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Review Article

CD84 cell surface signaling molecule: An emerging biomarker and target for cancer and autoimmune disorders

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ABSTRACT

CD84 (SLAMF5) is a member of the SLAM family of cell-surface immunoreceptors. Broadly expressed on most immune cell subsets, CD84 functions as a homophilic adhesion molecule, whose signaling can activate or inhibit leukocyte function depending on the cell type and its stage of activation or differentiation. CD84-mediated signaling regulates diverse immunological processes, including T cell cytokine secretion, natural killer cell cytotoxicity, monocyte activation, autophagy, cognate T:B interactions, and B cell tolerance at the germinal center checkpoint. Recently, alterations in CD84 have been related to autoimmune and lymphoproliferative disorders. Specific allelic variations in *CD84* are associated with autoimmune diseases such as systemic lupus erythematosus and rheumatoid arthritis. In chronic lymphocytic leukemia, CD84 mediates intrinsic and stroma-induced survival of malignant cells. In this review, we describe our current understanding of the structure and function of CD84 and its potential role as a therapeutic target and biomarker in inflammatory autoimmune disorders and cancer.

1. Introduction

Cosignaling molecules tightly regulate innate and adaptive immune responses by delivering downstream signals that ultimately influence leukocyte development, survival, activation, and effector functions. Some of these molecules are cell-surface glycoproteins that can function as costimulatory and coinhibitory receptors [1,2]. Costimulatory receptors are critical for effective immune responses against foreign pathogens, while coinhibitory molecules are essential for the termination of immune responses and for the establishment of immune tolerance to self-antigens [3]. The interest in cell-surface cosignaling molecules has steadily increased during the last years because of their utility as disease biomarkers and their potential use as therapeutic targets for the treatment of autoimmune disorders and cancer [4–7].

The number of cosignaling molecules and the complexity of their signaling pathways are far larger than originally thought. A substantial amount of these molecules belongs to the immunoglobulin superfamily (IgSF). Among them, signaling lymphocyte activation molecule (SLAM) family receptors have emerged as essential orchestrators of both innate and adaptive immune responses [8–11]. Here, we describe our current understanding of the structure, expression and function of the SLAMF receptor CD84 (SLAMF5). We also discuss its significance as a biomarker and future applications of CD84-directed therapies in several autoimmune diseases and hematopoietic malignancies.

2. CD84, a member of the SLAM family of receptors

Human CD84 is a cluster of differentiation first established in 1993 during the 5th International Leukocyte Differentiation Antigens Workshop. Human and mouse cDNAs were cloned by our group in the late 90's, and sequence analysis revealed that CD84 belongs to the IgSF and presents a striking homology with other receptors, later known as the SLAMF receptors [8,12,13].

2.1. Structure and ligand binding

CD84 is a single chain type-I glycoprotein of a molecular weight of 64 to 82 kDa. The CD84 ectodomain consists of a non-canonical

Abbreviations: CLL, chronic lymphocytic leukemia; EAT-2, Ewing's sarcoma-associated transcript 2; ITAM, immunoreceptor tyrosine-based activation motif; ITIM, immunoreceptor tyrosine-based inhibitory motif; ITSM, immunoreceptor tyrosine-based switch motif; MoDCs, monocyte-derived dendritic cells; SAP, SLAM-associated protein; SLAM, signaling lymphocyte activation molecule; XLP, X-linked lymphoproliferative disease

