



# CD300 Receptors in Immunity and Diseases

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## Abstract

The CD300 family consists of immunoglobulin-like receptors predominantly expressed in certain lymphocyte subsets and myeloid cells. They orchestrate immune responses through integrated activating and inhibitory pathways. The human CD300 family consists of eight members, including CD300a-CD300h. Based on their intracellular domains and coupling adaptors, CD300 members are categorized into inhibitory receptors, activating receptors, and adhesion molecule. By coupling extracellular lipid sensing to the signaling cascades, they regulate inflammation, cytoskeletal remodeling, and myeloid activation. They enhance host defense and facilitate tissue repair upon acute infection, but drive suppressive myeloid reprogramming and tumor immune evasion within the chronic inflammatory or oncogenic microenvironment. This review comprehensively outlines the structural biology, ligand recognition, and signaling architectures of CD300 receptors, evaluates their mechanistic roles in disease progression, and highlights the related targeted therapeutic strategies.

**Keywords:** CD300, Activating receptors, Inhibitory receptors, Targeted therapy, Immune regulation, Tumor microenvironment

## Introduction

The immune system maintains organismal integrity through coordinated interactions among immune cells, soluble mediators, and specialized tissues. Cell surface receptors convert extracellular signals into intracellular cascades that determine immune cell fate and function [1]. Cluster of Differentiation (CD) molecules regulate activation, tolerance, migration, and communication of immune cells [2]. Among them, the CD300 family forms a bidirectional regulatory system that integrates both activating and inhibitory signals within a homologous receptor cluster. The human CD300 family consists of eight members, including CD300a-CD300h. They are predominantly expressed in myeloid cells and certain subsets of lymphoid cells [3]. Based on their intracellular domains and coupling adaptors, CD300 members are categorized into inhibitory receptors containing immunoreceptor tyrosine-based inhibitory motifs (ITIMs) [4], activating receptors associated with adaptor

proteins containing immunoreceptor tyrosine-based activation motifs (ITAMs) [5], and the adhesion molecule CD300g [6]. They exhibit cell-type specificity and microenvironment-dependent functions, with some exerting opposing effects depending on context. This review focuses on their molecular structure, signaling mechanisms, roles in disease, and the related therapeutic strategies.

## Molecular and Functional Basis of the CD300 Receptors

The CD300 family comprises type I transmembrane receptors that regulate immune responses through either activating or inhibitory signaling pathways. Members of this family share a conserved structural organization that includes a single extracellular immunoglobulin-like domain and variable intracellular cytoplasmic tails.

Human CD300 genes form a cluster on chromosome 17 [7]. Based on the features of their cytoplasmic domains, most CD300 members are classified as either inhibitory receptors (CD300a and CD300f) or activating receptors (CD300b, CD300c, CD300d,

CD300e, and CD300h). CD300g represents an exception, as it lacks canonical signaling motifs and mainly functions as an anchoring adhesion molecule [8] (Table 1).

**Table 1:** Classification, Structural Features, and Ligand Recognition Profiles of Activating and Inhibitory CD300 Receptors.

Function type	Receptor	Key structural features	Adaptor protein/recruitment molecule	Ligand recognition
Inhibitory receptor	CD300a	Long intracellular tail, containing ITIM	SHP-1, SHP-2	PE, PS
	CD300f	Long intracellular tail, containing ITIM	SHP-1, SHP-2	PE, PS, PC, Cer, SM
Activating receptor	CD300b	Transmembrane region bearing positively charged lysine residues	DAP12, DAP10	PE, PS
	CD300c	Transmembrane region bearing negatively charged glutamate residues	DAP12, FcεRγ	PE, PS
	CD300d	Transmembrane region bearing negatively charged glutamate residues	DAP12, FcεRγ	Unknown
	CD300e	Transmembrane region bearing positively charged lysine residues	DAP12, FcεRγ	SM (Candidate ligand)
	CD300h	Transmembrane region bearing positively charged lysine residues	DAP12, DAP10	Unknown

### Inhibitory CD300 Receptors

CD300a and CD300f are inhibitory receptors with broadly similar signaling mechanisms in humans and mice. Both contain cytoplasmic immunoreceptor tyrosine-based inhibitory motifs (ITIMs) [9]. After ligand binding, Src family kinases phosphorylate these motifs, which then recruit the phosphatases SHP-1 and SHP-2. This dampens early activation signals and limits downstream inflammatory pathways, including MyD88, TRIF, NF-κB, and MAPK. As a result, both receptors act as negative regulators of immune cell activation and inflammation.

