CD84 and the Tumor Microenvironment (TME)

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Abstract

CD84, or SLAMF5, is a member of the Signalling Lymphocytic Activation Molecule Family (SLAM), a family of immunoreceptors that play key roles in immune cell function, particularly in T and B cells, and regulating immune cell activities. It behaves as a homophilic adhesion molecule; by binding onto other CD84 molecules in neighbouring cells, the protein can mediate cell-to-cell interactions and regulate immune responses, including tolerance. Recent findings have continued to highlight CD84's potential therapeutic target to reduce MDSCs and restore anti-tumour immunity in various autoimmune disorders and cancers, including multiple myeloma and triple-negative breast cancer, given its ability to help MDSCs accumulate in the tumour microenvironment and its suppression of anti-tumour immune responses. The protein is expressed on multiple immune cell types, including thymocytes (highest expression present in single positive cells), T cells, and follicular T helper (TFH) cells, activated B cells, macrophages, DC, platelets, basophils, mast cells, and eosinophils, and has shown great aptitude in immune evasion through enhancing regulatory B cell function, promoting myeloid-derived suppressor cell expansion, and upregulating immune checkpoint molecules like PD-L1 on the MDSCs, leading to T-cell exhaustion. Therapeutic methods with targeting CD84, such as monoclonal antibodies and CAR T-cell therapies, have shown promise in counteracting immunosuppression and improving treatment results, and highlights CD84's significance as a prognostic biomarker and a novel target in cancer immunology. This review will explore CD84 and its role in the tumor microenvironment, including solid tumour and hematologic malignance (such as multiple myeloma), and discuss CD84 as a therapeutic target in cancer immunology as described in recent research findings.

Keywords: CD84, tumour microenvironment, MDSC, PD-1/PD-L1, hematologic cancers, malignant cancers, solid tumours

Introduction

The Signalling Lymphocytic Activation Molecules (SLAM) family is composed of nine immunoglobulin proteins that are principally expressed on immune cells. These receptors regulate immune responses, which include cell activation, differentiation, and intercellular communication, and were first identified in lymphocyte function. CD84, also known as SLAMF5, has been heavily focused on in recent research because of its dual roles in cancer biology: facilitating tumour progression and supporting immune evasion, while also presenting promising therapeutic opportunities (1).

Cancer has the ability to manipulate the immune microenvironment, creating conditions that encourage tumour progression while suppressing antitumor immunity. The SLAM family of immunoglobulin proteins, particularly CD84, have come to our attention as key modulators within the tumour microenvironment (TME) by affecting immune cell dynamics and influencing therapeutic outcomes. CD84's expression on many diverse immune cells, including macrophages, T and B cells, and dendritic cells, further emphasize its central role in shaping immune interactions with tumours for the better (2, 3).

This review will be a comprehensive outline of CD84 and its dual roles in cancer, immune activation, and immune suppression, and highlight its emerging significance as a therapeutic target against haematological and solid tumours. Through the consolidation of current research knowledge, we aim to highlight both the opportunities and the challenges in targeting CD84 for future therapeutic and clinical applications. CD84 presents a promising strategy to address unmet needs by current immunotherapies by modulating immune evasion mechanisms and enhancing responses to immunotherapies.

I. What is CD84?

CD84 is part of the SLAM family of receptors, and is expressed in a diverse group of immune cells, including thymocytes (with the highest expression in single CD4 and CD8 positive cells), T cells, follicular T helper (TFH) cells, activated B cells, macrophages, platelets, DC, basophils, eosinophils, and mast cells. The protein is a single-chain cell-surface molecule with a cytoplasmic tail containing four tyrosine residues. Ligation of CD84 with a specific antibody results in rapid phosphorylation of the tyrosine residues in the ITSM motif, leading to the recruitment of adaptor proteins EAT-2 and SAP. It demonstrates significant self-association, with a dissociation constant (Kd) in the sub micromolar range, and is regulated by its immunoglobulin variable (Ig-V) domain. This forms orthogonal homophilic dimers. In splenic B cells specifically, CD84 can be distinguished into two populations: $CD84_{low}$ and $CD84_{high.}$ The $CD84_{high}$ population corresponds to memory B cells, characterized by a larger cell size, co-expression with CD27, somatically mutated immunoglobulin genes, and higher proliferation rates compared to its sister population (Fig1. CD84 protein structure)(4, 5, 6).

