SLAMF members (Fig. 1) [38].

Extracellular domain

Except for SLAMF2, which is anchored to the cell membrane in the lipid raft region via a glycosylphosphatidylinositol (GPI) tail and lacks the transmembrane domain, the remaining SLAMF receptors are the type I transmembrane glycoproteins belonging to the immunoglobulin CD2 superfamily [39, 40].

The extracellular domain of SLAMF receptors generally consists of two regions: a membrane-distal amino-terminal immunoglobulin variable (IgV)-like domain and a membrane-proximal Ig constant 2 (C2)-like domain [41]. The IgV-like domain lacks canonical disulfide bonds and exhibits strong self-affinity, enabling ligand or antibody binding. In contrast, the C2-like domain houses two disulfide bonds, which contribute to maintaining the structural stability of SLAMF receptors [41]. Notably, SLAMF3 is an exception with duplicated IgV-C2-like sequences, resulting in an extracellular domain containing four Ig-like domains [8, 14].

Intracellular domain

The intracellular domain of SLAMF receptors possess a cytoplasmic tail containing an immunoreceptor tyrosine-based switch motif (ITSM), with the canonical ITSM sequence being TxYxxV/I (where x represents any amino acid) [38]. This motif is crucial for transmitting signaling downstream of SLAMF receptors, as its activation facilitates the recruitment of SH2 domain-containing proteins. Most SLAMF receptors feature two ITSMs in their intracellular domains. However, some members, such as SLAMF2, lack a cytoplasmic domain and tyrosine residues, while SLAMF8 and SLAMF9 have short cytoplasmic domains that lack ITSMs. These features distinguish SLAMF2, SLAMF8 and SLAMF9 as atypical members in SLAMF receptors [20, 21, 38].

The structural variations among SLAMF receptors are significant for determining the specificity of downstream signaling pathway. A deeper understanding of their structural differences is essential for unraveling their special roles in regulating cell activities and functions, as well as in the development of diseases, such as cancer [37].

Signaling mediated by SLAMF receptors

Activation of SLAMF receptors

SLAMF receptors are primarily expressed on the surface of hematopoietic cells, though SLAMF3 is also present on hepatocytes [42].

Engagement of SLAMF receptors with ligands or antibodies initiates either positive or negative signaling pathways within cells. Most SLAMF receptors are homophilic, as they exhibit self-ligand interactions [37]. However, SLAMF2 interacts with SLAMF4 and CD2, with SLAMF4 exclusively binding SLAMF2 [43, 44].

Studies using surface plasmon resonance have shown that SLAMF1 forms the homodimers via interactions between the IgV-like domains located at the distal end of the membrane [45]. SLAMF3 also interacts with its self-ligand through the IgV-like domain, which has been confirmed by introducing point mutations in its IgV-like domains [46]. The self-ligand interaction is also observed in SLAMF4, SLAMF5, and SLAMF6, as confirmed through crystallographic studies [38, 47, 48]. In addition, flow cytometry analysis has also shown that SLAMF7 combines with its self-ligands via an IgV-like domain [49]. However, the ligands for SLAMF8 and SLAMF9 are yet to be fully defined, and these receptors may be activated by other mechanisms.

Intracellular proteins downstream of SLAMF receptors

Engagement of SLAMF receptors triggers intricate intracellular signaling networks through the recruitment of adaptor proteins and PTKs. These pathways regulate a variety of biological events, including immune cell activation and function (Fig. 2) [50].

Key adaptor proteins involved in SLAMF-receptor mediated signaling pathways include SAP, EAT-2, and ERT, which contain the SH2 domains that interact with the phosphorylated ITSMs of SLAMF receptors [41]. *SH2D1A* (encodes human SAP) and *Sh2d1a* (encodes murine SAP) are located on chromosome X, whereas *SH2D1B* (encodes human EAT-2), *Sb2d1b* (encodes murine EAT-2), and *Sb2d1c* (encodes murine

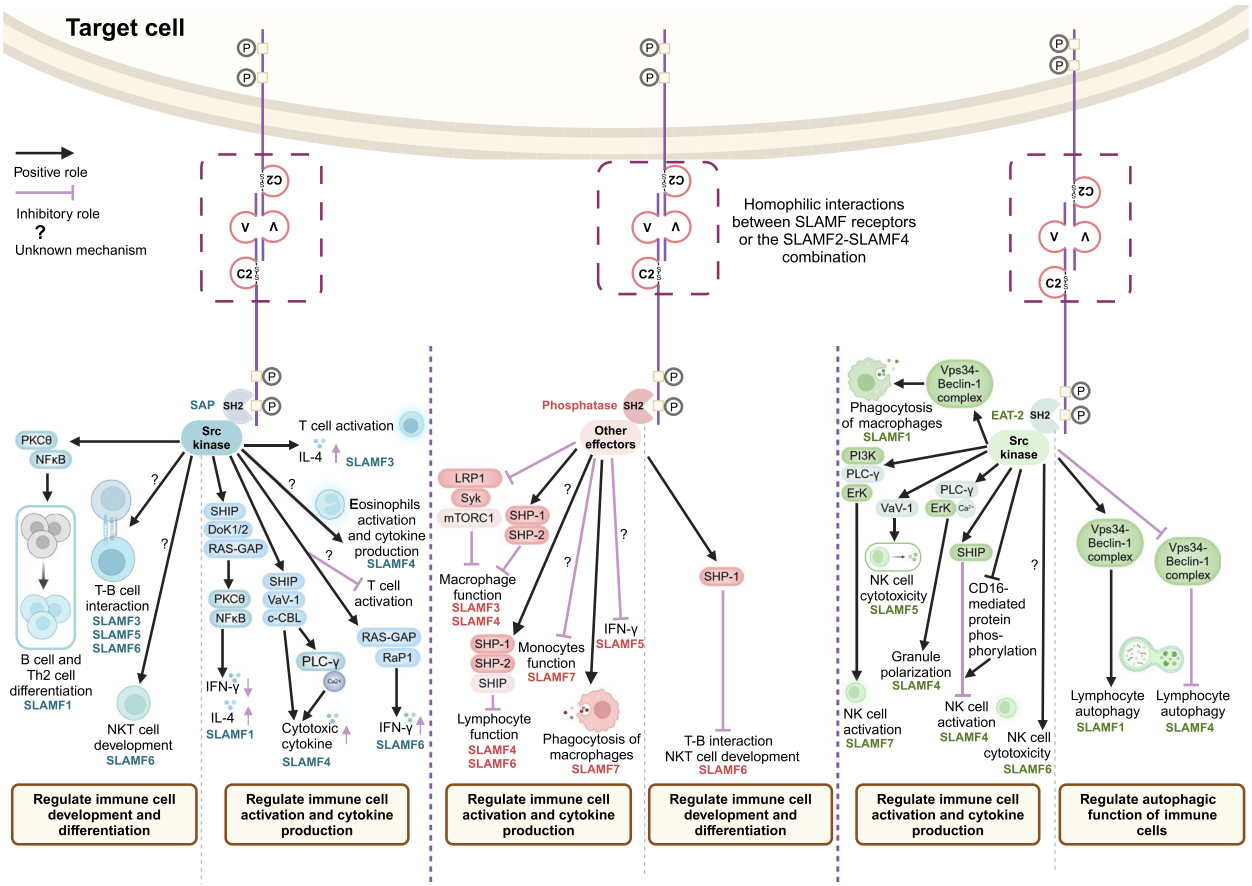

Fig. 2 Roles of signaling networks downstream of SLAMF receptors in regulating immune cells. The homophilic interaction of SLAMF receptors between immune cells and target cells will trigger a cascade of downstream protein activation. Most signaling transmitted by SLAMF receptors needs the involvement of the SAP adaptor family having an SH2 domain, like SAP, EAT-2, and ERT. In contrast, some SLAMF receptors transmit signals in the SAP adaptors-independent manner but recruit inhibitory phosphatases containing the SH2 domain, such as SHIP, SHP-1, and SHP-2. Finally, these signaling pathways downstream of SLAMF receptors play different roles in regulating immune cells. However, the specific mechanisms of some roles are still unclear. The graph on the left shows the SAP-dependent signaling pathway of SLAMF receptors and their corresponding roles. The graph in the middle shows the SAP adaptors-independent signaling networks and their roles in regulating immune cells. The graph on the right shows the EAT-2-dependent signaling pathway of SLAMF receptors and their corresponding roles. Abbreviation: SAP, SLAMF-associated protein; EAT-2, Ewing's sarcoma-associated transcript-2; ERT, EAT-2 related transducer; Th2, T helper 2; PKCθ, protein kinase C-theta; NF-κB, nuclear factor-kappa B; IFN-γ, interferon γ; Ca, calcium; c-CBL, c-Casitas B-lineage lymphoma; PLC-γ, phospholipase C gamma; Erk, extracellular signal-related kinase; SHIP, SH2-domain-containing inositol-5-phosphatase; SHP, SH2 domain-containing protein tyrosine phosphatases; Csk, C-terminal Src kinase. The figure is created with BioRender.com

ERT) are found on chromosome 1 [38, 51]. In addition, a recent study has identified a novel adaptor protein, SH2 domain-containing adaptor protein B (SHB), which interacts with SLAMF7 through its cytoplasmic 304 tyrosine sites [52].

Except for combining SAP families, SLAMF receptors also recruit SH2 domain-containing enzymes, such as SH2-domain-containing inositol-5-phosphatase (SHIP), SH2 domain-containing protein tyrosine phosphatases (SHP), docking protein 1 (DoK1), DoK2 and RAS-GTPase-activating protein (RAS-GAP) [50, 53–56]. Notably, SAP and EAT-2 can sterically shield their ITSMs from combining with other phosphatases, thus preventing dephosphorylated [23, 57, 58]. Of note, the distribution of these intracellular proteins varies across different hematopoietic cells, with distinct patterns observed between humans and mice, highlighting the complexity and cell-type specificity of SLAMF receptor-mediated signalings [41].

SAP-dependent signaling transmitted by SLAMF receptors

SAP is a 128 amino acids (14 kDa) intracellular adaptor protein featuring a single SH2 domain [38]. The SH2 domain of SAP binds to the ITSM of SLAMF receptors, recognizing a phosphorylated tyrosine and a hydrophobic binding pocket, with a preference for the TIYxxV/I/L/T

motif [59]. Upon binding to the ITSMs, SAP recruits Src-related kinases, including the lymphocyte-specific protein tyrosine kinases (LCK) and proto-oncogene tyrosine-protein kinase (Fyn), which phosphorylates other remaining tyrosine residues in the cytoplasmic ITSMs of SLAMF receptors, further activating the downstream pathways [26].

The SAP-recruited kinases then SAP interacts with the SH3 domain of protein tyrosine kinase and Fyn, without affecting the SLAMF binding sites [60]. The mutation of arginine (R) 78 residue in SAP disrupts the following signaling transduction mediated by the combination of SLAMF receptor activation [60, 61]. Therefore, the R32 residue within the SH2 domain of SAP interacts with the ITSM of SLAMF receptors, while the R78 residue binds to the SH3 domain of Fyn, forming a trimolecular complex [60, 61]. Although the SH2 domain of SAP typically engages with phosphorylated tyrosine residues, it can also combine with the non-phosphorylated tyrosine residues of SLAMF1 via a three-pronged binding mechanism [62].

Studies have identified that SAP exists in thymocytes, T cells, B cells, NK cells, natural killer T (NKT) cells, eosinophils, and platelets but is absent in neutrophils, monocytes, and dendritic cells (DCs) [6]. The SLAMF receptor-SAP axis plays significant roles in cellular functions, with the presence or absence of SAP greatly influencing the signals transmitted by the SLAMF receptors [63]. For instance, SLAMF1 phosphorylation in thymocytes necessitates SAP, which links SLAMF1 to Fyn [61]. Moreover, engagement of SLAMF1 potentiates the SAP-mediated signaling pathway in wild-type mice, but not in *Sh2d1a*-deficient mice [64].

SLAMF receptor-SAP axis regulates various cellular processes (Fig. 2). In T cells, this signaling cascade leads to the recruitment of protein kinase C-theta (PKCθ) to the immune synapse, which triggers nuclear factor-kappa B (NF-κB) activation and GATA-3 induction. This occurs through a cascade of protein tyrosine phosphorylation involving SHIP, DoK1, DoK2, and Ras-GAP, ultimately causing decreased interferon (IFN)-γ production and increased interleukin (IL)−4 production [64]. Therefore, the SLAMF-SAP axis plays a pivotal role in regulating the helper T (Th) 2 cytokine production and T cell development [65, 66]. Other studies also indicate that SLAMF1-SAP axis-mediated pathways are important for NKT cell development [67, 68]. Additionally, the SAP-dependent SLAMF receptor-mediated pathway influences B cell activation through regulating the SHIP/PI3K/AKT axis [69, 70], or the SHIP/Ras/Raf/mitogen-activated protein kinase (MAPK)-extracellular-signal-regulated kinase (Erk) kinase (MEK)/ Erk signaling pathway [71, 72]. Furthermore, SLAMF5 and SLAMF6 enhance T-B cell interactions in an SAP-dependent manner, as well as SLAMF4 modulates the cytotoxic effects of NK cells and $CD8^+$T cells also require SAP existence [54, 73].