CD300a mainly binds the membrane phospholipids phosphatidylserine (PS) and phosphatidylethanolamine (PE), with stronger affinity for PE. This interaction depends on key residues in its extracellular immunoglobulin-like domain, especially D106 and D115 [10]. In settings such as cancer and viral infection, PS and PE exposed on apoptotic cells or viral envelopes can engage CD300a and suppress immune cell activation.

CD300f recognizes a wider range of ligands than CD300a. In addition to PS and PE [11], it also binds phosphatidylcholine (PC) and ceramide, and in humans, sphingomyelin [12]. Ligand binding is highly sensitive to single amino acid changes in its immunoglobulin-like domain, suggesting that small structural differences can strongly influence binding specificity. Beyond inhibitory signaling, CD300f also contributes to apoptotic cell clearance, immune homeostasis, and the control of inflammation.

Together, CD300a and CD300f connect the recognition of exposed membrane lipids to the suppression of immune responses. Although they share similar intracellular inhibitory pathways, they differ in ligand range and functional scope, with CD300f showing broader regulatory activity.

### Activating CD300 Receptors

The activating CD300 receptors include CD300b, CD300c, CD300d, CD300e, and CD300h. These receptors share structural and signaling features that distinguish them from inhibitory CD300 family members. Most of them have short cytoplasmic tails and therefore do not signal directly. Instead, charged residues in their transmembrane regions allow them to associate with adaptor proteins such as DAP12, DAP10, and FcεRγ, which contain immunoreceptor tyrosine-based activation motifs [13-17]. Ligand binding leads to phosphorylation of these adaptor motifs and recruitment of Syk or ZAP-70 family kinases, which in turn activate PI3K-Akt, MAPK, NF-κB, and calcium-dependent pathways [18]. Through these signaling networks, activating CD300 receptors regulate cytokine production, phagocytosis, chemotaxis, cell survival, and immune cell differentiation.

Although this overall signaling strategy is shared, activating CD300 receptors are not fully conserved between species. Human and mouse orthologs differ in intracellular motifs, adaptor coupling, and receptor trafficking, indicating that signaling output may vary across species. For example, human CD300b contains an intracellular tyrosine motif that is absent from the mouse receptor, suggesting differences in receptor regulation and downstream signaling [13,14].

Some activating CD300 receptors bind lipid ligands that overlap with those recognized by inhibitory CD300 receptors, but they trigger different functional outcomes. CD300b binds PS and promotes clearance of apoptotic cells [19]. Unlike CD300a, which shows stronger preference for PE, CD300c binds both PS and PE with similar affinities [20]. For CD300e, sphingomyelin is the leading candidate ligand based on binding studies, reporter assays, and functional analyses in transduced cells, though its physiological

relevance *in vivo* has not yet been established [21]. However, the endogenous ligands of CD300d and CD300h are still unknown, and understanding how these activating receptors regulate immune responses in physiological settings is limited. Taken together, activating CD300 receptors convert extracellular lipid recognition into intracellular activating signals. Despite shared core signaling features, individual receptors differ in ligand preference, biological role, and, in some cases, species-specific regulation.

## CD300 Receptors in Disease

CD300 receptors are increasingly recognized as key regulators of immune responses in diverse diseases. Their functions are coordinated by tissue-derived cues that shape inflammation, myeloid cell activity, and tissue repair across different disease settings. Their effects vary with cell type, ligand availability, and disease stage, and can be either protective or harmful depending

on the setting.

This section examines their roles across four major disease contexts: tumor immunity, inflammatory homeostasis, host-pathogen interactions, and immunometabolism and tissue degeneration. The function of CD300h in disease remains unclear due to limited evidence. Further studies are needed to clarify its pathological relevance.

### Tumor Immunity

CD300 family members shape immune function within the tumor microenvironment and thereby influence tumor growth, immune escape, and treatment response. Their effects vary across tumor types and cellular compartments, arising either from direct actions on tumor cells or from indirect remodeling of the surrounding immune landscape (Figure 1).

