*Update review*

# Inhibitory receptors on eosinophils: A direct hit to a possible Achilles heel?

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**Since their discovery, much data have been accumulated on eosinophil differentiation, morphology, trafficking, and anatomical location(s) in health and disease. Although "classic" activation pathways (such as cytokines, chemokines, proinflammatory components, and adhesion molecules) regulating eosinophil activation have been widely explored, the presence of other activation molecules that might be disease specific is limited. Furthermore, the expression and function of inhibitory receptors on eosinophils have received scant attention. The need to identify new pathways that regulate eosinophil activation is a crucial goal as it can expand our knowledge on this peculiar cell and provide insights into important queries regarding the physiologic function of eosinophils. Over the past several years, it has become increasingly apparent that eosinophils express several receptors belonging to the immunoglobulin superfamily. In this review, we summarize the current knowledge on the expression and function of new pathways that govern eosinophil activation. In addition, we will propose some hypotheses regarding the ability to use these pathways as a future therapeutic approach. In conclusion, we assume that targeting inhibitory receptors on eosinophils may provide opportunities for immunoregulatory therapy in the near future. (J Allergy Clin Immunol 2007;119:1382-7.)**

***Key words:*** *Eosinophil, inhibitory receptors, IRp60/CD300a, ITIM*

*Abbreviations used*

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| IRp60: | Inhibitory receptor protein 60 (CD300a) |
| ITAM: | Immunoreceptor tyrosine-based activatory motif |
| ITIM: | Immunoreceptor tyrosine-based inhibitory motif |
| ITSM: | Immunoreceptor tyrosine-based switch motif |
| NK: | Natural killer |
| SH2: | Src homology domain 2 |
| SHIP: | Src homology domain 2–containing inositol phosphatase |
| SHP: | Src homology domain 2–containing protein tyrosine phosphatase |
| Siglec-8: | Sialic acid-binding Ig-like lectin-8 |

Achilles, the son of Thetis and Peleus, was the bravest hero in the Trojan War, according to Greek mythology. In an attempt to make Achilles immortal, his mother dipped him in the river Styx when he was born. As she immersed him, she held him by 1 heel and forgot to dip him a second time. Therefore, the place where she held him remained untouched by the magic water and that part stayed vulnerable. Many attempts have been made to identify an Achilles heel for eosinophils that may be used for targeting these cells in various diseases. In this review, we will summarize the current knowledge on the expression and function of inhibitory receptors on these cells and highlight their potential role as future targets for therapeutic agents.

## INHIBITORY RECEPTORS—HISTORICAL VIEW

Over the past several years it has become increasingly apparent that inhibitory receptors constitute a major self-regulatory pathway in which activation signals can be counterbalanced and tuned.[1] Certainly, gene-targeted mice with loss of inhibitory receptors display marked autoreactivity and/or inflammation,[2,3] which thus highlights a fundamental role for these pathways in immune regulation. Early studies, primarily on natural killer (NK) cells, indicated that inhibitory receptors mainly recognize MHC class I molecules. This recognition could explain the tolerance to normal cells expressing MHC class I molecules and the execution of transformed or virally infected cells that either lose MHC class I expression or express "non-self" MHC class molecules.[4]

However, substantial evidence now exists that inhibitory receptors can recognize diverse ligands other than MHC class I molecules.[4] Although these observations can

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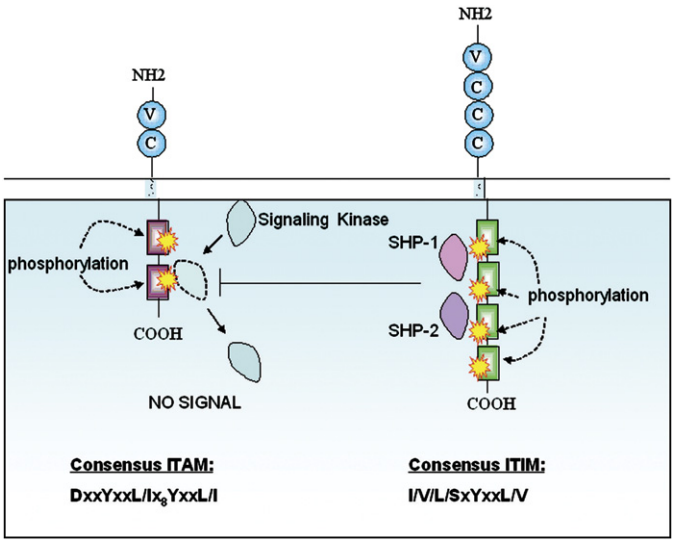