Besides lymphocytes, the SLAMF4-SAP axis aids the activation and cytokine production of eosinophils [74]. SLAMF5 contributes to platelet aggregation and functions in an SAP-dependent manner [75]. Thus, the SLAMF-SAP axis is crucial in regulating both lymphoid and non-lymphoid hematopoietic cells. Beyond the important roles of SAP in the hematopoietic system, it also has potential implications for studying the nervous system. Specifically, SAP was reported to bind to the phosphorylated tyrosine 674 on tropomyosin receptor kinase receptors, inhibiting the signaling transmitted by the interaction of neurotrophins and tropomyosin receptor kinase receptors [76]. These findings underscore the need for further investigation into the roles of SAP across various biological systems.

EAT-2 or ERT-dependent signaling transmitted by SLAMF receptors

EAT-2 is a 132 amino acid protein expressed in NK cells, DCs, $CD8^+$T cells, macrophages, B cells, and platelets. It also contains a single SH2 domain that interact with the ITSMs of several SLAMF receptors, including SLAMF1, SLAMF3, SLAMF4, SLAMF5, SLAMF6 and SLAMF7 [23, 77].

EAT-2 is similar to SAP structurally, and its free SH2 domain also binds to the intracellular tail of the phosphorylated SLAMF receptor, but not to the non-phosphorylated receptor [23]. In contrast to SAP, EAT-2 is most inclined to bind the TEYxxV/I/L/T motif of SLAMF7 [78]. In addition, EAT-2 lacks the binding region of kinase Fyn, so the kinases they recruit are not identical to SAP, following the signal transduction ways of EAT-2 are distinct from SAP [41]. Evidence from overexpression studies and Biacore binding assays indicates that Fyn can bind to phosphorylated tyrosine residues in EAT-2 [21, 79], although yeast two-hybrid analysis suggests a direct interaction between EAT-2 and the catalytic domain of Src family kinases [23]. The precise mechanisms remain unresolved.

EAT-2-mediated signaling pathways downstream of SLAMF receptors play various roles in regulating cell activities (Fig. 2). For instance, SLAMF1 is an activator, and SLAMF4 acts as an inhibitor in regulating lymphocyte autophagy [80, 81]. Specifically, the SLAMF4-EAT-2 axis plays a bidirectional role in modulating NK cell cytotoxicity by initiating different downstream proteins [30, 82, 83]. Furthermore, combining EAT-2 with either SLAMF5, SLAMF6, or SLAMF7 can enhance NK cell cytotoxicity [23, 77, 78, 84, 85]. Additionally, the SLAMF1-EAT-2 signaling

pathway is crucial for augmenting macrophage phagocytic activity [86].

ERT, expressed exclusively in mouse NK cells and functioning as a pseudogene in humans. Both EAT-2 and ERT can transmit negative signals downstream of SLAMF4 in NK cells, suppressing their cytotoxic functions, whereas SAP typically exerts a positive effect [21, 30]. However, the current knowledge about ERT remains limited, and ERT's preferential binding sequence is yet to be elucidated.

In summary, while EAT-2 and ERT, along with SAP, interact with various SLAMF receptors and protein kinases across different cell types, each of them uniquely contributes to the regulation of the SLAMF receptor-mediated intracellular signaling pathways, illustrating the complex roles of adaptor proteins in balancing immune responses.

Adaptor-independent signaling transmitted by SLAMF receptors

In addition to interacting with SH2 domain-containing adaptor proteins, SLAMF receptors can also transmit signals by directly recruiting the SH2 domain-containing inositol and tyrosine phosphatase, particularly in the absence or abnormal expression of adaptor proteins (Fig. 2).

SAP has been demonstrated as a natural inhibitor of the SHP-2 phosphatase [16]. In SAP-deficient B cells, SHP-2 can directly bind to SLAMF1 and in turn, associate with Grb2, leading to the activation of the Ras/Raf/MEK/Erk signaling cascade, which plays a crucial role in regulating cell development [87, 88]. SLAMF4 and SLAMF6, on the other hand, mediate inhibitory signals by recruiting SHP-1, SHP-2, SHIP, and inhibitory kinases C-terminal Src kinase (Csk), leading to the suppression of lymphocyte functions [54, 89]. Additionally, SLAMF3 and SLAMF4 can inhibit macrophage functions by recruiting SHP-1 and SHP-2 [90].

In the absence of SAP and EAT-2, SLAMF5 inhibits mast cell function [91, 92], while SLAMF7 contributes to the suppression of proinflammatory cytokine production by LPS-induced activated monocytes [93]. In addition, SLAMF7 also binds to a novel adaptor, SHB, which further recruits SHIP-1, ultimately suppressing the MAPK/ATF-2 signaling pathway and inhibiting CCL2 transcription [52].

Above all, these observations underscore the importance of adaptor-independent signaling in fine-tuning immune response, especially in cells where classical adaptor proteins are absent or mutated.

The competition between SLAMF receptor-associated intracellular proteins

In addition to the points discussed above, we are interested in understanding which adaptor-SAP or EAT-2 will bind to SLAMF receptors first when both are present in the same cell, and how to explain the competitive relationship between these intracellular SH2 domain-containing proteins.

The most straightforward explanation lies in the distinct localization of these adaptors and phosphatases across different cell types. Moreover, the competition between intracellular adaptors may also be influenced by cell states. For instance, EAT-2 preferentially binds SLAMF4 in resting and immature NK cells, whereas SAP predominantly associates with SLAMF4 during NK cell activation and maturation [84]. This difference in binding preference is a reflection of the dynamic regulation of immune responses during cell development and activation.

Many studies have highlighted the competitive nature of SAP and EAT-2 binding to SLAMF receptors. For instance, EAT-2 exhibits a higher binding affinity for the second ITSM of SLAMF7 compared to SAP, as shown in NK92 cells [94]. Despite SAP being present at concentrations more than four times higher than EAT-2, EAT-2 binds SLAMF7 with significantly greater affinity ($K_D = 0.003$ μM) than SAP ($K_D = 0.44$ μM). Furthermore, both SAP and EAT-2 demonstrate binding affinities for SLAMF4 ITSMs that are ten to a hundred times stronger than those of SHIP [94]. These findings indicate that the relative concentrations and binding kinetics of SAP and EAT-2 play a pivotal role in determining which adaptor binds first and their competition with intracellular SH2 domain-containing proteins for ITSMs of SLAMF receptors.

SAP and EAT-2 exhibit a steric hindrance effect, preventing inhibitory phosphatases from interacting with ITSMs. When the adaptors are absent or present at low concentrations, phosphatases are more likely to bind to ITSMs, albeit competing with each other. In the presence of SAP, SLAMF1 preferentially recruits SHIP while also combining with SHP-2 in SAP-deficient cells. Notably, the combination of SHP-2 with SLAMF1 is more pronounced in SAP-low B cell lines compared to SAP-high B cell lines [87]. This may be influenced by the B cell receptor (BCR) and CD40 signaling. Long-term BCR signaling enhances SAP expression, while short-term signals inhibit the interaction between SLAMF1 and SHIP. Additionally, the binding of SAP to the ITSM of SLAMF1 at Y281 can hinder the recruitment of SHP-2 to Y279, without affecting SHIP binding [87]. This finding suggests a

finely tuned regulation of protein interactions within SLAMF receptor signaling, where SAP's binding can selectively modulate the recruitment of other signaling proteins.

Overall, the complex interplay between adaptor concentrations, binding affinities, and cellular context critically governs the intracellular signaling pathways downstream of SLAMF receptors, underscoring the significant role of adaptor proteins.

Roles of SLAMF receptors on cancer-associated immune cells

Immune cells play indispensable roles in regulating tumor progression, with SLAMF receptors being critical contributors in this process. This section will explore the specific roles of SLAMF receptors on different immune cell types, focusing on their impact on immune cell development, maintenance, and activation (Fig. 3).

Lymphoid-lineage immune cells

T cell

T cells, which mainly include both classical αβT cells and unconventional T cells (e.g., γδT cells and NKT cells), play robust killing effects on autologous malignant cells [95]. Almost every member of the SLAMF receptors is expressed on T cells, where they influence T cell in multiple ways [96–98].

T cell development T cell development primarily occurs in the thymus, where T cells undergo selection and lineage commitment to acquire specific phenotypes. SLAMF receptors and intracellular adaptor proteins significantly participate in regulating the development of T cells [99–101].

SLAMF receptors regulate T cell development through functioning as co-receptors to regulate T cell receptor (TCR)-mediated signaling. The different degrees of TCR activation can shift the relative contribution of SLAMF1 signals during T cell development [101].

SLAMF receptor signaling is particularly important in the development of NKT cells, which require positive selection through interactions with CD1d-expressing thymocytes before exiting the thymus [102]. In mice lacking SLAMF1 and SLAMF6, NKT cell numbers are markedly reduced, indicating that these receptors mediate the essential homophilic interactions between NKT cells and double-positive thymocytes during positive selection [103, 104]. Moreover, the absence of SLAMF receptors impairs NKT cell survival and cytotoxic responses to CD1d-restricted antigens, likely due to the

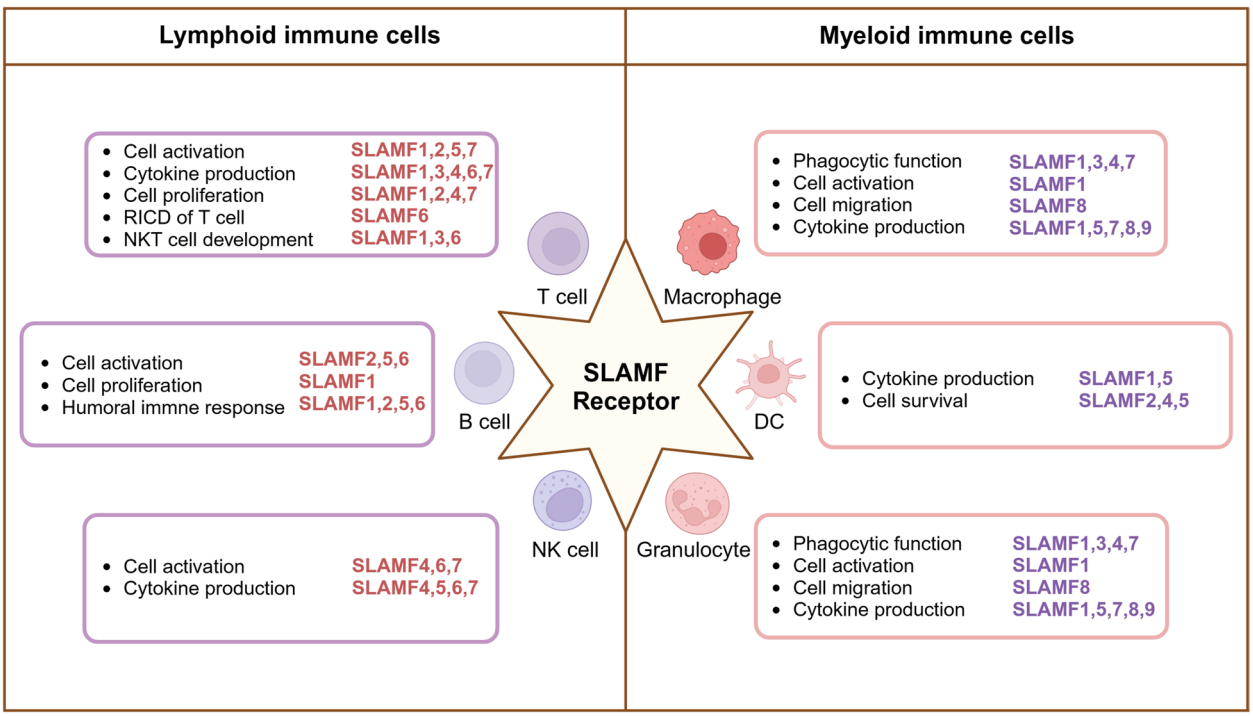

Fig. 3 Regulation s of SLAMF receptors on immune cells. SLAMF receptors are predominantly expressed on immune cells, including lymphoid and myeloid lineage immune cells. This figure shows the involvement of SLAMF receptors in regulating these cells in many aspects. Abbreviation: RICD, restimulation-induced cell death; DC, dendritic cell. The figure is created with BioRender.com

increased expression of inhibitory receptors such as programmed cell death-1 (PD-1) and lymphocyte activation gene 3 [105]. Conversely, SLAMF3 can restrict NKT cell development by limiting IL-4 production, a cytokine crucial for NKT cell maturation [106]. However, whether SLAMF receptors integrate with TCR signals to regulate NKT cell homeostasis remains unknown, and whether elevated inhibitory receptor expression could fully compensate for SLAMF receptor deficiencies has yet to reach a consensus. Investigating these questions will provide the deeper insights into the role of SLAMF receptors in modulating NKT cell biology.