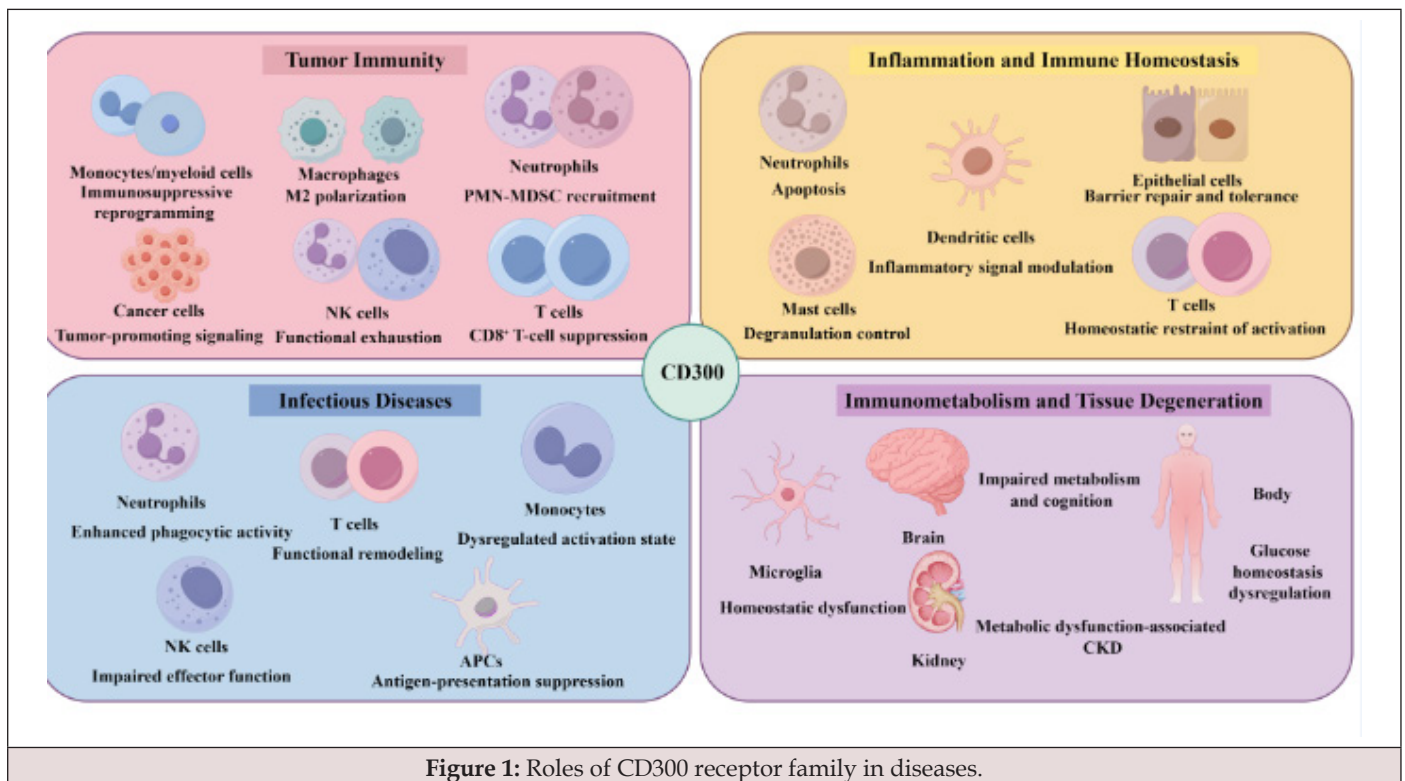


Figure 1: Roles of CD300 receptor family in diseases.

### CD300a: Immune suppression and tumor promotion:

The role of CD300a in cancer is determined by both cell type and the signals present in the local microenvironment. In acute myeloid leukemia (AML), the elevated CD300a expression correlates with upregulation of PECAM1 and ADCY7 and with activation of the AKT/mTOR signaling pathway, suggesting that CD300a may support tumor progression [22]. In solid tumors, CD300a appears to facilitate disease progression by impairing natural killer (NK) cell function. Tumor-infiltrating NK cells with high CD300a expression display an exhausted phenotype characterized by the weakened activating signals and the reduced cytotoxic activity. Importantly, CD300a blockade can restore the NK cell-mediated killing, providing a rationale for targeting this receptor in cancer immunotherapy [23].

Beyond NK cells, CD300a-mediated immunosuppression likely extends to other immune cell populations within the tumor microenvironment. In the breast cancer model, the phosphatidylserine PS and PE exposed on tumor cells can engage CD300a on mast cells. This interaction suppresses mast cell-mediated antitumor responses and may contribute to tumor progression [24].

### CD300c: Prognosis in solid tumors:

CD300c expression reflects features of the tumor immune microenvironment and associates with clinical outcomes in several solid tumors, though its prognostic significance is tumor-type specific. In triple-negative breast cancer (TNBC), CD300c expression correlates strongly with M2 macrophage infiltration. Transcriptomic analyses indicate that a prognostic

model incorporating CD300c alongside MS4A7 and SPARC may help stratify patients and predict immunotherapy response, with higher CD300c expression generally portending worse outcomes [25]. However, this pattern does not hold universally. In glioma, lower CD300c expression associates with higher tumor grade, IDH wild-type status, and poorer prognosis — a relationship that is directionally opposite to what is observed in breast cancer. These contrasting findings underscore that the clinical relevance of CD300c must be interpreted within tumor-specific contexts.

