Mast Cells Sensing Environmental Signals: Regulation of Responses via CD300

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The CD300 family of immunoreceptors is emerging as an important regulator of allergic inflammation through recognition of lipid ligands and damage-associated molecular patterns. By sensing phosphatidylserine, phosphatidylethanolamine, ceramide, and sphingomyelin exposed during cellular activation, stress, or death, these paired activating and inhibitory receptors fine-tune both IgE-dependent and IgE-independent mast cell responses and function as a molecular rheostat that limits excessive inflammation while preserving host defense. At the same time, mast cells are no longer viewed merely as terminal effector cells of allergy, but as versatile immune sentinels that integrate diverse environmental cues through a complex receptor network. Positioned at tissue-environment interfaces, they interpret local danger and homeostatic signals and shape immune responses through selective release of preformed and newly synthesized mediators. In this review, we discuss recent advances in CD300 biology and their implications for mast cell immunoregulation. We further highlight the emerging view that mast cells extend far beyond their classical role as allergy effector cells and instead serve as central orchestrators of tissue immune responses.

キーワード CD300, mast cells, ITIM

Introduction

Allergic diseases are an increasing global health burden[1)], driven by dysregulated immune responses to otherwise harmless environmental antigens. Mast cells (MCs), strategically located at barrier sites such as the skin, mucosa, and intestine, have long been viewed primarily as effector cells of allergy because they rapidly degranulate when allergens crosslink antigen-specific IgE bound to the high-affinity IgE receptor Fc ε RI. This classical view has expanded considerably over the past decade. MCs are now increasingly recognized as multifunctional immune cells that not only initiate allergic reactions but also contribute to immune regulation and tissue homeostasis. In parallel, the discovery that CD300 family members recognize lipid ligands has provided a new framework for understanding how the immune system senses cellular stress and damage to modulate allergic inflammation[2) 3)]. Together, these advances place MCs within a broader regulatory network that integrates environmental, metabolic,

and danger-associated cues to shape immune responses[4) 5)].

1 The CD300 family: structure and function

The CD300 family comprises activating and inhibitory immunoreceptors expressed predominantly on myeloid cells, including monocytes and macrophages[2)]. In humans, seven members have been identified, whereas nine structurally related proteins are present in mice. CD300 receptors are type I transmembrane glycoproteins with immunoglobulin-like extracellular domains that recognize lipid ligands. Inhibitory family members contain immunoreceptor tyrosine-based inhibitory motifs (ITIMs) in their cytoplasmic tails and recruit phosphatases such as SHP-1 and SHP-2 to suppress activation[2) 6)]. Activating receptors lack intrinsic signaling motifs and instead couple to adaptor proteins such as Fc ε RI γ or DAP12, whose immunoreceptor tyrosine-based activation motifs (ITAMs) propagate activating signals through kinases including Syk[7)].

2 Evolutionary insights into CD300 receptors

Comparative analyses across 33 primate species highlight the distinct biological importance of inhibitory and activating CD300 receptors[8)]. CD300a is highly conserved across all species, with preserved functional motifs, supporting an essential role in immune regulation[9)]. In contrast, CD300c shows a dynamic evolutionary pattern, including pseudogenization, functional impairment, and loss in certain lineages such as Hylobatidae and Lemur catta[8)]. This divergence indicates stronger evolutionary pressure to maintain inhibitory CD300 signaling. Notably, gene conversion has preserved extracellular domain similarity, allowing shared ligand recognition despite opposing signaling functions [8)].

3 Lipid ligand recognition by CD300 molecules

A defining feature of CD300 receptors is their ability to recognize lipids exposed on the outer leaflet of the plasma membrane during cellular activation, stress, apoptosis, or necrosis[2) 3)]. This positions them as sensors of damage-associated molecular patterns that convert altered membrane composition into immunoregulatory signals. binds In MC biology, several CD300 family members are particularly relevant. CD300a, an inhibitory receptor, phosphatidylserine (PS) and phosphatidylethanolamine (PE), aminophospholipids that are normally restricted to the inner leaflet but become externalized during apoptosis and activation[3)]. CD300f, another inhibitory receptor, recognizes extracellular ceramide, a bioactive lipid enriched in stressed or damaged tissues, and can also bind PS. This dual recognition of ceramide and PS generates a stronger inhibition than PS alone[10) 11)]. In contrast, the murine activating receptor CD300d3, which couples to Fc ε RI γ , binds specific sphingomyelin (SM) species and promotes MC cell activation[12)]. Different SM species show distinct receptor preferences: type I SM preferentially binds CD300d3 over CD300f and favors activation, whereas type II SM binds both receptors and shifts the balance toward inhibition. CD300c also recognizes PE, albeit with lower affinity than CD300a[7)], and when both receptors are co-expressed, CD300a predominates in ligand recognition and downstream signaling[8)].