Beyond NKT cells, SLAMF receptor expression profiles also define specific stages and subsets of γδT cells [107]. For example, immature γδT cells co-express SLAMF1 and SLAMF6 in the thymus, whereas mature subsets express only one or neither receptor. Scientists have also found that distinct SLAMF receptor expression patterns correlate with the functional outputs of γδT cells. For instance, lung-SLAMF1^{+}SLAMF6^{-}γδT cells resemble IL-17-producing subsets, while SLAMF1^{-}SLAMF6^{+}γδT cells preferentially secrete IFN-γ [107]. In agreement with these findings, SAP-deficient mice exhibit greatly impaired development and function of γδT cells, highlighting the critical implications of SLAMF receptor signaling in shaping these unconventional T cell compartments [107].

Taken together, SLAMF receptors and their intracellular signaling cascades are pivotal in orchestrating the development and functions of T cells.

T cell activation and homeostasis SLAMF receptors serve as co-receptors that can either potentiate or modulate TCR-mediated signals, thereby influencing T cell activation. For example, SLAMF1 delivers co-stimulatory signals crucial for naïve T cell activation [87]. Moreover, SLAMF6 recruits LCK via SAP to connect the SLAMF6 signal to proximal TCR pathway, resulting in the phosphorylation of the CD3ζ chain of TCR and subsequent recruitment of zeta-chain-associated protein kinase 70 (ZAP-70), effectively amplifying TCR signaling [108]. Additionally, SLAMF5 also augments TCR signaling in an SAP-independent manner [109, 110].

In addition to promoting T cell activation, SLAMF receptors play key roles in regulating T cell homeostasis. SLAMF6 gets involved in the activation-induced cell death and restimulation-induced cell death (RICD) in CD8^{+}T cells. Its binding with SHP-1 can prevent CD8^{+}T cells from overaction [10]. Aberrant SLAMF6/SAP signaling during infections (e.g., tuberculous) leads to the preferential recruitment of Fyn instead of LCK, impairing Th2 differentiation and IL-2 production, which is indispensable for the RICD of T cells [111, 112]. FOXP3 is a transcription factor (TF) that suppresses SH2D1A expression, also modulates susceptibility to RICD in regulatory T (Treg) cells, highlighting the regulatory role of SLAMF receptors and SAP in maintaining T cell homeostasis [112, 113].

T cell cytokine production

Cytokine production is a central function of T cells, in which SLAMF receptors are significantly involved. SLAMF1 inhibition has been shown to amplify T cell cytotoxicity, strengthen IFN-γ production, and promote T cell proliferation while inhibiting Th2 responses [114–116]. However, some studies indicate the positive roles of SLAMF1 in regulating T cell cytotoxicity, which is potentially linked to the magnitude of SLAMF1-SAP signaling, whereas others report opposite views, underscoring the context-dependent complexity of SLAMF1 functions [117–119]. A growing body of evidence has demonstrated that the SLAMF1-SAP axis predominately initiates Th2 responses while suppressing IFN-γ production, as evidenced by findings in mouse models lacking SAP, SLAMF1, or FynT, and in XLP1 patients [25, 64, 104, 120, 121]. In contrast, the SLAMF6-CD3 cross-talk in T cells elevates IFN-γ production and promotes proliferation by activating the downstream GTPase RAS and Rap1 [55, 98].

CD8^{+}T cells are crucial in controlling tumor progression by performing cytotoxic functions. The roles of SLAMF receptors on CD8^{+}T cells have been extensively studied, with some receptors exhibiting dual functionality [33]. For instance, SLAMF2-SLAMF4 interactions provides co-stimulatory signals to strengthen the proliferation and cytotoxic molecule production of CD8^{+}T cells [122–124]. The involvement of SLAMF7 enhances the cytotoxic effects of CD8^{+}T cells in multiple myeloma (MM) [125, 126]. Nonetheless, some SLAMF receptors transmit inhibitory signals for CD8^{+}T cells [127]. For example, the SLAMF4-EAT-2 axis suppresses expansion and cytotoxicity of intra-epithelial CD8^{+}T cells, preventing excessive inflammation and maintaining homeostasis in the small intestine [128].

As for CD4^{+}T cells, SLAMF1, SLAMF2, and SLAMF3 contribute to their proliferation and cytokine secretion, whereas SLAMF7 exerts negative regulatory effects. [31, 129–131] Notably, SAP expression in CD4^{+}T cells significantly affects GC formation, independent of Fyn recruitment, and is distinct from the Th1/Th2 differentiation mechanisms driven by the SLAM-SAP-Fyn axis [132]. In general, these findings indicate the multifaceted influence of SLAMF receptors on T cell cytokine production and their relevance to cancer immunity.

B cell

B cells are integral to humoral immunity, expressing nearly all SLAMF receptors, which regulate B cell activation, differentiation, and antibody production. Owing to the distinct expression patterns of SLAMF receptor across B cell developmental and activation status [133], SLAMF receptors participate in various B cell-related processes, including humoral responses, germinal center (GC) formation, B cell activation, and maintenance. They also get involved in B cell-derived malignancies such as chronic leukemia (CLL), MM, and Hodgkin's lymphoma (HL) [134].

After activation by antigen-specific $CD8^+$T cells and DCs, $CD4^+$Th cells migrate into the follicles and GCs, where they differentiate into follicular helper T (T_{FH}) cells that drive B cell maturation and antibody production [135]. The interplay between T cells and B cells is essential for the formation of GCs and the subsequent humoral immune response [134].

Roles of SLAMF receptors in B cell activation and antibody production SLAMF receptors play critical roles in promoting humoral immunity by enhancing the survival and function of antigen-specific B cells, upregulating pro-survival molecules such as BCR and Bcl2, and increasing antibody production [136].

SLAMF1 has been demonstrated to promote the proliferation and immunoglobulin production of activated B lymphocytes [137], and its blockade can inhibit B cell proliferation and differentiation [138]. Moreover, SLAMF2 and SLAMF3 also contribute to B cell activation and antibody production against T-independent antigens [139, 140]. In mice, SLAMF2-CD2 interactions protect B cells from apoptosis and enhance human B cell responsiveness to IL-4 or IL-10 when co-stimulated via CD40-CD40L [4]. In contrast, SLAMF6 can recruit SHP-1 in the absence of SAP, hindering T-B cell interaction [141].

SLAMF receptors in T_{FH}-B cell interactions and GC reactions SLAMF1, SLAMF5, and SLAMF6 are expressed on both T_{FH} cells and GC B cells. Although SLAMF6 has been implicated as a negative regulator of humoral immunity, the activation of SLAMF5 and SLAMF6 can also prolong T_{FH} -GC B cell interactions in an SAP-dependent manner [73].

Intriguingly, triple knockout mice lacking *Slamf1*, *Slamf5,* and *Slamf6* exhibit enhanced antigen-specific humoral immunity, including increased antibody production [142]. However, Zhong et al. reported that knocking out these three genes impaired antibody production but did not affect GC formation [136]. The reasons for the variability in these outcomes are unknown. A study even showed normal GC response despite the absence of seven SLAMF receptors [143]. But the SAP expression increases in T_{FH} cells [144], and its deficiency disrupts the recruitment of $CD4^+$Th cells, further breaking down interactions between $CD4^+$Th cells and cognate B cells, impeding GC formation and antibody production by reducing Th2-type cytokines [50]. Therefore, SAP in B cells appears more essential for sustaining normal GC reaction and effective humoral response.

Studying SLAMF receptor cross-linking in B cells is complicated by the close genomic proximity of SLAMF receptor genes on the same chromosome, making it technically challenging to generate multi-knockout models [145]. This constraint hinders efforts to fully dissect how overlapping or synergistic signals among various SLAMF receptors govern B cell function and humoral immunity.

NK cell

NK cells can non-specifically eliminate target cells without prior sensitization, playing critical roles in diverse immune processes [146]. They express all SAP family adaptors, and both SLAMF receptors and SAP families greatly participate in regulating NK cell biology [147, 148].

NK cell development and education During NK cell development, SLAMF receptor expression patterns vary across different stages. In mice, SLAMF1 and SLAMF6 levels gradually decreases, with SLAMF1 ultimately disappearing, whereas SLAMF4, SLAMF5, and SLAMF7 remain highly expressed throughout NK cell development [58, 149]. Therefore, each SLAMF receptor may exert its specific effects on NK cell maturation.

NK cell education refers to the process by which interactions between MHC-I or other molecules expressed on target cells and NK cell inhibitory receptors enable NK cells to acquire specific functions and self-tolerance [150, 151]. Recent evidence suggests that SLAMF receptors can also function as activating receptors in NK cell education, and the persistent activation of SLAMF receptors will increase NK cell tolerance, contributing to the pathogenesis of XLP1 [149, 152].

Mechanisms of SLAMF receptor-mediated NK cell activation Most SLAMF receptors transmit activating signals for NK cells in an SAP-dependent manner. Upon SLAMF receptor engagement, SAP and Fyn kinase are recruited to phosphorylated ITSM, driving the Vav-1 phosphorylation and facilitating immunological synapse formation between NK cells and hematopoietic target cells [53, 147, 153].

SAP-Fyn interactions can also trigger the PLCγ phosphorylation following the MAPK signaling activation and $Ca2^{+}$ flux, all of which support cytotoxic effector functions [53, 154]. For instance, SLAMF4 relies on SAP-Fyn-dependent phosphorylation event to further phosphorylate Vav1 and c-Casitas B-lineage lymphoma (c-CBL), thereby enhancing NK cell cytotoxicity [38, 58, 155].

Beyond SAP, EAT-2 can also transduce positive signals mediated by SLAMF receptors. EAT-2 serves as an intermedium that connects the ITSM of SLAMF4 with the PLCγ, promoting the Ca^{2+} influx and further Erk phosphorylation, facilitating NK cell activation by accelerating granulation and polarization, distinct from SAP-driven adhesion to target cells [30, 83, 89]. Additionally, SLAMF2-SLAMF4 interactions can reduce NK cell apoptosis via activating Erk/ Bcl-2 signaling, thereby enhancing anti-tumor activity [82].

Other SLAMF receptors also engage EAT-2 to drive NK cell cytotoxicity. For instance, SLAMF5 homophilic interactions between NK cells and tumor cells enhance NK cell cytotoxicity through Vav-1 activation [85]. The combination of SLAMF6 with EAT-2 also promotes NK cell cytotoxicity and avoid the binding of SH2-domain-containing phosphatase [23, 77]. Similarly, SLAMF7 augments NK cell cytotoxicity by recruiting EAT-2 to activate PI3K, PLCγ, and Erk pathways [78, 84].

Interestingly, SLAMF4 also combines with other adaptors to regulate NK cell functions. They promote the cytotoxicity of NK cells by activating the adaptor 3BP2 and downstream PI3K, Vav-1, PKC, and PLC-γ signaling cascades, illustrating the context-dependent nature of SLAMF receptor function [156].

Mechanisms of SLAMF receptor-mediated NK cell inhibition EAT-2 can also transmit inhibitory signals for NK cells under certain conditions. For example, EAT-2-deficient NK cells produce more IFN-γ and IL-12 downstream of the SLAMF4 engagement, whereas the EAT-2 existence suppresses protein tyrosine phosphorylation triggered by proximal activating receptors [30]. Additionally, some SLAMF receptor-mediated inhibitory pathways proceed independently of SAP families in NK cells, instead relying on SH2-domain-containing phosphatases [58].

In SAP-deficient NK cells, the SLAMF4-mediated NK cell cytotoxicity is significantly impaired by combining inhibitory phosphatases SHIP, SHP-1, SHP-2, or inhibitory kinase Csk with their intracellular ITSM. Genetic ablation of SHIP1, SHP-1, and SHP-2 can reverse this inhibition, underscoring crucial roles of phosphatases in NK cell suppression [53, 54].

Bidirectional roles and therapeutic implications Overall, SLAMF receptors impact both NK cell development and effector functions through multiple signaling networks [32].

For the same SLAMF receptor, the signaling nature depends on which adaptor proteins or phosphatases the receptor recruits. For example, the SLAMF4-SAP axis typically transmits positive signals, whereas the SLAMF4-EAT-2 axis inhibits NK cell activation [30, 83]. The competition between SLAMF4 and CD2 for SLAMF2 also contributes to SLAM4-mediated inhibitory signalings [157]. Furthermore, for the same intracellular adaptor, the different outcomes of intracellular signaling may be influenced by SLAMF receptor categories, such as their ITSM affinity and ligation. For instance, SLAMF6 and SLAMF7 generally transmit positive signals for NK cells by recruiting EAT-2 [23, 77, 158] whereas SLAMF4 commonly engages SAP for activation but switches to EAT-2 for inhibitory effects [30, 155].

Collectively, SLAMF receptors exhibit bidirectional influences on NK cell biology, making them promising targets for exploring NK cell-related pathologies and developing potential immunotherapeutic interventions. Elucidating the molecular basis of these dual roles may pave the way for precision therapies that harness NK cells to combat cancer and other diseases.