#### **CD300d: PMN-MDSC regulation**

Emerging evidence identifies CD300d as a regulator of polymorphonuclear myeloid-derived suppressor cells (PMN-MDSCs), implicating it in tumor-associated immune suppression. In mouse tumor models, CD300d expression correlates with activation of the STAT3–S100A8/A9 axis, enhanced PMN-MDSC recruitment to the tumor site, and suppression of CD8+ T cell function [26]. Collectively, these findings support a model in which CD300d reinforces an immunosuppressive myeloid niche that limits effective antitumor T cell responses.

#### **CD300e: Tumor microenvironment remodeling:**

CD300e is expressed predominantly in monocytes, macrophages, and myeloid dendritic cells, and its role in cancer is strongly tissue-dependent. Pan-cancer analyses demonstrate that CD300e is upregulated across multiple tumor types and frequently associates with poor prognosis. Proposed mechanisms include promotion of cell proliferation, migration, and invasion, as well as induction of M2 macrophage polarization. CD300e upregulation may impair antigen presentation and CD8+ T cell function, thereby fostering an immunosuppressive tumor microenvironment [27,28]. Nevertheless, the effects of CD300e are not uniformly detrimental. In the liver, CD300e-expressing macrophages have been reported to support tissue regeneration following injury [29], indicating that the function of this receptor varies substantially across tissues and disease states.

#### **CD300f: Targeting AML:**

CD300f has attracted interest as a therapeutic target in AML because it may support both direct tumor cell elimination and immunosuppressive remodeling of the tumor microenvironment. Antibody-drug conjugates directed against CD300f effectively kill AML cell lines and primary leukemia cells, act synergistically with fludarabine, and extend survival in the humanized mouse models [30]. Because these agents also deplete CD34+ hematopoietic stem cells, they may have additional utility in pre-transplant conditioning regimens. Beyond its value as a direct target, CD300f signaling in monocytes and macrophages upregulates PD-L1 expression and promotes M2 polarization, thereby suppressing T cell proliferation and further contributing to immune evasion [31].

#### **CD300g: Endothelial immunoregulation and tumor restraint:**

Among CD300 family members, CD300g is notable for its apparent tumor-suppressive properties, distinguishing it from most other members. CD300g is consistently downregulated in acute myeloid leukemia [32]. Machine-learning analyses have

identified CD300g as a candidate diagnostic marker in TNBC, particularly in combination with CIDEA, ASPM, and RGS1 [33], and prognostic models in diffuse large B-cell lymphoma have linked CD300g expression to overall survival [34]. CD300g may also contribute directly to antitumor immunity. In tumor-associated monocytes, it appears to promote the differentiation of CD8+ T cells toward a central memory-like phenotype through direct cell-cell contact, enhancing their long-term persistence and effector function [35]. This observation raises the possibility that CD300g could be leveraged in the context of adoptive T cell therapies. Taken together, CD300 family members influence tumor progression primarily by reshaping the immune microenvironment, particularly through effects on myeloid cells, NK cells, and T cell function, rather than through direct actions on tumor cells. These effects vary substantially across tumor types, cellular compartments, and disease stages, highlighting the need for context-specific interpretation when considering CD300 receptors as therapeutic targets.

### **Inflammation and Immune Homeostasis**

CD300 receptors maintain immune homeostasis by balancing activating and inhibitory signals across both myeloid and lymphoid cells. They modulate immune responses to prevent excessive inflammation while preserving effective host defense.

#### **CD300a: Anti-inflammatory control:**

CD300a generally restrains inflammation, reducing tissue damage and facilitating the return to homeostasis. During acute inflammation, it promotes resolution by enhancing the clearance of apoptotic cells. In gout models, CD300a deficiency results in persistent neutrophil infiltration, the elevated IL-1 $\beta$  production, and severe tissue injury, whereas CD300a activation accelerates neutrophil apoptosis and recovery [36]. Beyond acute inflammation, CD300a also suppresses neuroinflammatory and allergic responses. In central nervous system injury models, it reduces mast cell degranulation through the PPAR $\beta/\delta$ -CD300a-SHP1 pathway, thereby limiting inflammation and functional impairment [37]. In immediate hypersensitivity reactions, CD300a recognizes PS on mast cell membranes and suppresses degranulation locally [38]. In mucosal immunity, the PS-CD300a axis inhibits interferon- $\beta$  production in dendritic cells and supports immune tolerance by preventing excessive expansion of regulatory T cells [39]. However, the effects of CD300a are context-dependent and not uniformly beneficial. In myocardial and renal ischemia-reperfusion injury, CD300a deficiency improves clearance of apoptotic cells and reduces inflammatory damage [40]. Similarly, in ischemic stroke, CD300a worsens neuronal injury by inhibiting CD300b-DAP12 signaling and limiting phagocytic clearance [41]. Thus, although CD300a is often anti-inflammatory, its actions can become detrimental in specific disease contexts.