4 CD300 regulation of IgE-dependent and IgE-independent allergic responses

Fc ε RI is the principal trigger of MC cell degranu-

lation in allergic disease, but its activity is tightly, and likely context-dependently, modulated by CD300 receptors. Among inhibitory members, CD300a suppresses IgE-mediated activation through binding to phosphatidylserine (PS) and phosphatidylethanolamine (PE)[6) 13)~15)] and can colocalize with Fc ε RI, resulting in enhanced inhibitory signaling. In human mast cells, CD300a crosslinking inhibits degranulation and cytokine production via ITIM-dependent phosphatase recruitment and termination of calcium influx, whereas its neutralization in vivo augments inflammatory mediator release and eosinophil infiltration[6)]. CD300f exerts a similarly potent inhibitory function through recognition of extracellular ceramide[10)]. Following Fc ε RI engagement, CD300f colocalizes with ceramide and recruits phosphatases that attenuate proximal signaling, suppress calcium mobilization, and limit degranulation[10)]. Consistently, Cd300f deficiency exacerbates multiple models of allergic inflammation, suggesting that ceramide-rich tissue environments provide a constitutive inhibitory checkpoint. Cooperative inhibition by CD300a and CD300lf further underscores non-redundant regulatory functions, as double-deficient mice display enhanced anaphylaxis[11)]. In contrast, activating CD300 receptors amplify allergic responses. CD300d3 binds type I sphingomyelin, promotes colocalization with Fc ε RI, and enhances IgE-dependent degranulation and anaphylaxis, although it is not sufficient to trigger activation alone[12)]. Accordingly, Cd300d3 deficiency attenuates anaphylactic responses[12)]. Collectively, these findings define a lipid-dependent regulatory axis in which activating CD300d3–sphingomyelin signaling is counterbalanced by inhibitory CD300f–ceramide interactions, although the relative dominance of these pathways likely varies across tissue contexts.. Importantly, CD300-mediated regulation extends beyond classical IgE pathways. CD300 receptors modulate IgE-independent MC cell activation induced by complement, cytokines, neuropeptides, and pattern-recognition receptors[4)]. In this context, CD300f also negatively regulates MRGPRX2-driven pseudo-allergic responses[16) 17)]. Knockdown of CD300f enhances MRGPRX2-mediated degranulation and cytokine release, whereas ligands such as myricetin and dehydroandrographolide suppress signaling via SHP-1/2 activation and downstream inhibition of PLC γ1, AKT, p38, and ERK1/2[16)17)]. These effects translate in vivo into reduced vascular leakage and cytokine production. Beyond activation control, CD300a contributes to resolution of inflammation by regulating ALX/FPR2 expression[15)]. Conversely, CD300c acts as a costimulatory receptor, enhancing Fc ε RI-mediated responses and correlating with disease severity in allergic patients[18)]. Collectively, CD300 receptors integrate lipid signals from the tissue microenvironment to fine tune MC cell activation across diverse inflammatory contexts (Figure 1).

5 Therapeutic targeting of CD300-lipid interactions

The CD300-lipid axis represents an attractive therapeutic target, as it offers the possibility of modulating MC activity through endogenous inhibitory pathways, rather than broad immunosuppression. Intranasal administration of ceramide liposomes suppressed allergic rhinitis in a murine model by targeting CD300f[19)], reducing sneezing, MC cell degranulation, and eosinophil infiltration in nasal tissues. This effect depends on CD300f expression, particularly on MCs, as cell-specific deletion of CD300f abolished the therapeutic benefit. Conversely, disruption of the ceramide-CD300f interaction underscores its physiological importance. Pretreatment with antibodies against ceramide or CD300f, as well as CD300f-Fc fusion proteins that sequester extracellular ceramide, exacerbated allergic responses and passive cutaneous anaphylaxis[10)]. Together, these