Myeloid-lineage immune cells

Macrophages

Macrophages are the key members of the innate immune system and play an indispensable role in defending against pathogens and clearing aberrant host cells [159]. They express SLAMF1, SLAMF3, SLAMF5, SLAMF6, SLAMF8, and SLAMF9 [160] each influencing macrophages in many aspects.

Phagocytosis is the central capability of macrophages, and multiple SLAMF receptors modulate this process under pathological conditions. For example, SLAMF1 enhances the phagocytotic ability of macrophages, and their expression is positively associated with IL-12 production by macrophages [86, 104]. In contrast, SLAMF3 and SLAMF4 expressed on hematopoietic cells can inhibit macrophage phagocytosis via inhibiting the LRP1/Syk/mTORC1 signaling pathway in an SAP-independent manner but recruiting SHP-1 and SHP-2 [90]. Furthermore, chimeric antigen receptor macrophages (CAR-Ms) lacking SLAMF receptors show enhanced phagocytic abilities on $CD19^{+}$hematopoietic cells [90]. SLAMF5 mediates the production of pro-inflammatory cytokines like TNF-α and MCP-1 through intracellular MAPK and NK-κB signaling in macrophages [161]. Moreover, the

silenced expression of SLAMF8 and SLAMF9 downregulates Toll-like receptor (TLR) 4 expression and subsequently impairs the production of pro-inflammatory cytokines [160]. SLAMF9 is found to be expressed on tumor-associated macrophages (TAMs) in B16F1 mouse model, and SLAMF9$^+$ TAMs are also found in most human melanomas [162]. Although SLAMF9 can promote TNF-α production by macrophages and curb their migration upon LPS stimulation, its specific roles in regulating tumorigenesis are undefined [162].

S1PRα is an inhibitory receptor expressed on macrophages, and its ligand CD47 is expressed on tumor cells [163]. Blocking the CD47-S1RPα axis can increases macrophage phagocytosis of tumor cells, especially hematopoietic malignancies [164]. However, knocking out all SLAMF receptors in macrophages counteracts the prophagocytic benefic of CD47 blockade [165], suggesting that SLAMF receptor expression on hematopoietic cells is pivotal for macrophage-mediated clearance of hematopoietic tumors. Among the five SLAMF receptors (1, 3, 4, 5, 7) expressed on macrophages, the loss of SLAMF7 profoundly impairs macrophage phagocytotic capacity, and the reinstatement of SLAMF7 expression restores tumor engulfment [165]. Hence, SLAMF7 plays an indispensable role in the phagocytosis of hematopoietic tumor cells by macrophages.

Altogether, SLAMF receptors can both promote and inhibit macrophage activation and function, but the precise mechanisms warrant further investigation.

Granulocytes

According to the staining properties of the particles on the pigment, granulocytes are divided into three types, including neutrophils, eosinophils, and basophils. They play vital roles in pathogen defense and tumor immunity [166–168].

Neutrophils are the most abundant population among leukocytes, and they kill infectious pathogens or abnormal cells by degranulation [169]. SLAMF1 expression on human neutrophils increases upon the tuberculosis infection, and the SLAMF1 inhibition enhances neutrophil autophagy [170]. Moreover, neutrophil oxidative burst is crucial for early defense against invading microorganisms [171]. In mice lacking intact SLAMF6 expression, neutrophils fail to produce oxidative bursts against bacterial infection, highlighting SLAMF6 as an important regulator of neutrophil function [103].

Eosinophils are an indispensable player in parasitic infections and allergic inflammation. They express SLAMF2, SLAMF4, SLAMF5, SLAMF6, and SLAMF8, whereas SLAMF6 is absent in basophils [43, 74]. SLAMF2 can serve as an activating receptor on eosinophils, its ligation with exotoxins and *S.aureus* enhances eosinophil degranulation [172]. Additionally, SLAMF2 expressed on eosinophils promotes inflammatory processes during allergic response [173], and the interaction between SLAMF4 on eosinophils and SLAMF2 on mast cells further exacerbate allergic pathology by promoting eosinophil survival [174]. Cross-linking SLAMF4 can induce IFN-γ and eosinophil peroxidase production through the Erk signaling pathway, enabling eosinophils to kill both mouse mastocytoma cells and EBV-infected B cells [74].

Above all, the expression of SLAMF receptors on granulocytes broadens our understanding of their roles in immune-related pathologies. Nonetheless, their specific contributions to tumor immunity need to be further studied.

Dendritic cells

DCs are the most potent antigen-presenting cells, and they play indispensable roles in triggering anti-tumor immune responses. They express SLAMF1, SLAMF3, and SLAMF6, with EAT-2 as their principal intracellular adaptor [50, 175, 176].

IL-1 stimulation induces the SLAMF1 expression on DCs, and SLAMF1 serves as a maturity marker [175]. Moreover, homophilic SLAMF1-SLAMF1 interactions can disrupt CD40L-CD40-induced production of IL-12, IL-6, and TNF-α by DCs, thereby weakening Th1 differentiation [177]. The SLAMF2-SLAMF4 interaction between DCs and CD8$^+$T cells can contribute to maintaining the long-term survival of DCs. After this conjunction, DCs will produce the granzyme B (GZMB) inhibitor protease inhibitor-9, which decreases the cytotoxicity of GZMB secreted by CD8$^+$T cells. Correspondingly, the absence of the SLAMF2-SLAMF4 interactions can promotes DC apoptosis via GZMB production and autocrine IFN-β [178].

In CLL, bone marrow-derived dendritic cells (BMDCs) accumulate in the TME and facilitate tumor progression [179]. SLAMF4 can inhibit DC-mediated T and NK cell activation [180]. SLAMF5 promotes monocyte-derived DC autophagy and regulates cytokine production by preventing the degradation of interferon regulatory factor 8, a key molecule in the autophagic process, which is distinct from the mechanisms of lymphocytic autophagy mediated by SLAMF1 and SLAMF4 [80, 81, 181]. In the TCL-1 transgenic mouse model, SLAMF5 is overexpressed on BMDCs, extending CLL cell survival via homophilic interactions. The SLAMF5 engagement upregulates exhaustion markers on T cells and immune checkpoint molecules on CLL cells, ultimately hampering anti-tumor immunity [179].

SLAMF receptors have also been found to exist in non-immune cells, such as platelets and red blood cells, and even non-hematopoietic cells [75, 182–184]. A study

first reported that the individual expression of SLAMF3 on hepatocytes and identified the significant roles of SLAMF3 in suppressing hepatocellular carcinoma (HCC) progression [185]. Furthermore, the expression of SLAMF3 on hepatocytes also increases cell susceptibility to hepatitis C virus infection, leading to liver inflammation. [42] Moreover, SLAMF8 is detected on rheumatoid arthritis pathological synovial fibroblasts, where it fosters cell proliferation, invasion, and migration [186, 187]. These findings highlight that SLAMF receptors extend far beyond hematopoietic cells, indicating a need for deeper exploration of their roles in other cell types and diverse pathophysiological events, such as tumors.

SLAMF receptors orchestrate tumor progression

The TME is a complex ecosystem consisting of various cells, signaling molecules, and their intricate interactions. Signal transduction plays an indispensable role in regulating immune cell functions within the TME and modulating tumor immunity [188]. While extensive studies have focused on the involvement of SLAMF receptors in hematologic malignancies such as CLL, MM, and HL [189–191], emerging studies have shed light on their regulatory roles in solid tumors like breast cancer, liver cancer, colorectal cancer (CRC), and others [185, 192, 193]. This section will explicitly discusses the dual roles of SLAMF receptors in hematopoietic and solid tumors, emphasizing their potential as therapeutic targets in these malignancies (Fig. 4 and Table 1).

Hematopoietic tumors

Leukemia

Leukemia originates from the uncontrolled proliferation of malignant hematopoietic stem cells, and is categorized into chronic leukemia and acute leukemia based on disease progression [80, 211].

Chronic leukemia CLL is characterized by the clonal expansion of monoclonal, malignant $CD5^{+}B$ cells [212]. Studies have indicated that SLAMF1, SLAMF3, SLAMF5, SLAMF6, and SLAMF7 play complicated roles in CLL progression [49, 189, 213, 214].

SLAMF1 engagement induces ROS production and autophagosome formation in CLL cells, potentially attenuating CLL progression by triggering autophagic cell death [80]. Notably, clinical data also suggests that SLAMF1 expression on CLL cells is correlated with better outcomes of patients, indicating that SLAMF1 may function as a positive prognostic biomarker [80]. Moreover, SLAMF1 ligation enhances CLL cells susceptibility to chemotherapy, such as bendamustine and fludarabine, by reducing IL-10 production and facilitating drug-induced autophagy [80, 200]. Beyond SLAMF1, SLAMF3 can act as a tumor-associated antigen (TAA) in primary CLL, promoting antigen-specific T cell expansion and enhancing IFN-γ production, underscoring potential of SLAMF3 for immunotherapeutic applications [201]. Similarly, SLAMF4 co-stimulates TCR-mediated signaling and boosts T-cell cytotoxicity against leukemia cells [215, 216]. Furthermore, SLAMF7-SLAMF7 interaction between NK cells and leukemia cells has also been shown to augment NK cell-mediated cytotoxicity [49]. Collectively, these findings highlight the significant potential of leveraging SLAMF receptors as powerful tools for treating leukemia.

Conversely, SLAMF5 plays a negative regulatory role in CLL progression. Interaction between SLAMF5 and its ligand increases CCL3 production and CCL3-induced cytokine secretion, thereby supporting CLL survival and maintenance [214]. Additionally, SLAMF5 activation promotes immune evasion by upregulating PD-L1 on CLL cells and PD-1 on T cells, which ultimately impairs T cell-mediated cytotoxicity [217]. In parallel, the application of anti-SLAMF6 mAb performs complement-dependent cytotoxicity against CLL cells [189]. Altogether, SLAMF5 and SLAMF6 could serve as promising targets for developing therapies for CLL.

Acute leukemia In contrast to chronic leukemia, the disease progression of acute leukemia is more rapid and its malignant cell components are mainly immature cells [211].

Decreased expression of SLAMF2 on acute myeloid leukemia (AML) cells greatly impairs NK cell-mediated cytotoxicity by disrupting the SLAMF2-SLAMF4 interaction [218]. Additionally, epigenetic modification can downregulate SLAMF2 expression, further diminishing AML cell susceptibility to NK cell killing [198]. The application of hypomethylating agents restores SLAMF2 expression, thereby reversing the compromised antitumor immune response [198].

In summary, SLAMF receptors are emerging as both predictive biomarkers and therapeutic targets in leukemia. However, while some SLAMF receptors can enhance anti-tumor immunity, others facilitate immune suppression. Therefore, it is important to explore specific roles of SLAMF receptors in different subtypes of leukemia.

Multiple myeloma

MM is characterized by an accumulation of monoclonal plasma cells in the bone marrow. These malignant plasma cells can produce large amounts of monoclonal immunoglobulin that contribute to osteolytic leisions [219]. Classical manifestations of MM include pain, bone fractures, renal dysfunction, hypercalcemia,