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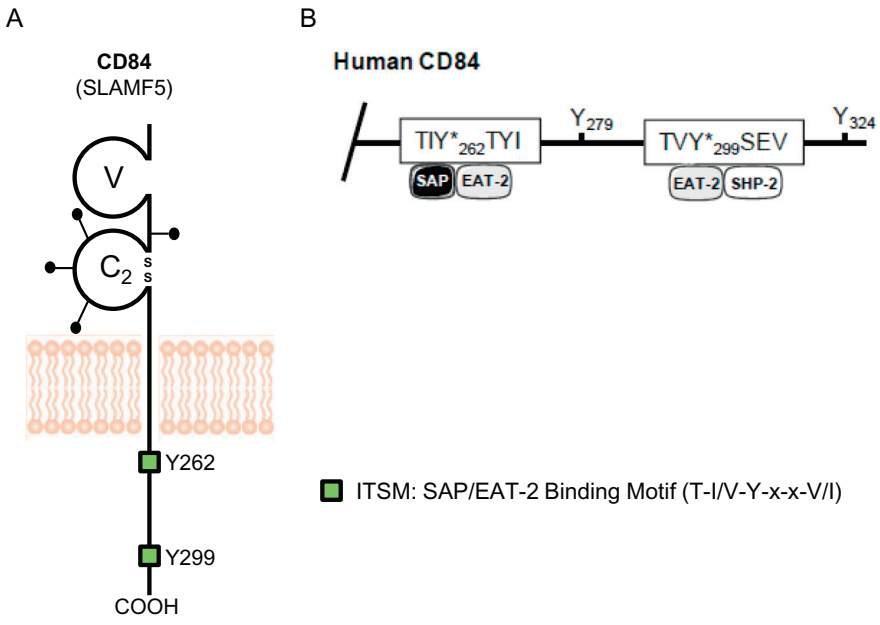

Fig. 1. CD84 structure and cytoplasmic tail. (A) CD84 ectodomain consists of two immunoglobulin (Ig)-like domains, a membrane-distal V-Ig domain and a membrane-proximal C2-Ig domain. CD84 cytoplasmic tail contains two tyrosine residues embedded in two consensus motifs for SAP/EAT-2 binding (green boxes). (B) Schematic representation of human CD84 cytoplasmic tail. Adapter and effector molecules that associate with ITSM (boxed) and with other phosphorylated (Y*) or non-phosphorylated (Y) tyrosine residues are shown. Tyrosine positions are indicated relative to the N-terminal end of the receptor. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

membrane-distal V-Ig domain, which lacks the usually conserved disulphide bonds between β sheets, and one membrane-proximal C2-Ig domain (Fig. 1A). The CD84 V-Ig domain is structured as a two-layer β-sandwich, with front and back sheets composed of A′GFCC′C″ and BED strands, respectively [14]. In the V-Ig domain, the two cysteines conserved in most members of the IgSF are replaced by a hydrophobic amino acid in the β strand B and by alanine in the β strand F. This structural feature is conserved by all SLAMF members [15]. It contains a cytoplasmic domain with several tyrosines implicated in cell signaling (Fig. 1B).

Both human and mouse CD84 function as homophilic adhesion molecules, as reported for other SLAMF members [14,16]. This receptor:ligand interaction involves the first IgV-like domain and is independent of the CD84 cytoplasmic tail [16]. Crystallographic studies performed by Almo's group further validated this observation [14]. Their results reveal that CD84 forms a tight association with a dissociation constant (K_d) in the submicromolar range. CD84 V-Ig domains form head-to-tail dimers. This interdomain organization is similar to that observed in Ly108 (SLAMF6) homophilic dimers. However, specific differences in the homophilic interfaces prevent the binding of CD84 to other SLAMF molecules [14,17]. Of particular note is the end-to-end distance between CD84 molecules (approximately 140 Å), since it is equivalent to the distance between other cosignaling molecule pairs within the immunological synapse [18].