SLAM family receptors are type 1 glycoproteins, and their extracellular ectodomain (except SLAMF3/CD229) consists of two Ig-like domains: one amino terminal variable (V)-like without disulfide bonds and a truncated Ig constant 2 (C2)-like domain with two intradomain disulfide bonds, as shown in Figure 1. On the other hand, SLAMF3/CD229 contains four Ig-like domains, with two repeats of V-Ig and C2-Ig sets. The intracellular tails of SLAMF receptors consist of multiple immunoreceptor tyrosine-based switch motifs, otherwise known as ITSMs, with a characteristic TxYxxV/I/L/T homology sequence, where x is any amino acid. The ITSMs then bind to SLAM-associated proteins, also known as SAP in the figure, and Ewing's sarcoma transcript-2 (EAT-2). Atypical SLAMF receptors, however, such as SLAMF2/CD48, are instead embedded in the cell membrane through a glycosylphosphatidylinositol (GPI) anchor and have no cytoplasmic domain and no ITSMs. SLAMF8 and SLAMF9 have no ITSMs and a short cytoplasmic domain (7).

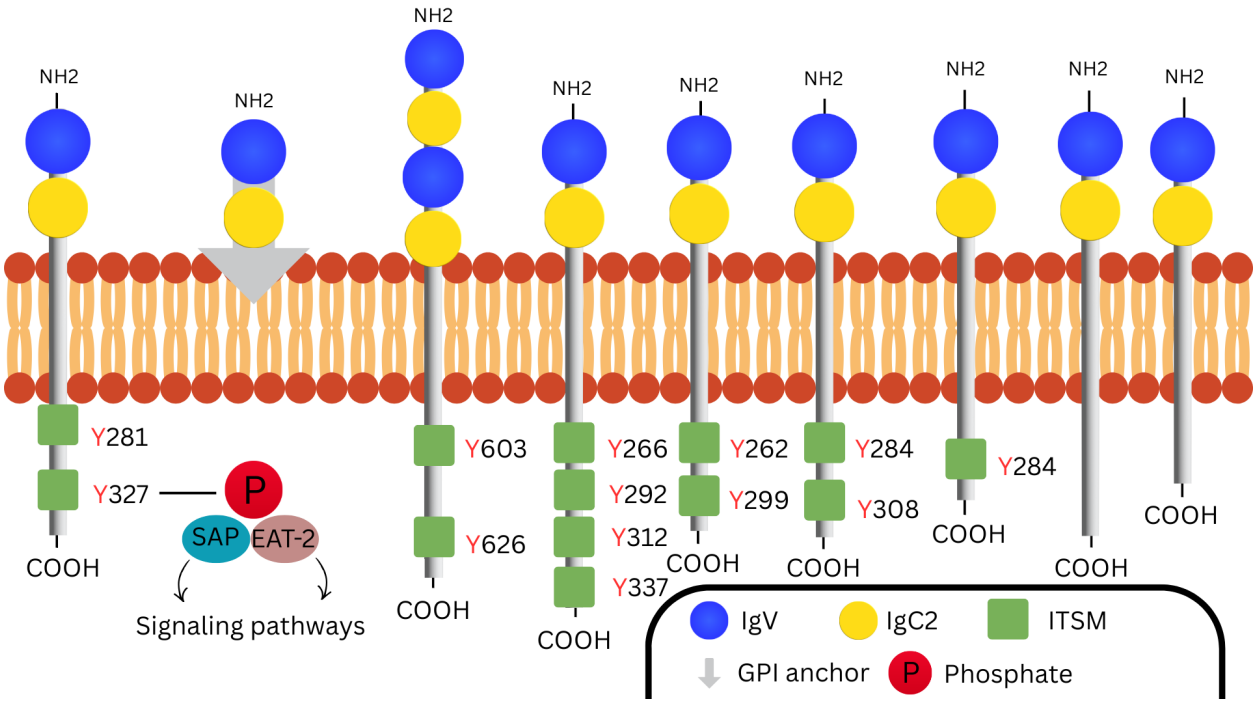

Figure 1: Schematic structure of SLAM family receptors.