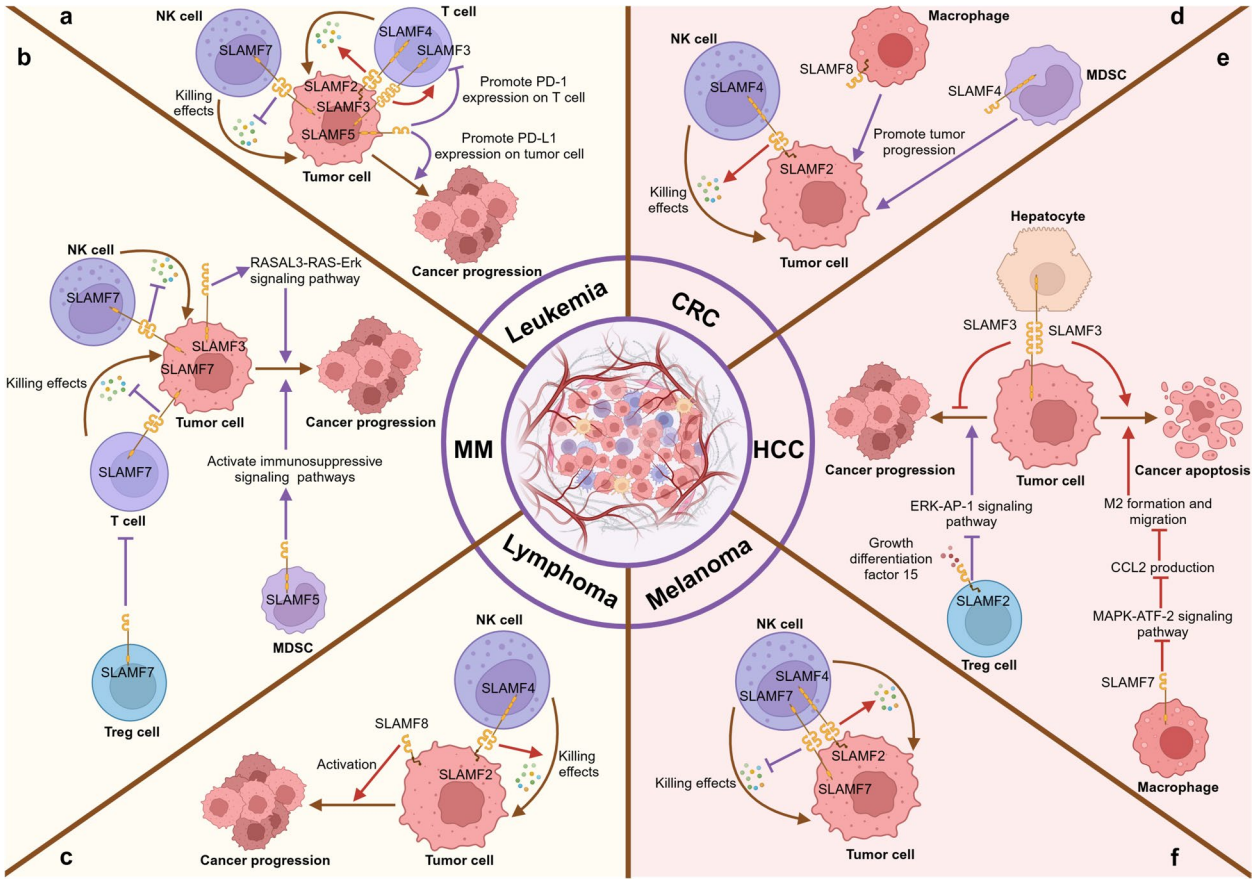

Fig. 4 SLAMF receptors modulate cancer progression. The regulatory roles of SLAMF receptors in cancer depend on both the specific types of SLAMF receptors and the type of cancer. **a** The homophilic interaction of SLAMF3 between leukemia cells and T cells contributes to activating T cells, and the SLAMF2-SLAMF4 interaction between them initiates cytotoxic anti-tumor effects mediated by T cells. However, the homophilic interaction of SLAMF7 between NK cells and leukemia cells inhibits the tumor killing effects mediated by NK cells. Moreover, SLAMF5 expressed on leukemia cells promote tumor progression by upregulating the PD-1 expression on effective T cells as well as the PD-L1 expression on leukemia cells. **b** The homophilic interaction of SLAMF7 between NK cells and MM cells or T cells and MM cells inhibits the anti-tumor responses mediated by NK cells or T cells. SLAMF3 expressed on MM cells also promotes tumor progression by activating the RASAL3-RAS-Erk signaling pathway. Moreover, other immune cells infiltrated in TME contributes to MM progression. SLAMF7^{+}Treg cells can inhibit the function of T cells, and SLAMF5^{+}MDSCs can induce immunosuppressive signaling pathways. **c** The interaction of SLAMF4 and SLAMF2 expressed on NK cells and lymphoma cells respectively enhance the anti-tumor effects mediated by NK cells. In addition, the activation of SLAMF8 expressed on lymphoma cells promote cancer progression, but the specific mechanisms are unknown. **d** In CRC, the interaction of SLAMF4 and SLAMF2 between NK cells and target tumor cells enhances cytotoxic effects. However, SLAMF8^{+}macrophages and SLAMF4^{+}MDSCs promote tumor progression. **e** The homophilic combination of SLAMF3 expressed on HCC cells and adjacent hepatocytes can promote tumor apoptosis while inhibiting cancer progression. Moreover, SLAMF7^{+} macrophages can inhibit MAPK-ATF-2-mediated CCL2 production, which further inhibit the formation and migration of type 2 macrophages. In contrast, the SLAMF2 stimulated by growth differentiation factor 15 can promote tumor progression by inhibiting ERK-AP-1 signaling pathway. **f** The combination of SLAMF4 and SLAMF2 respectively expressed on NK cells and melanoma cells enhances killing effects, which can be impaired by their homophilic SLAMF7 combination. The red lines represent the positive roles of SLAMF receptors in inhibiting cancer progression, while the purple lines indicate their negative roles in cancer progression. Abbreviation: MM, multiple myeloma; HCC, hepatocellular carcinoma; NSCLC, non-small cell lung cancer; CRC, colorectal cancer; PD-1, programmed cell death protein-1; PD-L1, programmed cell death protein-1-ligand-1; Treg, regulatory T; MDSC, myeloid-derived suppressor cell; RAS, rat sarcoma; RASAL3, RAS protein activator like 3; ERK, extracellular signal-regulated kinase; AP-1, activator protein 1; MAPK, mitogen-activated protein kinase; ATF-2, activating transcription factor 2; CCL, C–C motif chemokine ligand 2. The figure is created with BioRender.com

anemia, and recurrent infection [220]. SLAMF1, SLAMF2, SLAMF3, SLAMF5, SLAMF6, and SLAMF7 are expressed on MM cells and influence disease progression in various ways [104, 105, 203–205]. With the deeper understanding of critical roles of SLAMF receptors in MM, multiple immunotherapies targeting SLAMF receptors have been developed for MM [206, 208, 221].

Table 1 Roles and specific mechanisms of SLAMF receptors in cancer

Disease category	Specific disease	SLAMF member	Cell pattern	Function	Clinical response	Prognostic value	Ref
Hematological Cancer	RRMM	SLAMF7	$CD8^+$T cell	Enhance anti-tumor capacity and improve shortcomings of single-target CAR-T therapy	The one-year OS and PFS of responders increase	Positive	[126]
	MM	SLAMF3	Malignant plasma cell	Promote MM proliferation through activating the RASAL3/RAS/ERK signaling pathway	The expression level of SLAMF3 is negatively related to patient prognosis (OS)	Negative	[194]
			MM cell	Promote MM growth and chemotherapy resistance through activating the MAPK/ERK signaling pathway	The serum level of soluble SLAMF3 is negative with prognosis of MM patients (PFS)	Negative	[195]
		SLAMF5	MDSC	Promote the immunosuppressive TME through activating MDSCs and reducing cytotoxic functions of effective T cells, resulting in elevated tumor burden	/	Negative	[196]
		SLAMF7	$CD8^+$T cell	Enhance anti-tumor capacity through increasing $CD8^+$T cells and prolonged survival of experimental 5T33MM mice	/	Positive	[125]
	ALL	SLAMF4	NK cell	Increase the anti-tumor cytotoxicity and killing effects	/	Positive	[197]
	AML	SLAMF2	AML cell	Strengthen the susceptibility to anti-tumor cytotoxic functions mediated by NK cells	/	Positive	[198]
	ATLL	SLAMF2	Malignant T cell	Strengthen the susceptibility to anti-tumor cytotoxic functions mediated by NK cells	/	Positive	[191]
	ALCL	SLAMF8	ALCL cell	Promote tumor growth by interacting with SHP-2	/	Negative	[199]
	CLL	SLAMF1	CLL cell	Promote the sensibility of malignant B cells to chemotherapy	/	Positive	[200]
			CLL cell	Promote CLL autophagy	The expression level of SLAMF3 is positively related to patient prognosis (TFS and OS)	Positive	[80]
		SLAMF3	CLL cell	Represents a novel tumor-associated antigen and promotes the autologous $CD8^+$T cell expansion	/	Positive	[201]
		SLAMF5	BMDC	Promote the accumulation of BMDC in CLL TME, and prolong the survival of CLL cells through upregulating the PD-1/PD-L1 signaling pathway	/	Negative	[179]
		SLAMF6	B cell	The application of SLAMF6 monoclonal antibody can eliminate malignant B cells	/	Negative	[189]

Table 1 (continued)

Disease category	Specific disease	SLAMF member	Cell pattern	Function	Clinical response	Prognostic value	Ref
Solid Cancer	Cervical cancer	SLAMF2	T cell	Suppress tumor proliferation, growth, and migration	The expression level of SLAMF2 is negatively related to the cancer progression of CC patients (Stage, tumor size, lymphatic metastasis)	Positive	[96]
	NSCLC	SLAMF2	NSCLC cell	Elevate the interaction between cytotoxic NK cells and $SLAMF2^{+}$NSCLC cells	/	Positive	[202]
	HCC	SLAMF2	Treg cell	Inhibition of them enhances the functions of Treg cell	/	Positive	[203]
		SLAMF3	HCC cell	Suppress tumor proliferation and migration and promote apoptosis	/	Positive	[185]
		SLAMF7	HCC cell, macrophages	Suppress tumor progression by inhibiting the polarization and chemotaxis of intrinsic macrophages	The expression level of SLAMF7 is positively related to patient prognosis (DFS and OS)	Positive	[52]
	HNSCC	SLAMF4	$CD8^{+}$T, DC, MDSC	Promote tumor immunosuppression	/	Negative	[29]
	CRC	SLAMF8	Macrophages	Get involved in anti-tumor immune immunity	The high expression of SLAMF8 is correlated to a poorer clinical prognosis (OS)	Negative	[192]
	Glioma	SLAMF8	/	Enhance immune suppression	The higher expression of SLAMF8 is correlated with the shorter survival of glioma patients	Negative	[204]
		SLAMF5	TAM	Enhance immune suppression by inducing M2-like polarization of TAMs	/	Negative	[205]
	Melanoma	SLAMF4	NK cell	Promote cytotoxic effects of NK cells via SLAMF2-SLAMF4 interaction	/	Positive	[206]
		SLAMF7	NK cell	Suppress the cytotoxic effects of NK cells on melanoma	/	Negative	[78]
		SLAMF4	Monocyte	Enhance immune suppression by inhibiting macrophage maturation	/	Negative	[207]
		SLAMF9	Melanoma cell	Enhance immune suppression	/	Negative	[208]
	TNBC	SLAMF5	B cell	Promote tumor progression by inducing Breg cell formation and expansion	/	Negative	[209]
	Serous ovarian cancer	SLAMF7	T cell	/	The higher expression of SLAMF7 is correlated with the longer OS and DFS of serous ovarian cancer patients	Positive	[210]

Abbreviation: *SLAMF* signaling lymphocytic activation molecule family, *SAP* SLAMF-associated protein, *EAT-2* EWS/FIi 1- activated transcript-2, *SHIP* SH2-domain-containing inositol-5-phosphatase, *SHP* SH2 domain-containing protein tyrosine phosphatases, *PD-1* programmed cell death-1; IFN, interferon; CLL, chronic lymphocytic leukemia; MM, multiple melanoma, *DC* dendritic cell, *MAPK* mitogen-activated protein kinase, *ERK* extracellular signal-related kinase, *CAR* chimeric antigen receptor, *GZMB* granzyme B, *TNF* tumor necrosis factor, *IL* interleukin, *ATLL* adult T cell leukemia/lymphoma, *AML* acute myeloid leukemia, *MM* multiple myeloma, *RRMM* relapsed or refractory MM, *ALCL* anaplastic large cell lymphoma, *OS* overall survival, *PFS* progression-free survival, *DFS* disease-free survival, *HL* Hodgkin's lymphoma, *HCC* hepatocellular carcinoma, *CC* cervical cancer, *NSCLC* non-small cell lung cancer, *TNBC* triple-negative breast cancer, *TAM* tumor-associated macrophage, *Breg* regulatory B, *PLC-γ* phospholipase C gamma, *TME* tumor microenvironment

SLAMF3 is expressed in various B-cell malignancies, including MM and lymphoma [209]. It delivers pro-survival signals for MM cells by activating the MAPK/Erk signaling pathway. Knocking down SLAMF3 suppresses MM progression and increases their susceptibility to drug-induced apoptosis, suggesting SLAMF3 is a positive regulator of MM [195]. Another study also indicates that SLAMF3 promotes MM cell proliferation through the RAS protein activator like the 3/RAS/Erk signaling pathway, with higher SLAMF3 expression observed in high-risk MM patients [194]. Additionally, the serum level of soluble SLAMF3 positively correlates with both tumor burden and disease severity in MM, underscoring its prognostic value and potential as a target for developing novel therapies [190, 195].

SLAMF5 is minimally expressed on MM cells but is highly expressed on MDSCs within the MM TME [196]. MDSCs are the key contributor to shaping immunosuppressive TME, and SLAMF5 has been demonstrated to facilitate their accumulation and augment their immunosuppressive pathways, promoting T cell exhaustion and tumor progression [196, 222, 223]. In addition, SLAMF7 also contributes to MM progression by dampening the cytotoxic activities of NK cells and T cells while enhancing immunosuppressive functions of Treg cells [224–227]. Therefore, targeting SLAMF5 and SLAMF7 may present novel strategies for reversing immunosuppression in MM.

Above all, the multifaceted immune modulation exhibits critical roles of SLAMF receptors in MM, highlighting their great potential to offer targeted options for optimizing immunotherapies.

Lymphoma

Lymphoma is a group of hematological malignancies arising from aberrant lymphocytes proliferation, broadly subdivided into HL and non-Hodgkin's lymphoma (NHL) [228].