2.2. Signaling motifs

Human CD84 cytoplasmic domain consists of 83 amino acids and contains four tyrosine residues. Two of them (Y_{262} and Y_{299}) correspond to tyrosines embedded in the consensus immunoreceptor tyrosine-based switch motifs (ITSMs), while the other two (Y_{279} and Y_{324}) are enclosed in a motif believed to recruit SH2-containing proteins (Fig. 1B). Moreover, Y_{324} is contained in an ITIM motif. In the same way ITAMs or ITIMs become phosphorylated after receptor ligation, the homophilic engagement of SLAMF members triggers the phosphorylation of tyrosine residues. Subsequently, tyrosines serve as docking sites for intracellular adapter molecules such as SLAM-associated protein (SAP), Ewing's sarcoma-associated transcript 2 (EAT-2), and enzymes bearing SH2 domains such as SHP-2, SHP-1, Csk, and SHIP-1 [19–21]. Biochemical studies have demonstrated that Y_{262}, embedded in the first ITSM of CD84, is essential for the recruitment of SAP, whereas EAT-2 can be recruited to either of the ITSMs [22]. A study using spot arrays with phosphorylated and non-phosphorylated versions of the same CD84 peptide demonstrated that SAP, SHP-2, and SHIP can bind to the non-phosphorylated Y_{262} residue, although their recruitment is more efficient when this tyrosine is phosphorylated [23]. Homophilic CD84 interactions between NK cells from C57BL/6 (B6) mice and target tumor cells enhance *in vivo* NK cytotoxicity [24]. The adapter molecules EAT-2A/B and SAP are positive regulators of CD84-mediated NK cell killing in B6 mice [24]. Furthermore, EAT-2A and EAT-2B could regulate the phosphorylation of the downstream effector molecule Vav-1, which plays a critical role in NK cell cytotoxicity [24]. However, in contrast to the high expression of CD84 on mouse NK cells, human NK cells express low levels of this molecule [25].

Interestingly, CD84 can also signal in a SAP/EAT-2 independent way. Residues Y_{279} and Y_{324}, which are not involved in SAP and EAT-2 recruitment, are critical for CD84-mediated inhibition of FcεRI signals in mast cells [22,26] and CD84-mediated T cell activation and cytokine secretion [27].

2.3. Gene organization and spliced variants

The CD84-encoding gene is comprised of eight exons. The first exon encodes the leader peptide, the second and third the two Ig-like domains, the fourth codes for the hydrophobic transmembrane region, and exons five to eight correspond to its cytoplasmic tail [12,28]. Some alternative splice variants of human CD84 have also been described. Most of them differ principally in their intracellular segments [28]. Variations in the cytoplasmic tail could potentially affect the ability of CD84 to recruit key signaling molecules such as adapter proteins SAP and EAT-2, and tyrosine phosphatases. Unpublished data from our laboratory indicate that the isoform that lacks exon 5 (CD84Δ5) is the most prevalent expressed isoform. We have also observed that an isoform that lacks the cytoplasmic tail (CD84Δ5,6) is overexpressed in T lymphocytes and NK cells from SLE patients (Dr. Cox Terhorst, personal communication). Thus, although it's early to make a statement about the function of these splice forms, they are potentially interesting and worth further studies.