#### **CD300b: Inflammation and repair:**

CD300b plays a dual role in inflammatory disease by coupling early innate activation to subsequent tissue recovery. In acute sterile or inflammatory settings, CD300b promotes inflammatory signaling. It responds to lipopolysaccharide (LPS) and associates with Toll-like receptor 4 (TLR4), thereby enhancing MyD88-

and TRIF-dependent signaling through DAP12 while reducing interleukin-10 (IL-10) production, leading to robust release of pro-inflammatory cytokines [42]. Notably, CD300b remains stably expressed on the cell surface even under highly inflammatory conditions, unlike receptors such as MERTK and TIM-3, which are downregulated [43]. By recognizing phosphatidylserine and phosphatidylethanolamine (PE), it promotes clearance of apoptotic cells through PI3K-Akt signaling [44,45]. In addition, CD300b supports epithelial repair, as its deficiency delays regeneration in colitis models [19,46].

#### **CD300c: Immune regulation:**

CD300c primarily influences adaptive immune responses and myeloid cell behavior. Its soluble form inhibits activation, proliferation, and Th1/Th17 cytokine production in both CD4+ and CD8+ T cells with therapeutic potential in autoimmune disease models [47,48]. In myeloid cells, CD300c serves as a marker of myeloid-derived suppressor cells (MDSCs), by showing the increased expression and the enhanced suppressive activity with age [49]. CD300c also contributes to dendritic cell differentiation, particularly in the maturation of conventional dendritic cell type 2 (cDC2) subsets [50,51]. However, it functions as a co-stimulatory receptor and enhances immunoglobulin E (IgE)-mediated activation in basophils and mast cells, underscoring that CD300c function is strongly cell-type dependent.

#### **CD300e: Inflammation and tissue remodeling:**

CD300e regulates inflammation and tissue remodeling primarily through its effects on macrophages, with functions that vary across tissues and disease settings. In chronic inflammatory disease, CD300e can contribute to pathology. In IgA nephropathy, CD300e is highly expressed in M2 macrophages, where it supports the survival of profibrotic cells and thereby promotes glomerulosclerosis and interstitial fibrosis [52]. Conversely, CD300e may play a protective role during tissue repair. In the recovery phase of liver injury, CD300e-expressing macrophages promote NAD+ metabolism and hepatocyte proliferation through secretion of nicotinamide phosphoribosyltransferase (NAMPT), thereby supporting tissue regeneration [29]. Collectively, CD300e can adopt either pathogenic or reparative functions depending on tissue context and disease stage.

#### **CD300f: Dual roles in inflammation:**

CD300f exerts both anti-inflammatory and pro-inflammatory effects, with the outcome determined by ligand engagement and the responding cell type. In allergic inflammation, CD300f binds ceramide and delivers inhibitory signals that suppress IgE-mediated mast cell activation [53]. This regulatory axis may also be targeted by natural compounds. For example, quercetin suppresses mast cell degranulation through CD300f-SHP-1 signaling [54], while andrographolide derivatives inhibit MRGPRX2-driven pseudo-allergic responses by modulating SHP-1/SHP-2 pathways [55]. In inflammatory bowel disease, CD300f's role varies with disease stage. In acute colitis induced by dextran sulfate sodium (DSS), CD300f deficiency reduces inflammation [56]. In contrast, during chronic disease, CD300f-deficient dendritic cells produce increased tumor necrosis factor-alpha (TNF- $\alpha$ ) and interferon-gamma

(IFN- $\gamma$ ), leading to more severe pathology [57]. Consistent with its anti-inflammatory function, activation of CD300f by ceramide-containing liposomes suppresses ATP-driven inflammatory responses and alleviates colitis severity [58].

#### **CD300g: Metabolic inflammation:**

CD300g is expressed predominantly in vascular endothelial cells, where it regulates leukocyte trafficking and metabolic inflammation. During inflammation, CD300g controls immune cell adhesion and transendothelial migration, thereby shaping leukocyte recruitment into inflamed tissues and influencing local immune responses. CD300g may also contribute to metabolic homeostasis, consistent with emerging evidence linking it to systemic metabolic regulation [59]. In peripheral tissues, CD300g may link endothelial immune regulation to systemic metabolic balance. Collectively, the evidence presented in this section demonstrates that CD300 receptors are integral to inflammatory homeostasis rather than acting as uniformly pro- or anti-inflammatory molecules. Their primary impact lies in shaping the balance among inflammatory amplification, resolution, and tissue remodeling, with distinct receptors influencing outcomes such as repair, fibrosis, or chronic immune activation. This multifaceted regulatory capacity underscores the importance of understanding CD300 receptor function within specific disease and tissue contexts.