The SLAM family receptors are shown in order, from left to right: SLAMF1/CD150, SLAMF2/CD48, SLAMF3/CD229, SLAMF4/CD244, SLAMF5/CD84, SLAMF6/CD352, SLAMF7/CD319, SLAMF8/CD353, and SLAMF9/CD84-H1.

II. CD84 and Cancer

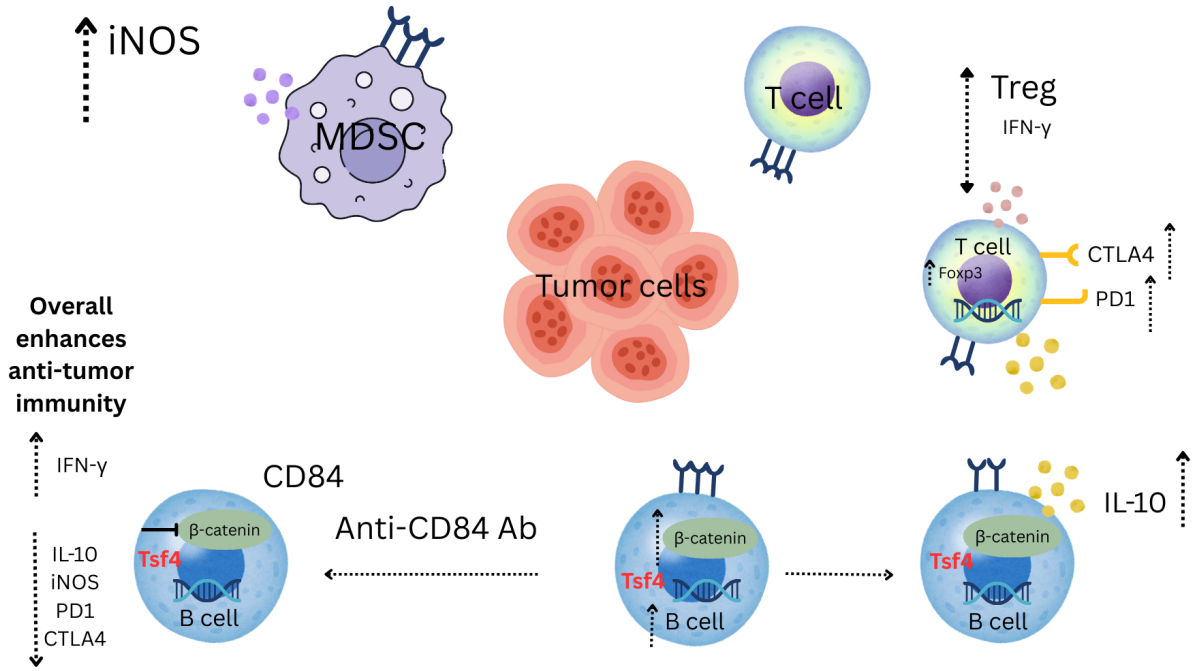

Figure 2. The role of CD84 in the tumor microenvironment and anti-tumor immunity.

Immune cells (e.g. MDSCs, T cells, and B cells) surround the tumor mass and communicate through CD84 signalling. MDSCs elevate iNOS levels and express

CD84, suppressing the immune system. T cells also express CD84 and immune checkpoints, suppressing effector T cells via IFN-y and IL-10. Finally, B cells express both CD84 and Tsf4 and are regulated by β-catenin, affecting immune responses through IL-10 secretion.

As shown in Fig.2, CD84 influences immune cell interactions, and modulates the tumor microenvironment and anti-tumor immunity, making it a crucial player. Its ability to affect immune responses can either promote tumor progression or antitumor immunity, making it a notable therapeutic target. In this section, we will focus on the eclectic roles of CD84 in cancer biology by exploring its mechanisms of action, implications for treatment, and its ultimate potential as a therapeutic target (2).