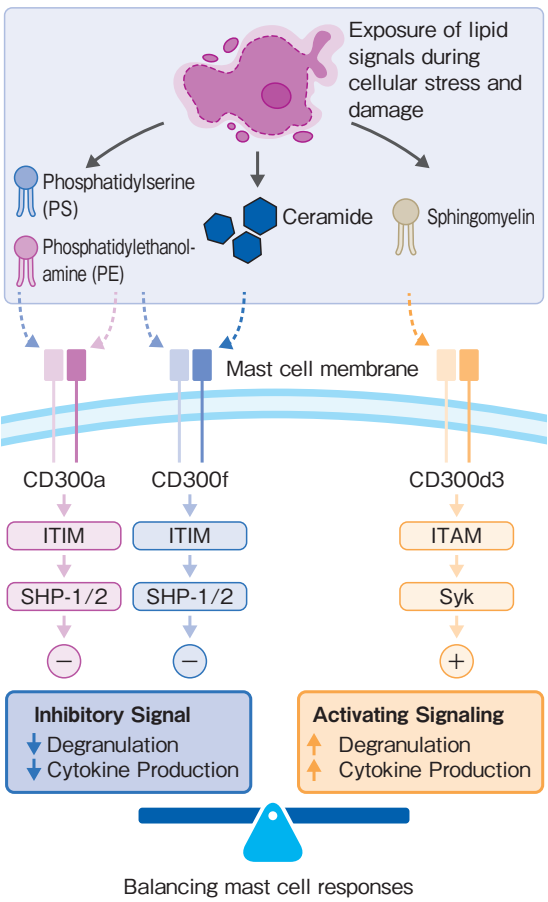

Figure 1. Regulation of mast cell activation by CD300 receptors

CD300a and CD300f recognize lipid signals exposed during cellular stress or damage, including phosphatidylserine (PS), phosphatidylethanolamine (PE), and ceramide, and suppress mast cell degranulation and cytokine production through ITIM–SHP-1/2 signaling. In contrast, CD300d3 promotes mast cell activation through sphingomyelin recognition and subsequent activation of the ITAM–Syk signaling pathway.

findings identify constitutive CD300f mediated inhibitory signaling as an endogenous brake on allergic inflammation and support therapeutic targeting of lipid–receptor interactions as a promising strategy for allergic disease.

6 Mast cells as regulatory hubs: beyond effector functions

① Strategic positioning and sentinel function

MCs are strategically positioned at tissue–environment interfaces, including the skin, airways, and gastrointestinal mucosa, as well as around blood vessels and nerves, where they continuously monitor the local milieu for allergens, pathogens, alarmins, metabolic stress, and tissue damage[4) 5) 20) 21)]. This anatomical positioning, together with their broad receptor repertoire, places MCs among the earliest responders to environmental change. Rather than functioning solely as terminal effector cells of IgE–mediated allergy, MCs are now recognized as versatile cells that integrate immunological, neural, vascular, and tissue–derived signals. These inputs are translated into highly context–dependent responses[4) 5) 20) 22)~24)]. Their perivascular localization is particularly important, as it enables rapid communication with the circulation and efficient initiation of leukocyte recruitment[20)].

② Orchestration of immune cell recruitment and activation

A central feature of MC biology is the ability to shape broader immune responses through selective mediator release. Depending on the stimulus, MCs can rapidly release preformed mediators, generate lipid mediators, and produce cytokines and chemokines that recruit and activate other leukocytes[21) 24) 25)]. In this way, they function as "first responders" that initiate a MC–leukocyte cytokine cascade[5) 23) 24) 26)]. MC–derived cytokines, chemokines, and lipid mediators promote the recruitment of neutrophils, eosinophils, monocytes/macrophages, dendritic cells, and lymphocytes, thereby amplifying and sustaining inflammation. Importantly, these interactions are not unidirectional. MCs engage in bidirectional crosstalk with eosinophils and T cells, two