Some HL patients show better prognosis following measles virus (MV) infection or measles vaccination [229, 230]. Pathologically, HL is characterized by mononuclear Hodgkin's cells and multinuclear Reed-Sternberg (HRS) cells, both of which highly express SLAMF1 [69, 231]. Therefore, SLAMF1 may play an important role in regulating HL. However, the involvement of other SLAMF receptors in HL remains largely unexplored. Moreover, there are limited studies regarding SLAMF receptors in NHL subtypes.

In cutaneous T-cell lymphoma, SLAMF1 is significantly expressed on malignant T cells, which promotes their susceptibility to MV infection. Administration of recombinant MV vaccine has demonstrated anti-tumor activity in vitro and in vivo [232]. However, other roles of SLAMF1 in regulating cutaneous T-cell lymphoma progression are less clearly defined.

By contrast, SLAMF2 expression on adult T cell lymphoma (ATLL) cells appears inversely correlated with disease progression, partly by increasing susceptibility of malignant T cells to NK cell-mediated cytotoxicity [191]. Scientists also identified the existence of SLAMF7 in the plasmablastic lymphoma (PBL) cell line BC2, which are vulnerable to elotuzumab-mediated killing via increased GZMB production by effector cells in an antibody-dependent cellular cytotoxicity (ADCC) manner [28]. Meanwhile, knocking out SLAMF8 expressed on anaplastic large cell lymphoma (ALCL) cells inhibits ALCL cell proliferation, implying SLAMF8 may become a novel therapeutic target [199].

Collectively, these findings demonstrate the diverse roles of SLAMF receptors across hematopoietic malignancies, underscoring their potential as prognostic biomarkers or therapeutic targets. However, evidence is limited in certain subtypes and the precise mechanisms need to be further elucidated in future research.

Solid tumors

Previous studies predominantly focus on exhibiting the importance of SLAMF receptors in hematopoietic malignancies. However, advanced technologies such as transcriptomic and proteomic analyses reveal that SLAMF receptors are also present on various immune cells within the TME of solid tumors, and they exert significant roles in regulating tumor progression [233].

CRC

Single-cell RNA sequencing analysis has shown that *SLAMF1* expression is upregulated in ILCs derived from both the peripheral blood and tumor tissues of CRC patients, relative to healthy counterparts. Moreover, SLAMF1^{+}ILCs appear more prevalent in tumor tissues than in adjacent normal tissues, correlating with improved survival [234]. Therefore, SLAMF1 may function as a favorable positive biomarker in CRC, although the underlying molecular mechanism remain to be further elucidated.

Peritoneal metastasis often occurs in advanced CRC and correlates with poor patient outcomes. In murine CRC models, peritoneal dissemination is associated with an increase in intra-peritoneal polymorphonuclear MDSCs (PMN-MDSCs) [193]. Notably, SLAMF4^{+}PMN-MDSCs exhibit a stronger capacity to suppress CD8^{+}T cell proliferation and function compared to SLAMF4^{-}PMN-MDSCs, indicating that SLAMF4 may be able to predict the CRC progression [193]. On the other hand, alloferin treatment upregulates SLAMF4 expression on NK cells, boosting their production of

IFN-γ, TNF-α and cytotoxic molecules, which in turn restricts CRC cell growth [235]. These distinct outcomes mediated by SLAMF4 may be context-dependent.

Scientists have identified that high SLAMF8 expression on macrophages is associated with poor prognosis of CRC patients and elevated PD-L1 expression [192]. Intriguingly, another study indicates that SLAMF8 expression is positively correlated with the response to anti-PD-1 treatment in murine models [236]. These findings suggest the complicated roles of SLAMF8 in tumor immunity. On the one hand, SLAMF8$^+$macrophages may foster an inflamed and immunosuppressive TME, thereby contributing to poor clinical outcomes. On the other hand, high SLAMF8-associated PD-L1 upregulation and immunological activation could render CRC cells more susceptible to anti-PD-1 treatment. Further studies are warranted to dissect the precise mechanisms by which SLAMF8 influences CRC progression and treatment responsiveness.

HCC

The interaction between SLAMF2 expressed on Tregs and growth differentiation factor 15 enhances Treg cell functions by inhibiting SLAMF2-mediated Erk/activator protein-1 (AP-1) signaling, which upregulates FOXP3 levels and fosters HCC progression [237]. In parallel, scientists have noted that among SLAMF receptors, only SLAMF3 is expressed on hepatocytes, prompting investigations into its roles in liver cancer [185].

Ingrid. et al. found that SLAMF3 expression is lower in HCC tissues compared with healthy livers. Elevated SLAMF3 expression suppresses HCC cell proliferation and migration by inhibiting the MAPK/Erk, JNK, and mTOR pathways, and it promotes HCC cell apoptosis [185]. Although these findings highlight tumor-suppressive roles of SLAMF3, its correlations with clinical outcome remain to be further explored.

A recent study indicates that anti-PD-1 therapy-responsive HCC patients perform the higher serum SLAMF7 levels and better prognosis than non-responsive patients [52]. Mechanistically, tumor cell-intrinsic SLAMF7 hinders HCC progression by regulating immune cells within the TME. Knockdown of *Slamf7* results in a more immunosuppressive TME, characterized by increased M2-like macrophages and exhausted CD8$^+$T cells with elevated expression of immune checkpoints [52]. Hence, SLAMF7 may serve as a positive biomarker for HCC.

Lung cancer

Although immunotherapy has achieved remarkable success in treating lung cancer, therapy resistance and limited efficacy underscore the essential for exploring novel therapeutic targets [238]. Recent findings suggest that multiple SLAMF receptors play important roles in lung cancer progression and they may further refine existing therapeutic strategies.

For example, interfering with SLAMF2 expression on non-small cell lung cancer (NSCLC) cells enhances their physical contact with NK cells, thereby promoting NK cell-mediated cytotoxic killing effects [202]. In addition, chimeric TCR-engineered NK92 cells containing an intracellular SLAMF4 co-stimulatory domain increase IFN-γ production and enhanced anti-tumor efficacy in both primary lung cancer cells and xenograft models [239]. Notably, in a sepsis animal model with pre-established lung cancer, SLAMF4 serves as a novel checkpoint and the anti-SLAMF4 treatment greatly prolongs animal survival and promotes T-cell activation [240]. Additionally, SLAMF5 appears to mark circulating PMN-MDSCs in NSCLC, but its precise role in tumor immunity are undefined [242].

Together, these studies illustrate the multifaceted contributions of SLAMF receptors to the immuno-oncological landscape of lung cancer, emphasizing their potential as direct therapeutic targets or in combination with established immunotherapies to improve patient outcomes.

Other solid tumors

Although SLAMF receptors have been studied most extensively in CRC, HCC and lung cancer, emerging evidence suggests SLAMF receptors also play less-defined roles in other solid tumors.

SLAMF1 expression has been demonstrated in multiple human central nervous system (CNS) tumors, including glioblastoma, anaplastic astrocytoma, and others [243]. It appears in a novel isoform in glioma cells, but its specific roles are unclear [243]. Moreover, high SLAMF8 expression contributes to enhancing immunosuppression in gioma [234]. In addition, the SLAMF5-SHP-2 axis promotes M2-like polarization of TAMs in glioma, contributing to immune evasion [244]. Therefore, developing therapies targeting SLAMF5 and SLAMF8 has the potential to attenuate glioma progression.

In cervical cancer (CC), SLAMF2 functions as a tumor suppressor, and its expression is negatively related to CC progression [96]. By contrast, head and neck squamous cell carcinoma (HNSCC) models with *Slamf4* knockout reveal reduced tumor growth compared to wild-type controls, and the SLAMF4 expression increases on MDSCs in both HNSCC patients and murine models. Consequently, SLAMF4 appears to promote tumor progression by establishing immunosuppressive TME, suggesting its potential as a therapeutic target in HNSCC [29].

Regulatory B cells (Breg cells) are an immunosuppressive cell population that greatly facilitates breast cancer progression [245]. In triple-negative breast cancer (TNBC), homophilic SLAMF5 interactions between tumor cells and B cells increases Breg cell expansion through activating the β-catenin/Tcf4 complex and subsequent IL-10 production in B cells, thereby promoting immune evasion. Therefore, targeting SLAMF5 may be beneficial for overcoming immune tolerance in TNBC [246].

The higher SLAMF7 expression correlates with the better survival of serous ovarian cancer (OC) patients, and SLAMF7 partially contributes to modulating T cell activity [247]. However, the specific mechanisms of SLAMF7 in regulating OC immunity are undefined. Moreover, elevated SLAMF3 expression level can predict OC patients who benefits from Poly (ADP-ribose) polymerase inhibitors [241]. Therefore, SLAMF receptors may provide novel targets for predicting the progression and outcomes of OC patients.

In melanoma, SLAMF7 inhibits NK cell-mediated immune surveillance in an SAP-independent manner [78]. Additionally, the engagement of SLAMF2 on melanoma cells suppresses cytotoxicity of NK cells and T cells [248]. Moreover, SLAM4 contributes to shaping the immunosuppressive phenotypes of monocytes, which significantly promotes melanoma progression by inhibiting the maturation and functions of macrophages [249]. In addition, the knockdown of SLAMF9 in B16F10 cell lines reduces tumor volume and increases the $CD8^{+}$T cell infiltration, suggesting SLAMF9 may contribute to inducing immunosuppression [245]. Taken together, these SLAMF receptors may serve as targets for developing novel therapies for melanoma.

In summary, these studies indicate that individual SLAMF receptor can display diverse and context-dependent roles in modulating tumor progression. Although numerous studies have underscored the significant potential of SLAMF receptors as novel therapeutic targets in solid tumors, the underlying mechanisms by which they operate remain incompletely understood. Moreover, additional work is required to unravel the clinical feasibility of SLAMF receptor-directed interventions.

Cancer immunotherapies targeting SLAMF receptors

SLAMF receptors play important roles in regulating tumor progression and anti-tumor immune responses, making them attractive therapeutic targets. Scientists have developed various immunotherapies targeting SLAMF receptors, including engineered CAR lymphocyte therapies and monoclonal antibody therapies (Fig. 5).

CAR-T and NK cell-based immunotherapy

Engineered CAR-T and CAR-NK cell therapies have achieved remarkable success in treating certain hematological malignancies. However, not all patients can benefit from them [250]. With the advancement of technologies, numerous innovative CAR products have been invented to amplify their antigen-specificity and tumor-killing efficacy, often by inducing more potent co-stimulatory signaling pathways.

SLAMF4-engineered co-stimulation in CAR therapies

Given that SLAMF4 functions as a costimulatory receptor in T cells, enhancing TCR-mediated signaling, scientists constructed a recombinant chimeric receptor that links TAA-specific extracellular single-chain variable fragment (scFv) domains to the signaling motifs of SLAMF4 [251, 252]. The chimeric SLAMF4-TCR receptor drives antigen-specific T cell expansion and strengthens NK cell cytotoxicity against autologous leukemia cells [251, 252].

CAR-NK cell therapy has also been applied to treat T-cell malignancies. For example, CD5-targeted CAR-NK cells equipped with intracellular SLAMF4 costimulatory domain exhibit stronger cytotoxic effects against $CD5^{+}$T cell in acute lymphoblastic leukemia than CAR-NK cells equipped with classical 4-1BB domain [197]. Similarly, claudin-6-targeted CAR-NK cells incorporating SLAMF4 domains demonstrate improved anti-tumor efficacy against ovarian cancer compared to CAR-NK cells with classical designs, highlighting the advantages of leveraging SLAMF4-mediated self-activation [253].

Single SLAMF-targeted CAR therapies

Based on the tumor-promoting roles of SLAMF3 in MM, scientists have developed the engineered SLAMF3-targeted CAR-T cells that display effective roles against MM cells, including MM-propagating cells, both in vitro and in vivo, without causing severe adverse effects like T-cell fratricide [254]. However, due to the low SLAMF3 expression on normal lymphocytes, scientists fine-tuned the CAR binding affinity by substituting a single amino acid and overexpressing c-Jun, a protein that naturally exists in CAR-T cells. Eventually, the improved SLAMF3-targeted CAR-T product displayed potent cytotoxicity against MM cells while protecting normal cells [255]. However, the clinical validation of this novel therapy needs to be further confirmed.