II-I CD84 and Hematologic Malignancies

a. CD84 and Chronic Lymphocytic Leukemia (CLL)

Kľoc D et al. found that normal B cells presented low levels of CD84 mRNA, while all patients with chronic lymphocytic leukemia (CLL) exhibited highly elevated levels of CD84 mRNA, with no connection to their disease stage. Flow cytometry analysis revealed that in CLL patients, cell-surface CD84 levels were much higher than in total and CD5+ normal B cells (7). This increased expression of CD84 in CLL B cells compared to normal B cells was further supported by additional flow cytometry analysis conducted by Coma et al. (8). However, CD84's role in CLL remains undetermined, but it is noted that its expression is significantly elevated beginning from the early stages of the disease and is regulated by MIF and its receptor, CD74. When CD84 is detected on the cell surface, it triggers a signalling cascade that ultimately promotes the survival of CLL cells, and reducing CD84 expression or blocking it through immunological approaches leads to cell death in vitro and in vivo.

Additionally, treatment of human subjects with humanized anti-CD74 antibodies (mmilatuzumab) resulted in decreased levels of CD84 mRNA and proteins in the treated cells. This downregulation was ultimately connected to a reduced expression of Bcl-2 and Mcl-1. CD84's activation initiates the Akt signaling pathway, enhancing the expression of the antiapoptotic gene Bcl2 and increasing CLL cell survival (7, 9). Research has proven that CD84 facilitates interactions between CLL cells and the tumor microenvironment, which, through both human and mouse CD84, leads to increased PD-L1 expression on CLL cells and their microenvironment, and T cells. This complete interaction ultimately suppresses T cell responses and activity in vitro and in vivo (10, 11).

Research has also shown that the overexpression of CD84 is critical for the survival of CLL cells and may be an early indicator of the disease. Blocking CD84, therefore, can interrupt the interactions between CLL cells and their microenvironment, ultimately leading to cell

death. Several studies have identified many differentiation antigens linked to CLL prognosis, but CD84 remains one of the most notably abundant ones (4, 9, 12).

b. CD84 and MM

Studies have shown that CD84 is a key player in multiple myeloma (MM) cancer biology, and while MM cells typically express low to undetectable levels of CD84, the receptor can induce its expression on the surrounding tumor microenvironment through macrophage MIF secretion. CD84 mediates PD-L1 expression on MDSCs and exhaustion markers on T cells, suppressing immune responses. Studies conducted in vivo have shown that blocking CD84 reduces MDSC accumulation, enhances T cell activity, and lowers tumor burden, suggesting that targeting CD84 in the MM microenvironment could prove a promising therapeutic strategy to boost T cell-mediated antitumor responses and activity (11).

Expression of CD84 was also found to be low to absent in human multiple myeloma cell lines and primary myeloma cells. However, it was found to be highly expressed on bone marrow stromal cells and CD14+ cells in patients diagnosed with MM, compared to matched CD14-negative fractions with statistical significance. Additionally, monocytic M-MDSCs were more prevalent in the peripheral blood of MM patients than in healthy donors. In in vitro and in vivo models, targeting CD84 both resulted in disrupted CD84 signalling, leading to reduced PD-L1/PD-1 expression, decreased M-MDSC expansion, and enhanced T cell activation. In the end, this inhibited myeloma cell proliferation. These findings further suggest that CD84 is a therapeutic target with much potential in MM treatment (15).

On the other hand, studies have shown significantly lower and more heterogeneous expression levels of CD84 in multiple myeloma. This change could reflect differences in disease stage and progression, the different genetic and epigenetic variables of myeloma cells, and the different interactions with specific parts of the bone marrow microenvironment, such as stromal cells and MDSCs. IL-10, hypoxia, TGF-β immunosuppressive cytokine milieu, and other signals can modulate CD84 expression and also contribute to intra- and inter-patient variability. Heterogeneity has been found in solid tumors too, where CD84 expression on tumor-infiltrating immune cells, including MDScs and regulatory B cells, are dependent on variables, such as tumor type and cancer stage. These discrepancies between many variables in the disease emphasize the need for a personalized approach for patients if CD84 is used as a promising therapeutic target. Further research is needed to fully understand the regulatory mechanisms of CD84 expression in different cancers and determine how said differences can potentially influence therapeutic outcomes and clinical responses (14).

c. CD84 and Solid Tumors

CD84 is a potential surface marker, especially in terms of detecting and enriching MDSCs in breast cancer. In a mouse model, CD84 distinguished MDSCs, and human MDSCs from peripheral blood also presented CD84 upregulation. $CD84_{high}$ MDSCs were found to inhibit T-cell proliferation in culture experiments (16). Other recent experiments have indicated that

surface marks CD52, CD84, and PTGER2 are expressed at significantly higher levels on PMN-MDSC-committed neutrophils compared to both normal, mature, and immature neutrophils. This supports the analysis of the mPMN-MDSC gene signature and that these markers are indicative of the immunosuppressive activity of PMN-MDSCs (17).