**FIG 1.** The paradigm of ITIM-ITAM interaction. On cell activation, the ITAM undergoes tyrosine phosphorylation and recruits a signaling kinase. When an inhibitory signal starts, the ITIM undergoes tyrosine phosphorylation and recruits cellular phosphatases such as SHP-1 and/or SHP-2. These phosphatases dephosphorylate the ITAM and suppress consequent cellular activation.

explain how NK cell tolerance is maintained in MHC class I–deficient individuals, they also highlight the ability of these receptors to regulate the functions of other cell types and in settings that are not confined to viral infections and cancer.

## INHIBITORY RECEPTORS—STRUCTURE AND MECHANISM

Inhibitory receptors can be broadly divided into 2 groups, belonging either to the immunoglobulin receptor superfamily, characterized by a single V-type Ig-like domain in the extracellular portion such as killer cell immunoglobulin-like receptors, leukocyte Ig-like receptors (LIRs)/Ig-like transcripts (ILTs), leukocyte-associated Ig-like receptors, gp49B1, inhibitory receptor protein 60 (CD300a) (IRp60)/CD300a and sialic acid-binding Ig-like lectins (Siglec-8s), or to the C-type (calcium-dependent) lectin superfamily, such as mast cell function–associated antigen or CD94/NKG2A.[5] The prototype immune inhibitory receptor can be identified by a consensus amino acid sequence, the immunoreceptor tyrosine-based inhibitory motif (ITIM), which is present in the cytoplasmic domain of these molecules. The ITIM sequence is composed of 6 amino acids (Ile/Val/Leu/Ser)-X-Tyr-X-X-(Leu/Val), where X represents any amino acid.[1,5] Importantly, inhibitory receptors can express either 1 or several ITIM domains.

Upon activation, these inhibitory receptors undergo tyrosine phosphorylation, often by a Src family kinase, which provides a docking site for the recruitment of cytoplasmic phosphatases having a Src homology 2 (SH2) domain such as SH2-containing inositol phosphatase (SHP)-1 and SHP-2 and SH2-containing protein tyrosine phosphatase (SHIP)-1 and SHIP-2.[1,5]

Conversely, recent reports suggest that intracellular motifs other than ITIMs such as immunoreceptor tyrosine-based switch motifs (ITSMs) or NPXY motifs can also initiate cellular inhibition by binding cytoplasmic phosphatases as well.[6,7] However, as this will be discussed, the exact mechanism of ITSM-dependent inhibition in eosinophil is yet to be clarified.

It is important to note that the classic dichotomy differentiating between inhibitory signals delivered by a phosphorylated ITIM as opposed to the activation signals mediated by immunoreceptor tyrosine-based activatory motifs (ITAMs) has been recently suggested to be much more complex and ambiguous.[8] For instance, in certain circumstances, ITIMs can mediate activation and ITAMs can propagate inhibition signals.[9,10] However, as this topic is a fresh avenue in eosinophil biology, we will use in this review the established paradigm (Fig 1) of ITIM-ITAM interactions.[1]

## EXPRESSION AND FUNCTION OF INHIBITORY RECEPTORS ON EOSINOPHILS

Although much data have accumulated on pathways regulating eosinophil activation,[11] the expression and function of inhibitory receptors on eosinophils have received scant attention. As illustrated in Fig 2, eosinophils were shown to express the inhibitory receptors FcγRIIB, ILT5/LIR3, CD33, p75/adhesion inhibitory receptor molecule, Siglec-8, Siglec-10, p140, and IRp60/CD300a.[12-14] Activation of human eosinophils by Siglec-8 inhibits their survival by inducing apoptosis and initiating mitochondrial injury, reactive oxygen species generation and rapid cleavage of caspase-3, -8, and -9.[15] Interestingly, Siglec-8 was capable of inducing eosinophil apoptosis even in