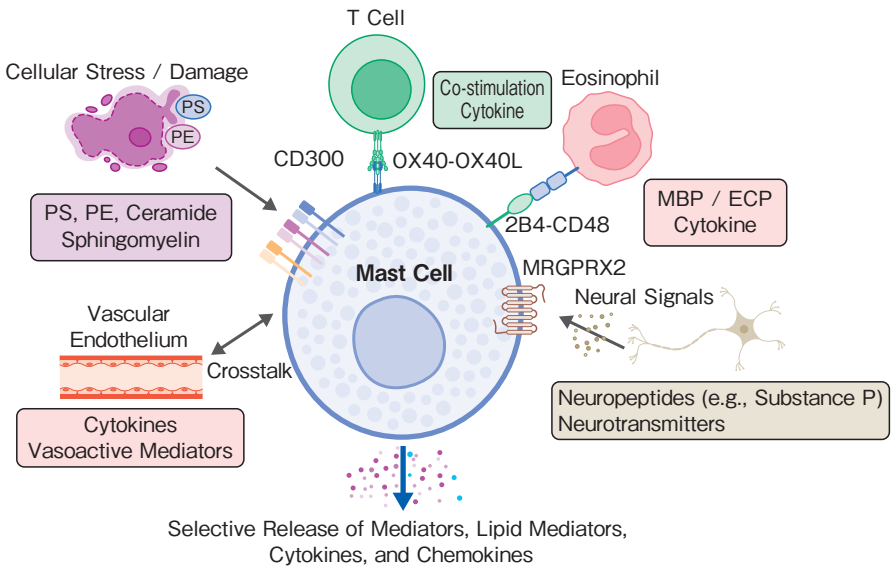

Figure 2. Mast cells as multifunctional regulatory hubs

Mast cells integrate signals derived from tissue damage, the nervous system, immune cells, and vascular endothelial cells. Lipid recognition through CD300 receptors, neuroimmune signaling via MRGPRX2, OX40–OX40L interactions with T cells, and 2B4–CD48-mediated crosstalk with eosinophils contribute to the selective release of mediators, lipid mediators, cytokines, and chemokines.

pathways of particular relevance in chronic inflammatory disease. MC–eosinophil interactions promote reciprocal activation and feed-forward inflammation, with clinical relevance in chronic spontaneous urticaria[26]. Likewise, MC–T cell interactions extend beyond soluble mediator exchange and may include antigen presentation, induction of pro-inflammatory MC programs, and participation in IL-17 driven skin inflammation (Figure 2)[27)~33)].

7 Conceptual advances and future directions

Recent work has fundamentally revised the MC field. MCs are no longer viewed simply as IgE triggered histamine-releasing cells, but as multifunctional regulatory hubs with marked plasticity. This broader concept is reinforced by the integration of lipid-sensing pathways such as CD300 receptors, which allow MCs to detect tissue damage and calibrate activation thresholds in concert with classical immune receptors. MCs therefore, act as immune orchestrators that couple local tissue status to multicellular inflammatory programs. Future research should identify how tissue microenvironments shape MC phenotype and function, clarify how CD300 and other regulatory pathways are integrated at the molecular level, and determine whether these pathways can serve as biomarkers or therapeutic targets. A major challenge will be to selectively suppress pathological MC-driven inflammation while preserving protective roles in host defense, tissue repair, and immune homeostasis.

Conclusion

The recognition of CD300 receptors as lipid-sensing regulators and of MCs as multifunctional

immune hubs has substantially advanced our understanding of allergic inflammation. Beyond their classical role as effector cells of IgE-mediated reactions, MCs are now understood as highly adaptable sentinel cells that integrate environmental, epithelial, neural, and immunologic signals within tissues. Through selective release of preformed mediators, lipid mediators, cytokines, and chemokines, they not only initiate immediate responses but also orchestrate the recruitment, activation, and functional polarization of other immune cells. In this way, MCs shape multicellular inflammatory networks through dynamic crosstalk with eosinophils, T cells, and other tissue-resident or recruited cells. CD300 receptors add an important regulatory layer to this process by linking tissue lipid composition and cellular stress signals to MC activation thresholds. Together, these advances reposition MCs as central coordinators of immune responses and highlight emerging therapeutic opportunities aimed at modulating their regulatory functions rather than simply blocking effector activity.

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profile

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