CD84 is thought to activate a signaling cascade in Bregs, involving the β-catenin and Tcf4 pathways, and thus induces the transcription of IL-10 via binding to its promoter and its regulatory promoter, AhR. Bregs then undergoes expansion and influences the activity of other immune cells, contributing to immune suppression. It also facilitates the proliferation and dissemination of tumor cells through dampening the activities of antitumor T cells (13).

While solid tumor cells usually minimally express CD84, its overexpression in the tumor microenvironment of TNBC patients is linked to increased immunosuppression and reduced survival rates. CD84 mediates immunosuppression within TNBC since cancer cells use it to promote the accumulation of tolerogenic immune cells in the TME, like Tregs, MDSCs, and Bregs. These tolerogenic immune cells, in turn, protect cancer cells from the antitumor immune response, supporting their survival and proliferation. The research indicates that targeting CD84 is a viable therapeutic strategy for overcoming immune tolerance in cancer. Inhibiting CD84 activity in TNBC patients shows promise in enhancing antitumor immunity and therefore lead to reduced tumor growth and overall improved patient outcomes (15). A study conducted in 2023 studied the differential expression of CD84 in lung cancer compared to healthy normal lung tissue and found that higher CD84 expression was linked to a poorer prognosis.

III. Targeting CD84 Therapeutic Approaches

a. Anti-CD84 monoclonal antibodies

Since the beginning, immunotherapy has revolutionized and developed cancer treatment paradigms, with activation of the immune system to fight cancer. For instance, anti-CD84 monoclonal antibodies modulate immune cell signaling by targeting CD84, which is expressed on T cells, dendritic cells, and macrophages. These antibodies play the role of enhancing T cell activation, cytokine production, and cytotoxic activity against tumor cells via the disruption of the immunosuppressive tumor microenvironment. Anti-CD84 therapies have shown great promise in hematological malignancies, such as CLL, AML, and MM, and in augmenting chemotherapy and immunotherapy by strengthening immune response (9, 10, 11, 18).

Anti-CD84 therapies might benefit solid tumors by enhancing T-cell responses against tumor-specific antigens. Preclinical models have shown improved tumor control through the inhibition of the immunosuppressive tumor microenvironment.

b. Therapeutic Combinations

By finding the most beneficial combinations with existing immunotherapies, resistance mechanisms can be overcome and patient outcomes improved. Integrating anti-CD84 cells

with immune checkpoint inhibitors (anti-PD-1, anti- CTLA-4), have demonstrated great efficacy in improving anti-tumor immunity and adequately addresses the limitations of monotherapy in immune-evasive tumors (15). Anti-CD84 therapies demonstrate a great amount of potential in improving the outcomes of patients with hematological and solid tumors through the enhancement of immune responses, and thus leading to better remission and survival rates.

c. Cellular Therapies, CART84, and Novel CD84-targeting Peptides

Anti-CD84 therapies have begun to focus on targeting CD84 on MDSCs in solid tumors, in addition to cellular therapies like CART84. Through the usage of advanced molecular dynamics and computation design, CD84-targeting peptides, mini-proteins, and engineered antibodies with significantly enhanced binding affinity compared to natural CD84 has been developed. They disrupt the CD84-mediated immunological synapse, reducing MDSC-mediated T cell exhaustion and improving antitumor immunity (13). While these strategies are still in their preclinical stages, they further highlight the therapeutic potential target CD84 presents beyond hematological cancers, develop novel CD84-targeting peptides, such as synthetic peptides and mini-proteins, which may reduce the limitations that full-length antibodies present induced Fc-mediated side effects and immunogenicity.

IV. Conclusion

Anti-CD84 therapies demonstrate a great amount of potential in improving the outcomes of patients with hematological and solid tumors through the enhancement of immune responses, and thus leading to better remission and survival rates. Further research is needed to unlock CD84's full potential in combating cancer. Present findings already highlight CD84's potential as a versatile target in immunotherapy, and calls for further experimental and clinical validation.

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