#### **Infectious Diseases**

In infectious disease, CD300 receptors shape host responses to viruses, bacteria, and parasites, thereby influencing pathogen clearance, immune evasion, and tissue injury. Their effects depend critically on both the pathogen type and the responding host cell. Some family members recognize the pathogen-derived or infection-associated signals and promote antimicrobial responses, whereas others are exploited by pathogens to suppress immunity and facilitate persistence.

#### **CD300a: Chronic infection:**

In infectious disease, CD300a is most commonly associated with immune suppression and pathogen persistence. Elevated expression dampens the activity of antigen-presenting cells and natural killer cells, thereby favoring chronic infection. This suppressive role is well illustrated in parasitic infection. In leishmaniasis, the parasite induces CD300a expression in antigen-presenting cells, which reduces their cytotoxic activity and shifts effector T cells toward an anti-inflammatory state. Blocking CD300a enhances the antiparasitic activity of macrophages and dendritic cells and promotes the differentiation of memory-like effector T cells, thereby accelerating pathogen clearance [60]. A similar pattern emerges in viral infection. In HIV-1 infection, CD300a is highly expressed in CD4+ memory T cells and correlates with susceptibility to infection, suggesting that it may mark or support viral reservoirs [61]. In natural killer cells, particularly the CD56-negative and CD56-bright subsets, CD300a inhibits CD16-mediated degranulation and cytokine release, thereby impairing antibody-dependent cellular cytotoxicity and contributing to natural killer cell exhaustion [62]. However, CD300a may also support effective immunity in specific settings. In chronic hepatitis B, CD300a-positive CD8+ T cells are enriched in patients who achieve functional

cure and display enhanced clonal expansion and antiviral activity. This population may therefore help predict responses to interferon therapy [63]. Collectively, the function of CD300a in infection is shaped by both pathogen type and host cell context.

#### **CD300b: Bacterial sensing:**

In bacterial infection, CD300b functions as a sensor linking microbial lipid signals to antibacterial effector programs. Its lipid-recognition capacity may enable CD300b to respond to bacterial extracellular vesicles and enhance phagocytosis as well as antigen processing, thereby connecting innate sensing with downstream adaptive immune responses [44,45]. Through this mechanism, CD300b may strengthen antibacterial defense at the host-pathogen interface. Nevertheless, excessive activation of this pathway may still contribute to tissue injury in severe infection [42].

#### **CD300c: Viral immune imbalance:**

Current evidence on CD300c in infectious disease has focused primarily on COVID-19, in which its expression varies with disease severity and immune status. In patients with COVID-19, CD300c expression on monocytes is reduced in moderate disease but increases again in severe disease. This pattern is accompanied by lower HLA-DR expression and correlates with clinical features such as oxygen requirement and thrombotic events [64]. These changes may reflect shifts in monocyte function during disease progression. Reduced CD300c expression may indicate monocyte dysfunction, whereas increased expression in severe disease may reflect abnormal activation or a compensatory response. CD300c therefore appears to be a useful marker of immune imbalance and may aid patient stratification and prognosis.

#### **CD300d: Host defense:**

CD300d contributes to host defense in bacterial infection by regulating neutrophil function and may also have diagnostic value. In sepsis and other bacterial infections, CD300d expression correlates with neutrophil phagocytic capacity. By activating Rac2 signaling and promoting cytoskeletal rearrangement, CD300d enhances the uptake and clearance of pathogens such as *Escherichia coli* and *Staphylococcus aureus*. Accordingly, CD300d activation reduces bacterial burden and attenuates inflammation in sepsis [65].

CD300d may also have diagnostic relevance beyond bacterial sepsis. In tuberculosis, it is significantly upregulated in multidrug-resistant and rifampicin-resistant disease and is co-expressed with TREML1 and FCGR family genes, consistent with an altered immune response to drug-resistant pathogens [66]. In viral infection, however, CD300d shows marked species specificity. Although it can mediate murine norovirus infection *in vitro*, receptor-blocking and organoid studies indicate that it does not serve as a functional receptor in humans [67,68]. Taken together, the studies reviewed here indicate that CD300 receptors do not function as uniform regulators of infection, but instead differentially shape pathogen sensing, leukocyte activation, and immune suppression across distinct infectious settings. This functional diversity is particularly evident in the contrast between receptors that enhance antimicrobial effector programs and those that are co-opted to support chronic infection or immune exhaustion. These observations position the

CD300 family as an important framework for understanding why protective immunity and immune dysregulation diverge during infection.

