 doi:10.20944/preprints201910.0331.v1

Review

Killer Immunoglobulin-Like Receptor 2DL4 (CD158d) Regulates Human Mast Cells Both Positively and Negatively: Possible Roles in Pregnancy and Cancer Metastasis

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 doi:10.20944/preprints201910.0331.v1

Abstract

Killer immunoglobulin-like receptor (KIR) 2DL4 (CD158d) was previously thought to be a human NK-cell-specific protein but its expression has also been demonstrated in human mast cells. Mast cells are involved in allergic reactions via their KIT-mediated and IgE receptor-mediated responses. We recently detected the expression of KIR2DL4 in human cultured mast cells established from peripheral blood derived from healthy volunteers (PB-mast), a human mast cell line (LAD2), and non-neoplastic mast cells, including pathological specimens. An agonistic antibody against KIR2DL4 negatively regulates the KIT- and IgE-receptor-mediated responses of PB-mast and LAD2 cells. In addition, agonistic antibodies and human leukocyte antigen (HLA)-G, a natural ligand for KIR2DL4, induce the secretion from these cells of leukemia inhibitory factor and serine proteases, which have been implicated in pregnancy establishment and cancer metastasis. Therefore, KIR2DL4 stimulation with agonistic antibodies and recombinant HLA-G protein may enhance both processes, in addition to suppressing mast-cell-mediated allergic reactions. (152/200 words)

Key words: allergic reaction; CD158d; IgE receptor; KIR2DL4; KIT; mast cell; pregnancy

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Introduction

Mast cells are hematopoietic lineage cells [1] whose functions are mediated by the KIT (CD117, stem cell factor receptor) and IgE receptor signaling pathways [2, 3]. KIT signaling is necessary for the survival, growth and proliferation of mast cells whereas the cross-linkage of IgE receptors induces mast cell degranulation and cytokine secretion. In addition, KIT signaling stimulates cytokine and chemokine release and augments IgE-receptor-mediated functions. Mediators secreted by mast cells play important roles in allergic diseases [4] and their regulation may be a promising route to control mast cell-mediated allergic reactions [5, 6].

Inhibitory receptors

KIT-mediated and IgE receptor-mediated responses in mast cells can be modified by other receptors expressed on the cell surface. These include inhibitory receptors [7-17] characterized by immunoreceptor tyrosine-based inhibitory motifs (ITIMs) within their cytosolic domains [18]. ITIMs comprise the homology sequence (I/V/L/S)xYxx(L/V) (x; any residue). When the receptors are stimulated, their tyrosine residues become phosphorylated following the activation of receptor or Src family tyrosine kinases. This is followed by the recruitment and activation of non-receptor protein phosphatases, such as Src homology 2 domain-containing tyrosine phosphatase (SHP)-1, SHP-2, and Src homology 2 domain-containing inositol 5-phosphatase (SHIP) 1. SHP-1 and SHP-2 dephosphorylate tyrosine-containing signaling molecules, thus reversing the action of tyrosine kinases. SHIP1 dephosphorylates phospatidylinositol 3,4,5

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 29 October 2019 doi:10.20944/preprints201910.0331.v1

trisphosphate at the 3′ position, thereby terminating phosphatidylinositol 3-kinase-driven signaling pathways [18].

In previous work, we identified the expression in human mast cells of the inhibitor receptor killer inhibitory receptor (KIR) 2DL4 (CD158d) [16, 17].

KIR2DL4

KIRs are human-specific transmembrane proteins that recognize major histocompatibility complex class I molecules and regulate human NK cell function both positively and negatively [19]. They are mainly categorized by the presence or absence of ITIMs in their cytoplasmic domain: KIRs with a long cytoplasmic domain containing ITIMs (KIR-L) or KIRs with a short cytoplasmic domain deficient in ITIMs (KIR-S) [19]. Therefore, KIR-Ls are inhibitory receptors and they include KIR2DL4, a transducer of inhibitory signals to NK cells [20], where they are mediated by SHP-1 and SHP-2 [21]. However, despite its ITIM, KIR2DL4 has also been shown to enhance NK activity and to induce interferon- secretion [22–25].

KIR2DL4 controls mast-cell-mediated allergic reactions

In previous work, we detected the expression of KIR2DL4 in human cultured mast cells established from the peripheral blood of healthy volunteers (PB-mast) [26], in a human mast cell line LAD2 [27], and in non-neoplastic mast cells, including pathological specimens. Both PB-mast and LAD2 cells were then used to examine the role of KIR2DL4 in human mast cell functions. IgE receptor-mediated and/or KIT-mediated reactions. Treatment of PB-mast and

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LAD2 cells with two agonistic antibodies against KIR2DL4, clone 181703 and clone 33, suppressed IgE receptor-mediated degranulation and KIT-mediated growth [16]. These results suggested that KIR2DL4 stimulation suppresses mast-cell-mediated allergic reactions. In addition, administration of the same antibodies induced the secretion of a serine protease, granzyme B. All of the detected KIR2DL4-mediated responses were SHP-2-, but not SHP-1-dependent [16].