2.4. Expression

Flow cytometric and gene expression analyses show that human

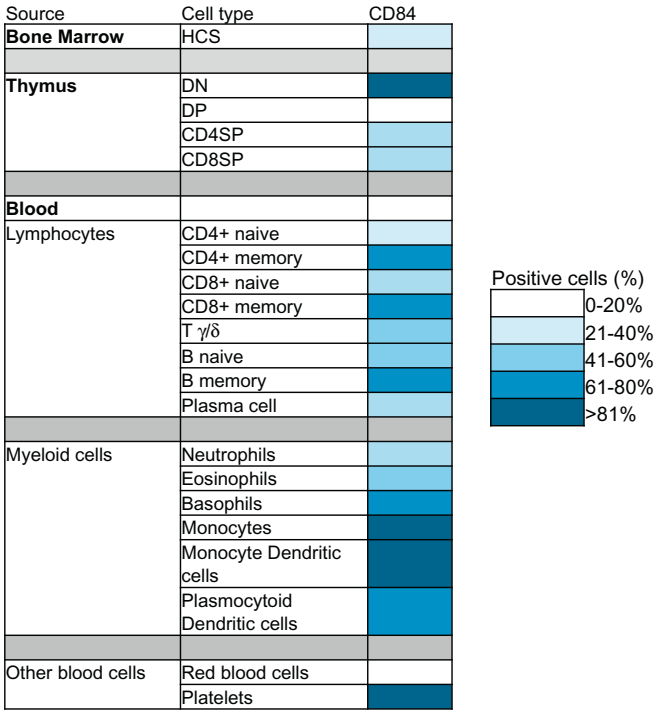

Fig. 2. Expression of CD84 in leukocyte subsets from bone marrow, thymus, and blood as determined by flow cytometry [25,29–33]. HCS, hematopoietic stem cell; DN, double negative T cells; DP, double positive T cells; SP, single positive; Tγ/δ, gamma delta T cells.

CD84 is present on multiple hematopoietic cell types. CD84 expression levels are quite heterogeneous depending on the cell type, the differentiation state, or the activation status of the cell (Fig. 2). CD84 appears very early during hematopoietic differentiation in bone marrow progenitor cells [29,30]. CD84 is expressed on most T and B cells, but with a significantly higher expression on memory T and B lymphocytes [21,25,31]. Importantly, both follicular helper T cells and germinal center (GC) B cells express high levels of CD84 [25,31,32]. Myeloid antigen presenting cells, such as monocytes and monocyte derived dendritic cells (DCs), are also markedly positive for human CD84 [25]. CD84 expression has also been reported on plasmacytoid DCs (pDCs) [33]. Granulocytes also express significant levels of CD84 with the highest expression on basophils and mast cells [16,22,25]. On the other hand, CD84 is expressed at low levels on human NK cells, and absent in human red blood cells [25].

Among all hematopoietic cells, platelets express the highest levels of CD84. CD84 was initially proposed as an aggregation-induced signaling receptor implicated in stabilizing platelet-platelet interactions [34]. However, although CD84 is highly expressed in platelets and is phosphorylated upon platelet aggregation, studies with CD84 deficient mice indicate that it does not play a significant role in hemostatic and thrombotic function [35]. It has been proposed that the interaction of platelets with leukocytes may mediate their recruitment to inflamed or injured endothelial cells and could favor tumor metastasis. Nevertheless, whether CD84-mediated platelet-leukocyte interactions play a determinant role in inflammation or cancer still needs to be elucidated.

2.5. The dual role of CD84 in the regulation of leukocyte function

As described for other SLAMF members, CD84 can act as an activator or an inhibitory receptor depending on the cell type and its stage of activation or differentiation [36,37]. Initial studies described that cross-linking of human CD84 with either anti-CD84 mAbs (clones: hCD84.1.1, hCD84.1.7, hCD84.1.21, hCD84.2.151, and 152-1D5) or CD84-Ig fusion protein increases proliferative responses and IFN-γ secretion in anti-CD3 mAb-stimulated human T cells, suggesting that CD84 enhances TCR-mediated signaling [16,27]. Nonetheless, this CD84-mediated phenomenon occurs independently of SAP signaling, since T cells from both healthy donors and SAP-deficient X-linked lymphoproliferative disease (XLP) patients respond equally to anti-CD3 stimulation. In this regard, CD84 can also be efficiently phosphorylated in SAP-deficient cells from XLP patients [21,27]. In contrast to other cells, CD84 negatively regulates FcεRI-mediated signaling in mast cells [22].