### **Immunometabolism and Tissue Degeneration**

Beyond their established roles in immunity, CD300 family members are increasingly recognized as regulators of metabolic and neurodegenerative processes. Emerging evidence indicates that these receptors connect immune cell function with metabolic signaling, tissue homeostasis, and neuroinflammation, extending their relevance well beyond classical inflammatory disease.

#### **CD300c: Metabolic dysfunction and kidney disease:**

Emerging evidence links CD300c to chronic kidney disease associated with metabolic dysfunction. In combined observational and Mendelian randomization analyses, CD300c was identified as a novel risk-associated protein for chronic kidney disease in individuals with metabolic abnormalities, suggesting that it may participate in the connection between metabolic dysregulation and renal injury [69]. The mechanisms responsible for this association, however, remain to be clarified.

#### **CD300f: Brain metabolism and neural injury:**

CD300f plays a key role in neuroimmune homeostasis, primarily through its effects on microglia—the resident immune cells of the brain. Loss of CD300f is associated with reduced cerebral glucose uptake, cognitive decline, accelerated microglial aging, and impaired protein quality control, collectively pointing to a role in sustaining neural and metabolic homeostasis [70]. CD300f is also required for effective microglial responses to brain injury. Its absence disrupts the detection of injury signals and the clearance of dying cells, resulting in the accumulation of cellular debris, defective intracellular degradation, and altered signaling through purinergic receptors. Although initial tissue damage may appear less pronounced, long-term recovery is significantly impaired, underscoring the importance of CD300f in neural repair [71]. Together, these findings position CD300f as a coordinator of brain metabolism, microglial activity, and tissue restoration.

#### **CD300g: Metabolism and neurodegeneration:**

CD300g appears to integrate systemic metabolic status with neurodegenerative processes. Large-scale cohort analyses show positive associations with physical activity and inverse associations with fasting glucose, post-load glucose, and glycated hemoglobin. Mendelian randomization analyses support a potential causal contribution of CD300g to glucose homeostasis, consistent with the impaired glucose tolerance observed in CD300g-deficient mice [59]. At the systemic level, CD300g has been linked to chronic kidney disease in individuals with metabolic dysfunction [72]. In addition, genetic analyses have associated CD300g polymorphisms with the age at onset of Alzheimer's disease, suggesting that CD300g may also influence neurodegenerative progression [73]. However, its precise functions in these tissues remain unclear. Taken together, current evidence places the CD300 family within a broader disease network that extends beyond classical immunity to encompass metabolic regulation, renal injury, and neurodegeneration. CD300c and CD300g may link metabolic dysfunction to chronic kidney

disease, while CD300f appears central to brain metabolism, microglial homeostasis, and neural repair. Although the underlying mechanisms are not yet fully resolved, these findings identify the CD300 family as a potential nexus between immunometabolic imbalance and neurodegenerative disease, warranting further investigation into their tissue-specific functions and therapeutic potential.

## Therapeutic Targeting of CD300 Receptors

Therapeutic approaches targeting CD300 receptors fall into three main groups: antibody-based therapies, gene-silencing methods, and indirect regulation of downstream signaling. Because each CD300 family member has a distinct role in immune responses and disease, most therapeutic efforts have focused on individual receptors (Table 2).

**Table 2:** Summary of disease associations and targeted therapeutic strategies of CD300 family members.

Receptor	Disease Associations (as discussed in main text)	Targeted Therapeutics
CD300a	Acute myeloid leukemia	TNAX103
	Solid tumors	
	Gout	
	Central nervous system injury	
	Immediate hypersensitivity	
	Mucosal immune tolerance abnormality	
	Myocardial ischemia-reperfusion injury	
	Renal ischemia-reperfusion injury	
	Ischemic stroke	
	Leishmaniasis	
	HIV-1 infection	
	Chronic hepatitis B	
	CD300b	Acute infectious diseases
Colitis		
Renal ischemia-reperfusion injury		
CD300c	Allergic inflammation	CL7
	Rheumatoid arthritis	CB201
	Graft-versus-host disease	
	Triple-negative breast cancer	
	Glioma	
CD300d	Immunosenescence	
	Norovirus infection	CD300d-ECD-hFc fusion protein
	Bacterial infections	Recombinant CD300d extracellular domain protein
	Drug-resistant tuberculosis	PGH@siRNA
	Tumor immune suppression	
CD300e	Cancer vaccine resistance	
	Kidney fibrosis	No receptor-specific targeted therapy reported yet
	Helicobacter pylori infection	
	Liver regeneration in cirrhosis	
	Solid tumors	
CD300f	Obesity-associated insulin resistance	
	Acute myeloid leukemia	Anti-CD300f antibody-drug conjugate
	Allergic inflammation	
	Pseudo-allergic responses	
	Inflammatory bowel disease	
	Acute colitis	
	Chronic colitis	
	Brain metabolic dysfunction	
	Neural injury	