In addition, SLAMF7 represents another promising target in MM. Chu et al. demonstrated that CAR-NK cells targeting SLAMF7 significantly exhibit potent anti-MM effects, including increased IFN-γ production and

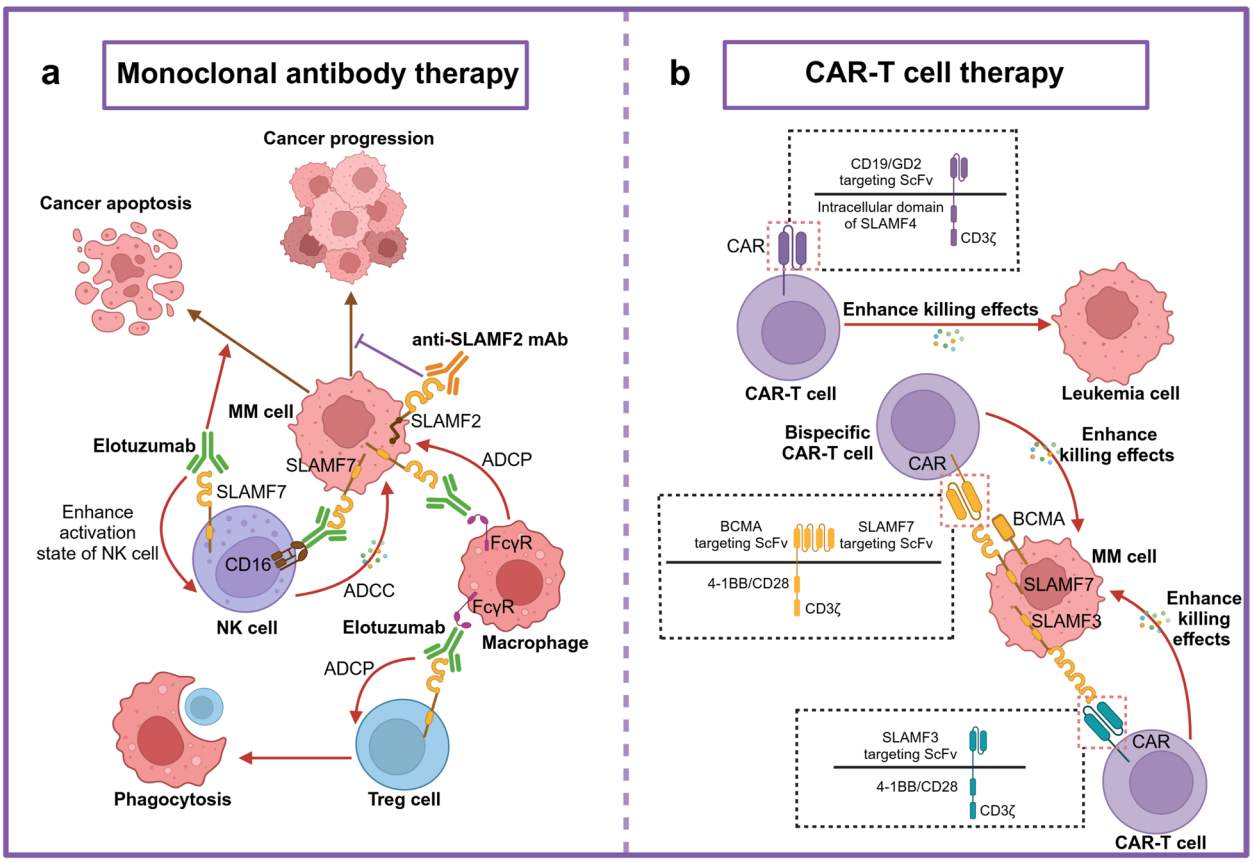

Fig. 5 Cancer immunotherapies targeting SLAMF receptors. **a** Elotuzumab is a monoclonal antibody targeting SLAMF7. It specifically recognizes SLAMF7 expression on immune cells and the Fc fragments of it can combine with CD16 expressed on NK cells or FcγR expressed on macrophages. The combination of Elotuzumab can enhance activation state of NK cells and initiate their anti-tumor effects in an ADCC-dependent manner. Moreover, Elotuzumab also induces phagocytotic functions of macrophages on MM cells or Treg cells in an ADCP-dependent manner. In addition, the blockade of SLAMF2 expressed on MM cells by anti-SLAMF2 mAb can inhibit cancer progression. **b** The structure of engineered CAR-T products against leukemia cells includes the CD19/GD2 targeting ScFv in the extracellular domain, and the intracellular signaling domain of SLAMF4 is combined with CD3ζ of TCR. Extracellular domain of BCMA-SLAMF7 bispecific CAR-T cells contain SLAMF7-targeting scFv and BCMA-targeting scFv derived from their respective molecule-targeting antibodies, and the extracellular domain of SLAMF3-targeted CAR-T cells include SLAMF3-targeting ScFv. Their intracellular domains are composed of co-stimulatory domain and activation domain. Abbreviation: mAb, monoclonal antibody; ADCC, antibody-dependent cellular cytotoxicity; ADCP, antibody-dependent cellular phagocytosis; FcR, Fc receptor; GD2, ganglioside D2, ScFv, single-chain variable fragment; BCMA, B cell maturation antigen; CAR, chimeric antigen receptor. The figure is created with BioRender.com

enhanced tumor cell cytolysis [256]. Nevertheless, the potential of designing CAR products targeting other SLAMF receptors continue to be explored in the future.

Bispecific CAR therapies

Tumor cells can avoid immune killing through down-regulating antigen expression, which limits the efficacy of single-target CAR therapies [257]. To remove this obstacle, scientists have designed bispecific CAR therapies incorporating SLAMF receptors alongside other tumor antigens.

Bispecific CAR-T therapy targeting B cell maturation antigen (BCMA) and SLAMF7 has revolutionized MM treatment [258–260]. However, its long-term clinical efficacy is restricted to increasing BCMA loss, but scientists found the expression of SLAMF7 remains in MM patients treated with BCMA-targeted therapy [261]. Therefore, the bispecific BCMA-SLAMF7 CAR-T therapy significantly compensates for the shortcomings of single-target CAR-T therapy and highlights their efficacy in treating heterogeneous MM [262].

The combination of bispecific BCMA-SLAMF7 CAR-T therapy with anti-PD-1 antibodies accelerates early tumor control [258]. A phase I clinical trial reports that the administration of bispecific BCMA-SLAMF7 CAR-T therapy can improve outcomes of RRMM patients, including those who have been treated with BCMA-targeted CAR-T therapy [126]. Similarly, another research

constructed a dual CAR-T cell product targeting CD38 and SLAMF7, exhibiting enhanced efficacy and safety in treating preclinical MM models [263]. Given that SLAMF7 also plays significant roles in regulating NK cell functions in MM, targeting SLAMF7 with CAR-NK cells may also offer therapeutic potential for melanoma treatment.

Fratricide remains a major challenge upon applying CAR-T therapy. One study shows that the deletion of *SLAMF7* in T cells prior to constructing IgV-domain of SLAMF7 (Luc90)-targeted CAR-T cells can mitigate $CD8^+$T cell fratricide while preserving potent anti-MM activity [264]. Additionally, in RRMM patients previously treated with BCMA-targeted CAR-T therapy, T-cell dysfunction is frequently observed. SLAMF4 is found to be upregulated on these dysfunctional T cells, but whether it contributes to compromising the therapeutic efficacy of BCMA-targeted CAR-T therapy remains unclear [265].

Integrating SLAMF signaling elements, whether as costimulatory domains or direct CAR targets, offering novel insights into developing CAR therapies, particularly in hematopoietic malignancies. Additional clinical trials are also required to validate the safety and efficacy of advanced CAR therapies and to refine personalized approaches, ultimately expanding the potential of applying SLAMF-focused immunotherapies.

Antibody-based targeted immunotherapy

Monoclonal antibody therapies targeting tumor-associated antigens have achieved success in optimizing cancer treatment. Given their universal expression on tumor-associated immune cells and immunoregulatory functions, SLAMF receptors offer promising targets for antibody-based interventions, potentially complementing existing immunotherapies.

Targeting SLAMF2 and SLAMF5 in MM

SLAMF2 is prominently expressed on MM plasma cells, and the administration of anti-SLAMF2 mAbs can deplete MM cells via ADCC and robust complement-dependent cytotoxicity [266]. Daratumumab is an anti-CD38 mAb that plays an effective role in treating MM. A study indicates that the SLAMF2 expression on MM cells increases their susceptibility to Daratumumab-mediated ADCC by activating NK cells, implying the potential of SLAMF2 as a adjuvant therapeutic target [266, 267].

Furthermore, the tumor-promoting roles of SLAMF5 in MM can be reversed by blocking SLAMF5 in both human MM patient samples and murine models [196]. Additionally, depleting MDSCs significantly enhances the sensitivity of melanoma mouse models to anti-PD-1 therapy. Based on the pivotal roles of SLAMF5 in driving MDSC accumulation within the TME, SLAMF5 may serve as a promising target for overcoming anti-PD-1 resistance [268].

Elotuzumab and other SLAMF7-directed therapies in MM

SLAMF7 is highly expressed on MM cells and has become a key target for antibody-based therapy. The humanized mAb Elotuzumab (Huluc63) is the official product that is specifically developed to combine with SLAMF7 in treating MM [269].

Elotuzumab drives significant anti-MM effects through multiple mechanisms, including inhibiting MM cell adhesion to bone marrow stromal cells [236]; triggering ADCC and enhance NK cell cytotoxicity via Fc component of Elotuzumab binding on NK cells and intracellular EAT-2/Erk signaling activation [237]; and enhancing macrophage-mediated phagocytosis. Moreover, scientists have also found that Elotuzumab can augment SLAMF7-SLAMF7 interactions between NK cells and targeted MM cells, further boosting NK cell cytotoxicity [158].

Beyond NK cells, other immune cells existing in the TME are also involved in Elotuzumab-mediated anti-tumor effects. For instance, Elotuzumab promotes depletion of $SLAMF7^+CD8^+$Treg cells, primarily via triggering the macrophage-mediated antibody-dependent cellular phagocytosis (ADCP) [238, 270]. Approved in combination with lenalidomide and dexamethasone for RRMM patients, Elotuzumab is being tested in multiple clinical trials to refine its optimal use [271–274].

Expanding SLAMF-targeted antibody therapies

With the rapid development of cancer treatment, targeted radionuclide therapy has attracted many scientists [275].

In 5T33MM (MM cell line) models, a single-domain Ab against SLAMF7 labeled with actinium-225 ($[^{225}Ac]$-sdAb1) exerts potent anti-tumor activity, enhancing $CD8^+$T cell infiltration and prolonging murine survival [125].

In addition, scientists have also constructed a novel product called SLAMF7-Bispecific T-cell engagers (BiTE), a bispecific single-chain antibody consisting of α-Slamf7 and α-CD3 Fv fragments joined through a Gly-Ser linker. Although the SLAMF7-BiTE effectively killed MPC-11 cells in vitro [276], they performed more significant side effects than SLAMF7 mAb and SLAMF7-targeted CAR-T cells in vivo syngeneic model [276]. Therefore, striking the right balance of efficacy and safety remains a challenge.

SLAMF-targeted antibody therapies in solid tumors

Although antibody-based SLAMF receptor therapies have primarily targeted hematological tumors, emerging studies suggest their roles in solid tumors.

Table 2 Therapies targeting SLAMF receptors for cancer treatment in clinical trials

NCT Number	Study Status	Implications	Interventions	Phases	Enrollment
NCT01441973	COMPLETED	High-risk smoldering MM patients	Elotuzumab	2	41
NCT02420860	ACTIVE_NOT_RECRUITING	MM patients treated with ASCT	Elotuzumab + Lenalidomide	2	113
NCT03713294	COMPLETED	RRMM patients	Dexamethasone + Elotuzumab + Pomalidomide	2	41
NCT02279394	COMPLETED	High-risk smoldering MM patients	Elotuzumab + Lenalidomide + Dexamethasone	2	51
NCT01478048	COMPLETED	RRMM patients	Elotuzumab + Bortezomib + Dexamethasone	2	185
NCT02843074	COMPLETED	MM patients treated with ASCT	Elotuzumab + Lenalidomide + Dexamethasone	2	53
NCT02252263	COMPLETED	MM patients	Elotuzumab + Lirilumab + Urelumab	1	44
NCT02495922	COMPLETED	MM patients	Elotuzumab + Lenalidomide + Dexamethasone + Bortezomib + ASCT	3	564
NCT02655458	COMPLETED	MM patients treated with ASCT	Elotuzumab + Lenalidomide	1	15
NCT05002816	RECRUITING	RRMM patients	Elotuzumab + Belantamab mafodotin	1/2	24
NCT04835129	RECRUITING	RRMM patients	Isatuximab + Pomalidomide + Elotuzumab + Dexamethasone	2	53
NCT01335399	COMPLETED	MM patients	Lenalidomide + Dexamethasone + Elotuzumab	3	748
NCT05560399	RECRUITING	RRMM patients	Iberdomide + Elotuzumab + Dexamethasone	1	6
NCT03155100	COMPLETED	RRMM patients	Elotuzumab + Dexamethasone + Carfilzomib	2	15
NCT02654132	COMPLETED	RRMM patients	Elotuzumab + Pomalidomide + Dexamethasone	2	117
NCT02612779	COMPLETED	RRMM patients	Elotuzumab + Pomalidomide + Dexamethasone + Nivolumab	2	74
NCT01239797	COMPLETED	RRMM patients	Lenalidomide + Dexamethasone + Elotuzumab	3	646
NCT03030261	ACTIVE_NOT_RECRUITING	RRMM patients	Elotuzumab + Pomalidomide + Dexamethasone	2	25
NCT06185751	RECRUITING	MM patients	WS-CART-CS1	1	25
NCT03778346	UNKNOWN	RRMM patients	CAR-T	1	30
NCT04156269	UNKNOWN	MM patients	BCMA-CS1 compound CAR T	1	12
NCT04662099	RECRUITING	RRMM patients	BCMA-CS1 compound CAR T	1	24
NCT04499339	ACTIVE_NOT_RECRUITING	MM patients	CS1 Targeted CAR T-cells	1/2	38
NCT03958656	COMPLETED	MM patients	CS1 Targeted CAR T-cells	1	13
NCT02954796	TERMINATED	MM patients	SGN-CD352A	1	27

ASCT autologous stem cell transplantation, *CAR* chimeric antigen receptor, *BCMA* B-cell maturation antigen

In a HNSCC murine model, anti-SLAMF4 mAb increases $CD8^{+}$TIL accumulation and reduces tumor growth [29]. Moreover, SLAMF4 expression is positively correlated with the production of suppressive molecules by intra-tumoral DCs and MDSCs, such as arginase-1, IL-10, and TGF-$\beta 1$ [29]. Therefore, SLAMF4 plays an immunosuppressive role in HNSCC and may serve as a promising antibody-based therapeutic target.