3. Role of CD84 in humoral and cellular immune responses

3.1. CD84 modulates T-B cell dynamics in the germinal centers (GCs)

Long-lasting T-B contacts are required for the delivery of T cell-derived help signals for B cells, therefore sustaining GC reactions and the development of long-term immunity [38]. CD84 expression on T cells has been proposed to contribute to their optimal adhesion to cognate B cells, since *CD84*-deficient CD4+ T cells are impaired in their ability to form stable antigen-specific T:B cell conjugates [39]. Interestingly, reduced CD84 expression on B cells deficient in the adaptor molecule ITSN2 correlates to their reduced capacity to establish long-lasting interactions with cognate T lymphocytes [40]. Furthermore, *in vitro* T:B cell conjugate formation is impaired in the presence of anti-CD84 monoclonal antibodies that reduce CD84 homophilic interactions [39]. In line with these results, a recent report shows that antibody ligation of CD84 (mAb clone: hCD84.1.21) completely abrogates *in vitro* plasma cell differentiation and IgG production induced by PD-$1^{hi}CXCR5^{+}$ T_{FH} cells and PD-$1^{hi}CXCR5^{-}$ T peripheral helper (T_{PH}) cells, a newly described CD4+ T cell subset markedly expanded in the synovium of rheumatoid arthritis (RA) patients [41].

However, the non-redundant contribution of CD84 to the outcome of T-Dependent (T-D) antibody responses to protein antigens remains to be fully determined. It was initially described that, following NP-OVA immunization, CD84 deficiency led to reduced numbers of T_{FH} and GC B cells and to slightly reduced NP-specific IgG levels [39]. In contrast, other studies have shown unaltered antibody production and normal GC B and T_{FH} cell differentiation in *CD84*-deficient mice after immunization with NP-OVA [42,43], sheep red blood cells [43,44], or viral infection with either lymphocytic choriomeningitis virus (LCMV) or vaccinia virus (VACV) [37]. Moreover, *in vivo* CD84 targeting with monoclonal antibodies (clone mCD84.7) does not alter either antibody production nor T_{FH} and GC B cell numbers after NP-OVA immunization [42]. Thus, despite its role in stabilizing T:B cell contacts, absence or targeting of CD84 alone is apparently not enough to significantly impair humoral responses against protein antigens in mouse *in vivo* models. However, *in vitro* T-B co-cultures of RA patient cells show that CD84 ligation with monoclonal antibodies reduces T_{FH}- and T_{PH}-driven plasma cell differentiation [41], establishing a rationale to further explore therapeutic targeting of CD84 to restrain pathological B cell activation in inflammatory autoimmune disorders.

3.2. CD84-mediated regulation of autophagy in monocyte-derived dendritic cells (MoDCs)

Beyond its role in recycling cellular material for maintenance of cellular homeostasis at periods of starvation, autophagy has recently emerged as a major regulator of both cell-intrinsic and systemic antimicrobial immunity [45]. Autophagy is the main pathway by which intracellular protein-derived peptides are delivered and presented to CD4+ T-cells during thymic T-cell selection [46,47] or anti-viral responses [48]. Yet, autophagy is equally important for the control of exuberant inflammatory responses by eliminating danger signals, suppressing accumulation of reactive oxidative species and controlling proinflammatory cytokine responses during infection or autoimmune

processes [49,50].

Although much has been uncovered about the function of CD84 in the regulation of T cell-B cell communication, little is known about its role in DCs. In a *CD84*-deficient murine model, T cells showed no apparent defects in their ability to form antigen-specific conjugates with DCs [39]; nevertheless, compensatory mechanisms implemented by other SLAMF receptors may mask a DC phenotype. Alternatively, stress conditions, or specific microbial challenges may be required to reveal unique contributions of CD84 to DC functions.

Recently, we examined the effect of CD84 on LPS + IFNγ-induced MoDC functions by silencing CD84 expression. At decreased level of CD84 expression we observed enhanced production of the inflammatory cytokines IL-1β and IL-23 [51]. These changes were concomitant with a significant decrease of the CD1a + subset, reminiscent to that of MoDCs treated with autophagy inhibitors [52–55]. These data suggested that CD84 may act as a cell surface regulator of autophagy in human DCs. Significantly, other members of the SLAM receptor family have also been described as activators (CD150) or inhibitors (CD244) of autophagy [56,57].