CD300g	Triple-negative breast cancer	No receptor-specific targeted therapy reported yet
	Diffuse large B-cell lymphoma	
	Metabolic inflammation	
	Metabolic dysfunction-associated chronic kidney disease	
	Alzheimer's disease	

Among these receptors, CD300a has been studied mainly in acute neural injury. Blocking CD300a has shown protective effects in preclinical models, including better clearance of dying cells, less neuronal loss, and improved recovery. In models of ischemic stroke, the humanized monoclonal antibody TNAX103 improved neurological outcomes and survival, suggesting that CD300a may be a useful target for neuroprotection [74,75].

CD300c has emerged as a potential target in both cancer and neurodegenerative disease. In cancer models, the agonistic anti-CD300c monoclonal antibody CL7 drives macrophages toward a pro-inflammatory, tumor-fighting state. In preclinical models of triple-negative breast cancer and non-small cell lung cancer, CL7 reduced tumor growth and increased the presence of inflammatory macrophages and cytotoxic CD8<sup>+</sup> T cells [76]. Its effects were stronger when combined with PD-1 blockade, suggesting that CD300c-targeted therapy may improve the response to immune checkpoint inhibitors [77,78]. Outside cancer, the anti-CD300c antibody CB201 has shown promise in Alzheimer's disease models by promoting a phagocytic macrophage state, reducing amyloid- $\beta$  buildup, and improving cognitive performance [79].

CD300d-targeted strategies have been developed to counter the immunosuppressive tumor microenvironment driven by PMN-MDSCs. One approach focuses on receptor blockade. A CD300d-ECD-hFc fusion protein suppresses tumor growth and enhances the efficacy of anti-PD-1 therapy in preclinical models [26]. In line with this, the limited efficacy of STING-activating nanovaccines in advanced tumors has been linked to increased activity of the same pathway. Blocking this pathway with a recombinant CD300d extracellular domain protein reverses PMN-MDSC-mediated immunosuppression, restores CD8<sup>+</sup> T cell function, and improves vaccine responses in advanced tumor models [80]. The second is selective gene silencing. An ultrasound-responsive nanocomposite, PGH@siRNA, was designed to deliver CD300d-targeting siRNA locally. When combined with sonodynamic therapy, this system triggered immunogenic cell death, reduced PMN-MDSC infiltration, and reshaped the tumor environment, leading to stronger antitumor effects [81].

In contrast, therapeutic work on CD300f has focused largely on hematologic cancers. In AML, antibody-drug conjugates targeting CD300f showed efficient internalization and selective killing of AML cells as well as hematopoietic stem and progenitor cells. Preclinical studies also reported improved survival, with greater benefit when these agents were combined with fludarabine [30,82].

CD300b and CD300e remain less well developed as therapeutic targets. For CD300e, current strategies are mostly indirect rather than receptor-specific. Glucocorticoids can increase CD300e

expression, whereas imidazoline-based immunosuppressive agents inhibit this pathway and slow the progression of kidney disease [52]. Inhibition of the downstream PI3K-Akt pathway with Wortmannin has also been explored. However, these approaches are not specific to CD300e and may affect multiple pathways, raising concerns about off-target effects and toxicity.

Overall, different CD300 receptors appear to have distinct therapeutic roles in preclinical studies: CD300a in neuroprotection, CD300c and CD300d in cancer immunotherapy and immune remodeling, and CD300f in hematologic malignancies. Future work should focus on developing receptor-specific strategies with better selectivity, more precise delivery, and improved safety.

## Conclusions

The CD300 receptor family comprises a group of lipid-sensing immune regulators that translate signals of cellular stress into diverse immune and disease responses. Rather than functioning uniformly, individual CD300 receptors influence distinct areas of pathology, including tumor-associated immune suppression, the resolution or persistence of inflammation, host-pathogen interactions, and immunometabolic and neurodegenerative diseases.

Although evidence for these roles continues to accumulate, several critical gaps remain. For some receptors, particularly CD300d and CD300h, the endogenous ligands and receptor-specific signaling pathways remain poorly characterized. Moreover, the same receptor can exert different effects depending on tissue context and disease stage, complicating the interpretation of its biological and therapeutic significance.

Future research should prioritize three key objectives: clarifying ligand specificity, elucidating signaling mechanisms in specific cell types, and determining how receptor function evolves during disease progression. These advances will be essential for translating knowledge of CD300 receptors into clinical biomarkers or targeted therapeutic interventions.

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## Conflict of Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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