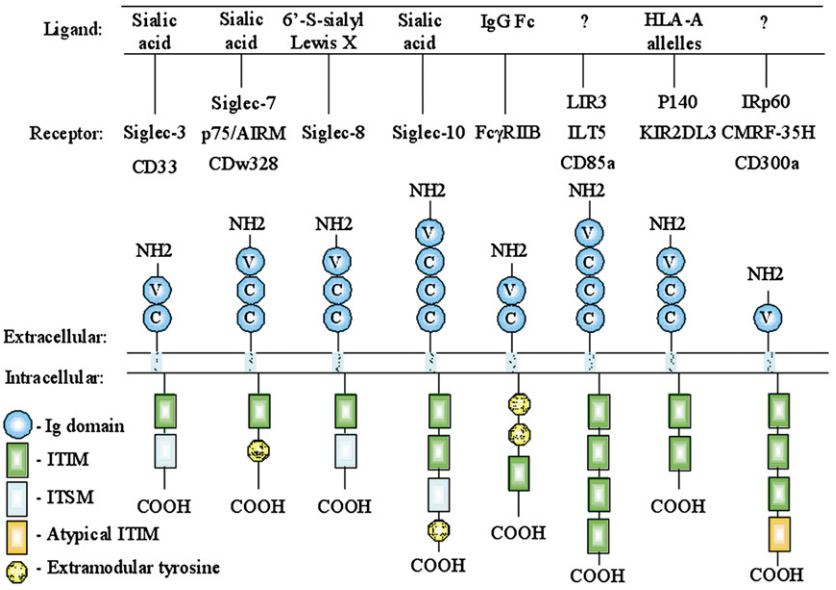


**FIG 2.** Expression of immune inhibitory receptors on human eosinophils. This is a schematic representation of the structure and identified ligands of the inhibitory receptors that are expressed by human eosinophils.

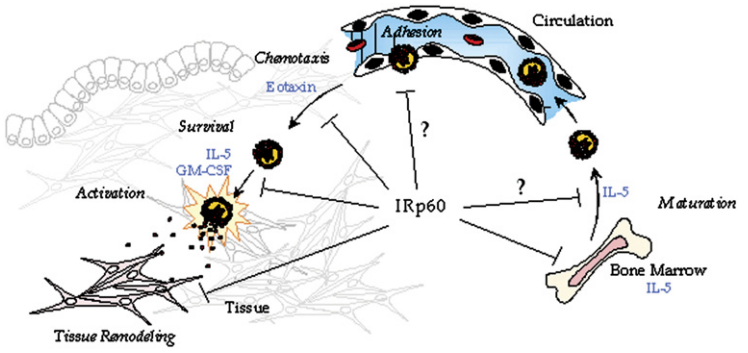


**FIG 3.** CD300a/IRp60 regulates critical eosinophil checkpoints. This is a schematic representation of the known inhibitory functions of CD300a/IRp60. CD300a/IRp60 can inhibit eosinophil chemotaxis, survival, and mediator release.

the presence of IL-5, IL-3, and granulocyte-macrophage colony-stimulating factor (GM-CSF), the hallmark "eosinophil survival cytokines."[16] In addition, Bochner et al[17] undertook an elegant screening approach using a glycan array identifying 6'-sulfo-sLEX, which is a unique sugar structure that is a potential ligand for Siglec-8. Yet, the biological relevance of these findings has yet to be determined.

Recent data indicate that engagement of p75/AIRM or CD33 can inhibit proliferation and/or differentiation of CD34+ myeloid precursors induced by stem cell factor and GM-CSF.[18,19] Interestingly, CD33 seems to act via the induction of apoptosis similar to Siglec-8, whereas p75/AIRM blocks cell proliferation without induction of apoptosis.[19] Importantly, we have recently established that eosinophils express p75/AIRM.[12] Thus, p75/AIRM may regulate eosinophil differentiation as well. Nevertheless, the function of this receptor on eosinophils is yet unknown.