To examine the role of CD84 in the regulation of DC-autophagy siRNA-mediated gene silencing, crosslinking experiments were performed that established CD84 as a positive regulator of autophagy [51]. This autophagy-promoting effect was required to maintain steady state levels of autophagy as well as for the recovery of steady state autophagy in dendritic cells treated with LPS + IFNγ [51,58].

Strikingly, while both CD150 and CD244 were shown to act *via* modulation of the Beclin-1/Vps34 complex, CD84 appears to act *via* a novel, alternative pathway targeting interferon regulatory factor 8 (IRF8), a master regulator of the autophagy process [59]. In support of this model, we found that silencing of CD84 and/or IRF8 generated an overlapping DC-phenotype. More importantly, the enhancement of autophagic flux detected in response to CD84-specific antibody crosslinking (clone 152-1D5) was eliminated by transfection of IRF8-specific siRNA. In line with these findings, the level of IRF8 protein is significantly decreased in CD84-silenced DCs compared to controls. Our experiments also revealed that rather than regulating the expression level of the *irf8* gene CD84 inhibits proteolytic degradation of IRF8 by a mechanism dependent on the E3 ubiquitin ligase tripartite motif-containing protein 21 (TRIM21) [51]. Since neither Bafilomycin A1 nor rapamycin rescued the autophagy defect seen in CD84-silenced MoDCs, we propose that CD84 should act on the early events of autophagy in a manner independent of mTOR [51].

The above described experiments identify CD84 as a novel member of the few known cell surface regulators of autophagy potentially suitable for targeting by specific antibodies. Although most details of the affected signaling pathways are yet to be identified, it is tempting to suggest that activity of the CD84/IRF8 axis may influence the outcome of immune responses to intracellular pathogens. In this regard, Garcia et al. recently found a correlation between clinical response of patients to mycobacterial infection and the intensity of autophagy induced by *M. tuberculosis* antigen in the adherent cell fraction of patient's PBMCs [60]. Notably, CD84 could also be targeted to treat pathologies that develop due to defects in the process of autophagy. Defective autophagy and phagocytosis have been implicated in neuropathologies including Alzheimer's and Parkinson's disease [61]. Interestingly, CD84 was found as one of the differential markers in subsyndromal symptomatic depression [62], further implicating CD84 as a potential regulator of neuroinflammatory responses.

3.3. Monocyte activation and cytokine secretion are enhanced by CD84 signals

Studies in mice demonstrated that CD84 is able to modulate signaling pathways downstream of TLR4 [63]. CD84 enhances LPS-induced monocyte activation by increasing ERK-1/2, p38, and JNK-1/2 phosphorylation levels and NF-κB/AP-1 activity, inducing a higher secretion of proinflammatory cytokines such as TNF-α while lowering IL-10 production. This modulatory effect was mediated by tyrosines within the second ITSM of CD84 [63].

4. CD84 in autoimmune disorders

4.1. CD84 regulates B cell tolerance at the GC checkpoint

In GCs, somatic mutations in B cell Ig genes can generate autoreactive clones. Thus, tolerance mechanisms at the GC level are required to prevent the rise of self-reactive B cells and the consequent production of autoantibodies. SLAMF receptors are involved in the loss of tolerance to nuclear antigens and the development of autoimmunity in B6.*Sle1b* mice [64]. This lupus-prone mouse strain contains DNA segments (*i.e.* the *Sle1b* locus) derived from New-Zealand white (NZW) mice embedded in the C57BL/6 (B6) genome [64]. In this setting, autoantibodies develop because of epistatic interactions between the embedded *Slamf1-7* genes, present in the *Sle1b* locus, and B6 genes [64–66]. The presence of the *Sle1b* sublocus also alters B cell tolerance at the GC checkpoint, leading to the development of anti-nuclear antibodies (ANA) [67].