However, due to restricted studies on investigating SLAMF receptors in solid tumors, the development of antibody-based therapies targeting SLAMF receptors for treating solid tumors still at an early stage.

SLAMF receptor-targeted therapies in clinical trials

Given the bright promise of SLAMF receptor-targeted immunotherapies in treating cancer patients, such as mAbs and CAR products, numerous clinical trials have been initiated to evaluate their safety and efficacy. This section presents representative SLAMF-focused clinical trials and highlights their significance (Table 2).

SLAMF receptor-targeted mAbs

Improving MM in early stages

High-risk-smoldering MM (HR-SMM) is an early, asymptomatic form of MM that is preferential to progress to active MM. Early pharmacological intervention can attenuate this progression [277]. In HR-SMM patients treated with different doses of Elotuzumab, scientists observed a negative correlation between $CD56^{dim}$ NK cell proportion and the reductions in serum monoclonal protein, suggesting immune function may influence effectiveness of Elotuzumab (ClinicalTrials.gov Identifier: NCT01441973). Moreover, the higher dose of Elotuzumab showed a better long-term therapeutic potential, but it raised safety concerns that merit additional research. Additionally, the combined Elotuzumab, Dexamethasone, and Lenalidomide strategy significantly

increased the objective response rates of HR-SMM patients, though cytotoxic side effects warrant further attention (ClinicalTrials.gov Identifier: NCT02279394).

Reducing recurrence

Disease recurrence remains a major obstacle for MM management, but combination therapies have shown potential to improve that.

For MM patients resistant to Daratumumab, scientists tried to explore the therapeutic potential of combining Dexamethasone, Elotuzumab, and Pomalidomide (ClinicalTrials.gov Identifier: NCT03713294, NCT03030261), as well as the regimens such as "Isatuximab + Pomalidomide + Elotuzumab + Dexamethasone" (ClinicalTrials.gov Identifier: NCT04835129), "Carfilzomib + Elotuzumab + Dexamethasone" (ClinicalTrials.gov Identifier: NCT03155100), and "Iberdomide + Elotuzumab + Dexamethasone" (ClinicalTrials.gov Identifier: NCT05560399). Moreover, additional trials repot that Elotuzumab contributes to improving RRMM patient prognosis when added to "Bortezomib + Dexamethasone" (ClinicalTrials.gov Identifier: NCT01478048) or "Lenalidomide + Dexamethasone" (ClinicalTrials.gov Identifier: NCT01239797) [226]. In one study, the combination of Elotuzumab with Pomalidomide and Dexamethasone significantly lowered mortality and disease progression of RRMM patients resistant to Lenalidomide and proteasome inhibitors (ClinicalTrials.gov Identifier: NCT02654132) [227]. In contrast, a phase 3 clinical trial indicated the addition of Elotuzumab to Lenalidomide and Dexamethasone provided limited benefit in improving the prognosis of newly diagnosed MM patients (ClinicalTrials.gov Identifier: NCT01335399) [278], suggesting patient status and disease stage significantly influence treatment outcomes.

SGN-CD352A is an antibody–drug conjugate targeting SLAMF6, was evaluated in MM or RRMM patients but the study terminated without publicy stated reasons (ClinicalTrials.gov Identifier: NCT02954796). This example illustrates the challenges in advancing novel SLAMF-targeted therapies to later clinical stages.

Combining ASCT and Elotuzumab

ASCT is an effective approach for MM patients. However, ASCT-treated MM patients often need additional therapies to maintain therapeutic efficacy and prevent recurrence [279].

Scientists have investigated Elotuzumab in combination with Lenalidomide in the post-ASCT setting. (ClinicalTrials.gov Identifier: NCT02420860, NCT02655458) Moreover, the combination of Elotuzumab, Lenalidomide, and Dexamethasone had been demonstrated to improve the overall response rate and (progression-free survival) PFS in ASCT-treated MM patients, albeit with universal adverse events, implying the cytotoxicity of this strategy (ClinicalTrials.gov Identifier: NCT02843074).

However, a phase 3 trial indicated the addition of Elotuzumab neither enhanced induction and consolidation therapy with Bortezomib, Lenalidomide, and Dexamethasone, nor improved maintenance efficacy of Lenalidomide for newly diagnosed ASCT-eligible MM patients (ClinicalTrials.gov Identifier: NCT02495922) [272]. These divergent findings highlight the complexity of integrating Elotuzumab into ASCT regimens.

Combining SLAMF receptor-targeted antibodies with other immunotherapeutic agents

In addition to chemotherapy, scientists have also investigated the therapeutic efficacy of combining Elotuzumab with immunotherapeutic agents in clinical trials. For instance, a phase 1 trial assessed Elotuzumab co-administered with Lirilumab or Urelumab in MM patients, aiming to define safety, tolerability, and the maximally tolerated dose, though no results have been posted to date (ClinicalTrials.gov Identifier: NCT02252263).

ICIs have shaped the immunotherapeutic landscape of cancer patients, particularly anti-PD-1 antibodies like Nivolumab [280]. The addition of Nivolumab to "Elotuzumab + Pomalidomide + Dexamethasone" regimen was established to evaluate the therapeutic efficacy in RRMM patients (ClinicalTrials.gov Identifier: NCT02612779). Belantamab Mafodotin is an approved antibody–drug conjugate and shows effective anti-MM responses by specifically targeting the BCMA, which is highly expressed on MM cells [281]. Scientist also explored whether the combination of Belantamab Mafodotin and Elotuzumab can strengthen therapeutic efficacy in RRMM patients (ClinicalTrials.gov Identifier: NCT05002816).

SLAMF receptor-targeted CAR-T therapy

In addition to administrating molecule-targeted therapies, scientist have also generated CAR-T cell products targeting SLAMF receptors, predominantly focused on SLAMF7.

A series of clinical trials have been conducted to evaluate the efficacy and safety of SLAMF7-targeted CAR-T therapies (ClinicalTrials.gov Identifier: NCT06185751, NCT04499339). One study observed that all participants receiving SLAMF7-targeted CAR-T therapy showed Grade 2 or the lower adverse events, while participants in the higher dose group encountered severe toxicity. Although efficacy was limited, the safety profile of this therapy was deemed acceptable (ClinicalTrials.gov Identifier: NCT03958656). In addition, SLAMF7-targeted CAR-T products may also perform effectiveness by combining with other molecule-targeted CAR-T products (ClinicalTrials.gov Identifier: NCT03778346).

Beyond single SLAMF7-targeted CAR-T products, the BCMA-SLAMF7 compound CAR-T products have also entered clinical testing to assess its safety and tolerability in RRMM patients (ClinicalTrials.gov Identifier: NCT04156269, NCT04662099). Despite this progress, SLAMF7-targeted CAR-T therapies remain largely confined to MM, with limited data on their potential in other malignancies. Nevertheless, there is a significant lack of clinical trials evaluating therapies targeting other SLAMF receptors, such as SLAMF3, SLAMF4 and SLAMF5. Elucidating the broader translational impact of SLAMF receptor-directed immunotherapies will require more preclinical research and well-designed trials.

Conclusion

In this review, we have presented a comprehensive overview of current discoveries on SLAMF receptors, focusing on their structural features, downstream signaling networks in tumor-associated immune cells, roles in regulating tumor progression, and related immunotherapeutic strategies under clinical evaluation.

The specific signals transmitted by SLAMF receptors are contingent upon the ligand types, cellular contexts, and intracellular protein components. Acting as adhesion molecules, co-stimulatory factors, or even inhibitory receptors, SLAMF receptors coordinate immune responses by bridging innate and adaptive immunity [41, 51, 98, 105, 145, 282, 283]. Of note, SAP families and SH2-domain-containing phosphatases critically shape these pathways, influencing SLAMF-mediated functions [43, 53, 284, 285].

Although early studies focused on roles of SLAMF receptors in hematopoietic malignancies, mounting evidence now supports SLAMF receptor involvement across a broad range of solid tumors. [192, 286] Owing to homophilic interaction characteristics and tissue-specific expression patterns, SLAMF receptors represent promising targets for developing novel cancer immunotherapies. Numerous therapeutic strategies targeting SLAMF receptors have been investigated, including CAR-based therapies (CAR-T cell, CAR-NK cell, bispecific CAR-T cell), monoclonal antibodies (e.g., Elotuzumab), and various combination regimens, with some already in clinical trials [126, 254, 255, 261, 264, 265, 272].

In conclusion, SLAMF receptors exert key roles in regulating immune cells by transmitting context-dependent signals, largely mediated by intracellular SH2-domain containing proteins. They significantly regulate tumor progression through various mechanisms and have emerged as both predictive biomarkers for improving cancer diagnosis and as targets for developing novel immunotherapies. In addition, evidence from clinical studies shows that some SLAMF-targeted therapies can attenuate tumor progression, yet additional rigorous research is needed to translate their theoretical promise into safe and effective treatments that truly benefit cancer patients.

Future perspectives

Despite considerable advances have been made in understanding SLAMF receptor biology and their regulatory roles in tumor immunity, several critical challenges need to be solved.

First, the context-dependent signaling of SLAMF receptors warrants further investigation. Each SLAMF receptor can exert distinct or even opposite roles depending on tumor types, immune cell subsets, and different intracellular adaptors. A thorough understanding of these context-specific roles is pivotal for designing precise targeted therapies and uncovering tumor heterogeneity in different cancer types. Secondly, studies investigating the roles of SLAMF receptors in regulating solid tumor immunity remain limited, especially specific regulatory mechanisms. In addition, emerging evidences underscore the important contributions of different SLAMF receptors in various cancer types, including SLAMF3 in MM [194], SLAMF4 in CRC [193], and SLAMF7 in HCC [52]. Therefore, there are numerous immunotherapeutic candidates beyond SLAMF7 in MM.

Thirdly, immunotherapy tolerance or resistance greatly hinders long-term efficacy of immunotherapies in treating cancer patients, with immunosuppressive TMEs playing a central role. SLAMF receptors expressed on cancer-associated immune cells can either promote or suppress immunosuppression [287]. In addition, many studies have highlighted the potential roles of SLAMF receptors in regulating existing immunotherapies, especially for anti-PD-1 antibody treatment. For example, mice lacking SLAMF4^{+}monocytes displayed a better response to anti-PD-1 antibody treatment [207]. Moreover, mice bearing with SLAMF9-knockdown melanoma cells exhibited improved prognosis upon anti-PD-1 and anti-CTLA-4 treatment [208]. In addition, the higher SLAMF8 expression level correlates with the better response to anti-PD-1 treatment in CRC murine models and GC patients [286, 288]. These findings highlight the potential of combining SLAMF-targeted therapies with existing immunotherapies to amplify therapeutic efficacy.

Finally, since SLAMF receptors are also expressed on normal hematopoietic cells, including red blood cells and platelets, specificity remains a priority in designing SLAMF-targeted treatments [75, 182]. Furthermore, comprehensive clinical trials are needed to evaluate the safety and efficacy of those novel therapies, as well as evaluate potential drug-drug interactions in combination strategies.

In summary, we need to focus on clarifying the context-dependent roles of SLAMF receptors in different settings, expanding research on solid tumors, and developing novel cancer treatment targeting other SLAMF receptors. Furthermore, SLAMF receptor-targeted therapies have great potential to attenuating classical immunotherapeutic resistance mediated by immunosuppressive TME. In the end, ensuring target specificity and clinical safety will be indispensable for translating SLAMF-targeted strategies into successful clinical applications.

Authors' contributions

J.H. and C.L. conceived and supervised the work. J.L. and T.F. drafted the manuscript. J.L. and T.F. designed figures and performed visualization. T.F. and C.X. edited the manuscript. Z.D. and W.C. reviewed the manuscript and provided essential suggestions. J.L. and Y.J. participated in literature screening and analysis of relevant studies. C.L. and J.H. revised the manuscript. D.W. made substantial contributions during the revision phase. All authors have read and approved the final manuscript.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

Not applicable.

Competing interests

The authors declare no competing interests.

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