In addition, although CD33 and p75/AIRM could inhibit proliferation of myeloid cell precursors, CD300a/IRp60, an additional inhibitory receptor, could not suppress this feature, which suggests distinct functions for various inhibitory receptors.[18]

Recently we demonstrated that CD300a/IRp60 can also inhibit eosinophil survival.[12] In contrast to Siglec-8, which induces eosinophil apoptosis, IRp60/CD300a inhibits survival signals delivered to eosinophils via the IL-3/IL-5/GM-CSF receptor βc.[12] Cross-linking experiments have revealed that upon IRp60/CD300a activation, JAK2, p38, and extracellular signal-regulated kinase 1/2 phosphorylation are inhibited, probably from the recruitment of SHP-1 and not SHP-2. Furthermore, IRp60/CD300a activation could inhibit eosinophil chemotaxis (in response to eotaxin and $LTB_4$) and activation (in response to IL-5 and GM-CSF). Nevertheless, although

IRp60/CD300a regulates several eosinophil checkpoints (Fig 3), its role(s) in eosinophil maturation, adhesion, and eosinophil-related diseases is yet to be determined. Interestingly, IRp60/CD300a and Siglec-8 share a unique property regarding eosinophil inhibition. It seems that the presence of eosinophil survival cytokines prime the responses elicited by these 2 inhibitory receptors. Therefore, activation of Siglec-8 in the presence of these factors ablates the requirement for an additional cross-linking antibody. In addition, the ability of IRp60/CD300a to inhibit eosinophil survival was enhanced upon increasing concentrations of IL-5 and GM-CSF. These findings are important becausee they highlight a potential cross-talk between eosinophil activation pathways and inhibitory ones, which may be further exploited therapeutically.

The different outcome of Siglec-8 activation (induction of apoptosis) as opposed to IRp60/CD300 activation (inhibition of survival signals) may be partially explained by the fact that Siglec-8 contains both ITIM and ITSM motifs. ITSM motifs may recruit either inhibitory phosphatases such as SHP-1 and/or SHP-2 or activatory molecules such as slam-associated protein (SAP) and/or 2-Ewing's sarcoma-FLI activated transcript 2 (EAT-2).[4,6] Therefore, the interaction between these intracellular components may tune the outcome of Siglec-8 activation on human eosinophils directing it toward apoptosis. Alternatively, ITSM motifs may not be functional in eosinophils, but it is not likely becausee eosinophils express several receptors belonging to the SLAM-subfamily that have been described to recruit SAP and/or EAT-2[20] (Fig 4).

Interestingly, a novel role for monokine induced by IFN-γ (or CXCL9) (Mig) in inhibition of murine eosinophil recruitment was recently demonstrated.[21] In their study, Fulkerson et al[22] reported that the binding of Mig to CCR3, which is a hallmark eosinophil chemokine receptor, activates an inhibitory cascade (yet to be defined). Although this study was not conducted on a classic ITIM-bearing receptor, it suggests that different chemokines and perhaps other agonists can use CCR3 to inhibit eosinophil functions. Mechanistically, these findings could imply that a substantial cross-talk occurs between inhibitory receptors and ''eosinophil-specific'' cytokine receptors such as CCR3. Supporting such an hypothesis are the findings that abnormal chemotactic responses to stromal cell-derived factor 1 were observed in SHP-1–deficient mice (viable motheaten mice).[23] Furthermore, the inhibitory receptor paired immunoglobulin-like receptor B has been shown to regulate neutrophil chemotaxis in a Hck-Fgr–dependent fashion, which indicates a functional link between chemokine receptors and inhibitory ones.[24]

An additional non–classic inhibitory receptor expressed on eosinophils is CD52. CD52 is a glycosilphosphatidilinositol-linked protein that is expressed on various cell types but not on neutrophils.[25] Antibody cross-linking of CD52 resulted in inhibition of C5a, platelet activating factor, and GM-CSF–induced production of reactive oxygen species in eosinophils.[25] Although the mechanism for this inhibitory effect has not been addressed, it suggests that lipid rafts in eosinophils may be a cellular compartment for eosinophil regulation.