Polymorphisms in SLAM family genes are implicated in both murine and human lupus [10,68–72]. Importantly, in the B6.*Sle1b* model, *co*-expression of autoimmune-associated polymorphisms of CD84 and Ly108 in GC B cells is sufficient to drive loss of B cell tolerance at the GC checkpoint, leading to an increase in autoantibody production and the acquisition of a lupus-like phenotype [44]. Using a BAC-transgenic rescue approach, Wong and colleagues have demonstrated that B6.*Sle1b* mice overexpressing CD84 and Ly108 alleles derived from non-autoimmune B6 mice exhibit significantly reduced ANA titers and a lower incidence of spontaneously developed GCs. Pathogenic allelic variations in CD84 and Ly108 genes in mice help autoreactive B cells escape the negative selection at the GC by attenuating BCR signaling strength after engagement of self-antigens and reducing the formation of B:T cell conjugates [44]. Currently, to the best of our knowledge, no polymorphisms in CD84 have been associated with human SLE.

4.2. CD84 as a biomarker in RA, psoriasis and SLE

The introduction of biological disease-modifiers has considerably improved the treatment of patients with autoimmune diseases. However, many of these drugs are ineffective in a substantial fraction of patients. The identification of biomarkers is an essential tool to predict which patients are more likely to respond to specific therapies allowing personalized treatment. In this regard, CD84 expression has been shown to serve as a distinctive predictor of disease activity and response to anti-TNF therapy among RA patients [73]. This study, which analyzed 2706 RA patients treated with three anti-TNF drugs, identified that a single nucleotide polymorphism in the *CD84* gene (rs6427528) was associated with a better response to the TNF-α inhibitor etanercept, but not adalimumab or infliximab. More recently, another study showed that the same polymorphism of CD84 is associated with better responses to etanercept in patients with psoriasis [74]. Collectively, these findings highlight the potential of CD84 as a biomarker to predict treatment efficacy in autoimmune diseases.

Several miRNAs have been implicated in SLE pathogenesis. Recently, expression levels of miR-142-3p have been shown to be significantly downregulated in CD4+ T cells of SLE patients [75]. This miRNA is responsible for direct inhibition of CD84 expression. Consistently, CD84 expression in SLE CD4+ T cells is significantly increased compared with that in control CD4+ T cells [75]. In this report, Ding et al. propose that the elevated expression of CD84 in T cells from SLE patients could contribute to SLE pathogenesis. In line with this, the proportion of CD8+ T cells expressing CD84 is significantly lower in lupus patients in clinical remission compared with SLE patients with active lupus nephritis [76]. Therefore, targeting CD84 with antagonistic

monoclonal antibodies could be a useful therapeutic approach in SLE patients overexpressing CD84 in CD4+ and CD8+ T cells.

5. CD84 mediates intrinsic and stroma-induced survival of CLL cells

Chronic lymphocytic leukemia (CLL) is a malignancy characterized by the accumulation of CD19 + CD5+ B lymphocytes in peripheral blood, bone marrow, and lymphoid tissues. The clinical course of CLL is heterogeneous: in some patients, the disease is very stable, and therapy can be dispensable for many years; in others, the disease is more aggressive, and treatment is required soon after diagnosis. The risk for disease progression is evaluated in each patient based on clinical and biological prognostic factors, which are also considered to establish personalized treatment strategies [77].

CD84 expression in CLL cells is higher than on healthy B cells, and it can be detected in all malignant cells regardless of the stage of the disease [78]. By using a DotScan™ CD antibody microarray, which enables a high-throughput evaluation of the expression of 182 CD antigens simultaneously, CD84 was found to be significantly upregulated in patients with progressive CLL as compared to patients with a more stable or slow-progressive disease [79]. Consistent with this observation, a recent report has identified CD84 as a survival receptor for CLL cells [78]. In CLL cells, CD84 ligation with the anti-CD84 mAb 152.1D5 triggers a signaling cascade that involves phosphorylation of Akt and EAT-2, and the subsequent binding of Lck to EAT-2. Anti-CD84 targeting with the 152.1D5 mAb significantly increases the levels of anti-apoptotic molecules BCL-2 and MCL-1 in CLL B cells, and the opposite effect is observed when blocking CD84 homophilic interactions with truncated CD84 fragments, further reinforcing the idea that CD84 activation triggers a survival signaling cascade in CLL cells [78].