Involvement of KIR2DL4 in the establishment of pregnancy

The natural ligand of KIR2DL4 is human leukocyte antigen (HLA)-G, whose expression occurs in fetal tissues during pregnancy and in certain types of cancer [20, 21]. We therefore hypothesized that human mast cells expressing KIR2DL4 would interact with HLA-G-positive trophoblasts during pregnancy establishment and with HLA-G-positive cancer cells during cancer progression. Interactions between KIR2DL4 and HLA-G have been investigated in the context of decidual NK cell-trophoblast interactions during pregnancy establishment. Decidual NK cells play important roles in pregnancy by enhancing angiogenesis in decidual tissues [28]. In some women with recurrent spontaneous abortion, the expression of KIR2DL4 protein in NK cells is reduced [29]. By interacting with HLA-G derived from trophoblasts at the fetal–maternal interface, KIR2DL4 is thought to suppress the cytotoxic activity of human decidual NK cells against the embryo [29]. Recent studies have examined the involvement of decidual mast cells in pregnancy. Using mast cell-deficient mice, they showed that while mast cells are dispensable for the establishment of

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pregnancy they have an enhancing function [30, 31]. Mast cell chymase was subsequently shown to be important for angiogenesis in the decidual tissues of mice and humans [32].

We observed that mast cells in the decidual tissues of parous women expressed KIR2DL4 and that in infertile women the numbers of decidual mast cells and, therefore, KIR2DL4 expression was reduced [17]. HTR-8/SVneo cells, a human trophoblast cell line, showed enhanced migration and tube formation when co-cultured with LAD2 cells and the enhancement was KIR2DL4-dependent [17]. The KIR2DL4-mediated secretion by LAD2 cells of leukemia growth factor and matrix metalloprotease (MMP)-9 was involved in these processes [17]. Thus, human decidual mast cells, via KIR2DL4, participate in the establishment of pregnancy.

Involvement of KIR2DL4 in cancer progression

HLA-G is expressed in some neoplasms, including breast cancers [33, 34]. The association of HLA-G-positive neoplasms with metastatic phenotypes has been explained by immune escape from human NK cells and by the induction of immune-suppressive Treg cells [33, 34]. A role for mast cells in cancer progression has also been described and mast cell infiltration may be related to the invasive or metastatic phenotypes of various cancers [35, 36]. We therefore examined the association between HLA-G, its receptor KIR2DL4, mast cells, and cancer progression.

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Using clinical samples, we found that HLA-G-positive breast cancer cells interact directly with KIR2DL4-positive tissue mast cells and that the interaction correlates significantly with the presence of lymph node metastasis and lymphovascular invasion [16]. The co-culture of LAD2 cells and a human breast cancer cell line, MCF-7, enhanced the invasion of the cancer cells via KIR2DL4-mediated secretions of MMP-9 by the mast cells [16]. Thus, human mast cells are associated with the invasive phenotypes of HLA-G breast cancers.

KIR2DL4 as a potent therapeutic target

KIR2DL4 can be activated by recombinant HLA-G or by the agonistic antibodies clone 181703 and clone 33. The ability of these molecules to enhance the establishment of pregnancy suggests their therapeutic use in the treatment of infertility. They may also be of interest in the treatment of allergic reactions, by interfering with the actions of mast cells. However, these molecules might enhance cancer progression, such that patients treated with them should first be carefully screened for the presence of malignancy. In addition, because KIR2DL4 is also expressed by dendritic cells [37], drugs based on the antibody cells may have undesirable effects on these cells.

Conclusion

KIR2DL4, a member of the KIR family, is expressed by human mast cells, human NK cells and dendritic cells. It positively and negatively regulates the functions of human mast cells such that its stimulation may suppress mast cell-mediated allergic reactions and enhance the establishment of pregnancy.

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Abbreviations

HLA: human leukocyte antigen; IFN: interferon; ITIM: immunoreceptor tyrosine-based inhibitory motif; KIR: killer immunoglobulin-like receptor; MMP: matrix metalloprotease; PB-mast: human cultured mast cells established from peripheral blood derived from healthy volunteers; SHIP: Src homology 2 domain-containing inositol 5-phosphatase; SHP: Src homology 2 domain-containing tyrosine phosphatase.

Acknowledgment

This study was financially supported by grants from JSPS KAKENHI (15K08362 & 16K19080). The authors thank Ms. K. Ijiri (Department of Diagnostic Pathology, Kyoto University Hospital, Kyoto, Japan) for her secretarial assistance.

Competing interests

The authors have declared that no competing interest exists.

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Figure legend

The current model. HLA: human leukocyte antigen; KIR: killer immunoglobulin-like receptor; LIF: Leukemia inhibitory factor; MMP: matrix metalloprotease.