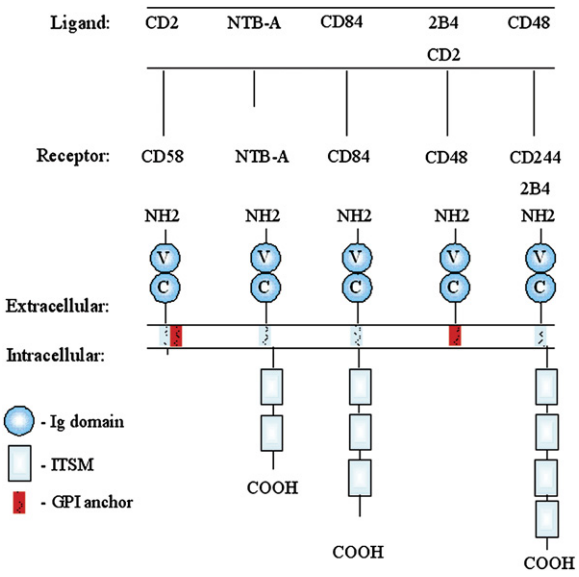


**FIG 4.** Expression of CD2 subfamily receptors on human eosinophils. This is a schematic representation of the structure and ligands of various CD2 subfamily receptors on human eosinophils. Notably, eosinophils express a wide variety of ITSM-bearing receptors. Nevertheless, the function of this motif in eosinophil regulation is yet to be defined.

## TARGETING INHIBITORY RECEPTORS AS POTENTIAL THERAPEUTIC APPROACH

In recent years, antibody therapy has become a new treatment modality for a vast array of diseases, including allergy, cancer, and malaria.[26,27] Despite this fact, it is widely agreed that the antibody therapeutical approach requires further improvement. Bispecific antibodies are proteins that have 2 different binding specificities usually designed to recognize 2 separate antigens on 2 different cells. This technology has been studied in the context of immune regulation mostly in cancer and parasitic diseases.[26,27] Thus, 1 binding site is specific for an antigen on the target cell (that is, infected or cancer cell), whereas the other binding site recognizes specifically an antigen on the immune effector cell. Accordingly, the effector cell mechanisms will be exerted upon the target cell leading to an appropriate immune response. To date, most bispecific antibodies have been designed for cancer settings. It is noteworthy to mention that products representative of all these technologies are currently under clinical trials such as the 2B1 antibody (quadroma-based bispecific antibodies, that is, somatic fusion of 2 different hybridoma cell lines)[28,29] and the MDX-H210 (bispecific $F(ab')_2$ chemically conjugated).[30-32]

Several groups including ours have used inhibitory receptors for anti-allergic treatment. Tom et al[33] have designed a bispecific antibody against IgE and FcγRIIB that

inhibits antigen-induced histamine release by human mast cells and basophils *in vitro*. In addition, Zhu et al[34] have generated a fusion protein that inhibits FcεRI-mediated responses by cross-linking it to FcγRIIB and have shown promising results *in vivo*. Notably, the latter studies did not attempt to target inhibitory receptors on eosinophils. As our data demonstrated that cross-linking of CD300a/IRp60 in the presence of eotaxin or IL-5/GM-CSF inhibits eosinophil chemotaxis, survival, and signaling cascades,[12] we attempted to inhibit these functions of the eosinophils using a bispecific antibody fragment capable of recognizing CCR3 and CD300a/IRp60. Intranasal administration of the antibody fragment in a murine chronic model of established allergic eosinophilic airway inflammation, reversed the inflammatory process, and inhibits remodeling.[35,36] Although this antibody fragment is not entirely eosinophil specific, and binds to some extent mast cells and basophils, it clearly has an inhibitory function on these cells, and collectively, this highlights a route to target these inhibitory pathways *in vivo* and perhaps in clinical settings.

## CONCLUSION

Immune system homeostasis, as with other physiological systems, is a tightly regulated process governed by an intricate balance between inhibitory and stimulatory signals toward diverse stimuli.[1,4,11] The best described paradigm of this immune ''yin-yan'' comes from the NK cell. Although the eosinophil is still a mysterious cell,[37] undoubtedly the eosinophil effector functions may have detrimental consequences. Accordingly, there is a need to define pathways capable of inhibiting their functions. Definition of these routes and the potential ligands that interact with such inhibitory pathways will enable us to:

1. Gain insight into the molecular mechanisms involved in eosinophil cellular inhibition/activation.
2. Provide us with an opportunity to inhibit eosinophil functions in different experimental settings, thus expanding our knowledge on their function in the examined disorder(s).
3. Provide us with novel tools to combat detrimental eosinophil functions in disease states.

In this review, we have summarized the current knowledge on eosinophil inhibitory pathways and raised points for future investigations. We stressed the importance of inhibitory receptors as one Achilles heel of eosinophils. This ''heel'' may serve as an innovative route for suppressing eosinophil effector functions. Therefore, we assume that investigating inhibitory receptors on eosinophils will become a fundamental avenue in the near future of eosinophil research.

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