During CLL progression, interaction of malignant cells with the tumor microenvironment contributes to disease pathogenesis by promoting CLL survival, retention in protective niches, and proliferation of therapy resistant clones. Remarkably, homophilic CD84 interactions between CLL cells and BM stromal cells promote the survival of both cellular components [80]. Co-culture of CLL cells with the stromal cell line M210B4 promotes *in vitro* CLL cell survival and BCL-2 upregulation, while siRNA-mediated knockdown of CD84 on stroma cells significantly reduced survival of CLL cells [80]. Similarly, in this co-culture setting, CD84 ligation with the anti-CD84 mAb B4 reduced stroma-mediated survival of CLL cells. Thus, Marom and colleagues defined the anti-CD84 mAb B4 as antagonistic, since the functional outcome of B4 ligation is similar to that of CD84 knockdown [80]. Importantly, CD84-mediated CLL-stroma interactions promote CCL3 secretion from CLL cells, which in turn increases BCL-2 expression and IL-6 production in stromal cells, creating a positive feedback loop that ultimately supports CLL resistance to apoptosis [80]. In an *in vivo* mouse model for progressive CLL, *CD84*−/− mice displayed a significantly lower numbers of malignant cells in spleen, peripheral blood, peritoneum and bone marrow (BM) compared to their wild-type counterparts [80], suggesting that CD84 is also important for the retention of malignant cells in specific niches. Furthermore, *in vivo* treatment with the anti-CD84 mAb B4 impairs retention of CLL cells in the BM and spleen, and reduces tumor burden in the peripheral blood of treated animals [80]. In line with these results, culture of CLL cells from patients with both stable and progressive CLL on CD40L-expressing fibroblasts upregulates CD84 expression on CLL cells, along with other markers important for cell adhesion and activation, including other SLAMF members such as CD229 (SLAMF3) and CD150 [81]. Interestingly, treatment with Ibrutinib (BTK inhibitor) and idelalisib (PI3Kδ inhibitor), drugs that interfere with the accumulation and retention of CLL cells in bone marrow and lymph nodes, decreased CD84 expression in CLL cells following co-culture with CD40L-expressing fibroblasts [81].

6. Concluding remarks

Signaling through the cell-surface receptor CD84 is involved in several immunological processes involving different leukocyte subsets, such as cytokine secretion by T cells and monocytes, NK cell cytotoxicity, DC autophagy, cognate T:B interactions, and regulation of B-cell tolerance at the GC checkpoint. Although further research is needed to clarify the non-redundant role of CD84 in the regulation of *in vivo* T-D humoral responses, *in vitro* experiments and enhanced CD84 expression in some autoimmune diseases strongly suggest that CD84 blockade may help controlling pathological T_{FH} and T_{PH}-dependent autoantibody production. It should be noted, however, that using CD84 as a therapeutic target may be challenging due to its broad expression and complex biological functions in different cell types. Despite the lack of severe human immunodeficiency in the absence of CD84, and the relatively mild phenotype of the *CD84*-KO mice, the effects of CD84 deficiency should be further studied in murine models kept under non-SPF conditions. Importantly, association of CD84 polymorphisms with better therapeutic responses to etanercept in RA and psoriasis patients paves the way to explore how SNPs in CD84 -and maybe other SLAMF receptors- could be used as biomarkers to predict response to treatment with biological agents. Finally, identification of CD84 as a critical mediator for CLL cell survival sets the basis to assess the potential of CD84 targeting as a treatment for stroma-dependent B cell malignancies.

Conflict of interest disclosure

The authors declare no commercial or financial conflict of interest.

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