The inhibitory collagen receptor LAIR-1 (CD305)

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Abstract: The immune system protects the body from invaders such as viruses and bacteria. Immune cells must be activated in the correct context to function properly. It is critical that the receptors, costimulatory molecules, and cytokines that orchestrate this activation are carefully regulated to prevent uncontrolled inflammation and autoimmunity. Inhibitory receptors play an important role in regulation of immune cell function, usually upon interaction with ligands present on other cells. In contrast, the function of the inhibitory leukocyte-associated Ig-like receptor (LAIR)-1 can be regulated by extracellular matrix collagens. LAIR-1 is expressed on most cells of the immune system, and its function has been studied on multiple cell types. This review summarizes current literature about LAIR-1, a receptor that potentially is able to regulate multiple steps of an immune response. *J. Leukoc. Biol.* 83: 799–803; 2008.

Key Words: *extracellular matrix · ITIM · ITAM*

INTRODUCTION

Inhibitory receptors containing ITIMs play an important role in the regulation of the immune system. Phosphorylation of the tyrosine in the ITIMs is the central signaling event for the function of these receptors. The term ITIM was introduced to designate molecular motifs that antagonize ITAM-dependent cell activation [1]. Tyrosine phosphorylation of ITAMs is essential for the function of many activating receptors, including the antigen receptors on B and T cells. The majority of cells in the immune system expresses at least one and often many inhibitory receptors, and studies using knockout mice have shown that they have crucial and nonredundant roles in the regulation of the immune system [2]. This lack of redundancy illustrates the importance of these receptors in prevention of autoimmunity. Indeed, single nucleotide polymorphism in the inhibitory receptors FcγRIIB and programmed death 1 is associated with the development of systemic lupus erythematosus in humans [3, 4].

The nonredundant roles of inhibitory receptors can be mediated at different levels. First, ITIM-bearing receptors may use specific intracellular effector pathways, thus affecting different activation signals. Second, ITIM-bearing receptors recognize distinct ligands, whose localization differs. Lastly, ITIM-bearing receptors are differentially expressed between cell types and during differentiation and activation of cells. Here, the identification of leukocyte-associated Ig-like receptor (LAIR)-1 as a broadly expressed inhibitory receptor and how its function is determined by its signaling partners, its unique ligand, and its regulated expression are discussed.

CLONING AND STRUCTURE OF LAIR-1

Human LAIR-1 (hLAIR-1) was molecularly cloned in 1997, characterizing the molecule recognized by the DX26 antibody that inhibits human NK cell cytotoxicity [5]. In retrospect, two earlier described antibodies, which inhibit NK cells, also recognize the same molecule. The NKTA255 antibody was described in 1995 [6], and the 9.1C3 antibody was raised over 20 years ago and was reported to inhibit NK cell-mediated target cell lysis and to influence in vitro colony formation of human bone marrow cells [7–9]. LAIR-1 was assigned cluster of differentiation number CD305 [10].

LAIR-1 is a type I transmembrane glycoprotein of 287 aa containing a single extracellular C2-type Ig-like domain and two ITIMs in its cytoplasmic tail [5]. It is structurally related to several other inhibitory Ig superfamily members localized to the leukocyte receptor complex (LRC) on human chromosome 19q13.4, suggesting that these molecules have evolved from a common ancestral gene [11]. In 2004, the mouse homologue of LAIR-1 was cloned (mLAIR-1) [12]. The predicted protein shares 40% sequence identity with hLAIR-1 and contains two ITIM-like structures in its cytoplasmic tail and is 71% homologues to rat LAIR-1, which was cloned in 2005 [13].

LAIR-1 consists of 10 exons and shows considerable homology to *LAIR-2*. The *LAIR-2* gene encodes a protein that is ~84% homologous to hLAIR-1 but lacks a transmembrane and intracellular domain [5, 14]. The *LAIR* genes lie close together in the LRC and are transcribed in opposite directions, suggesting that one locus arose from the other by a large genomic inverse duplication event [15]. Of note, the mouse and rat genome lack the *LAIR-2* gene, indicating that this duplication was a relatively late event in evolution [12, 13, 16].

Several different splice variants of the LAIR-family have been cloned (**Fig. 1**). LAIR-1b and LAIR-2b lack 17 aa in the stalk region between the transmembrane and Ig-like domain as compared with the full-length LAIR-1a and LAIR-2a forms, which may affect their glycosylation [5, 14]. LAIR-1a and

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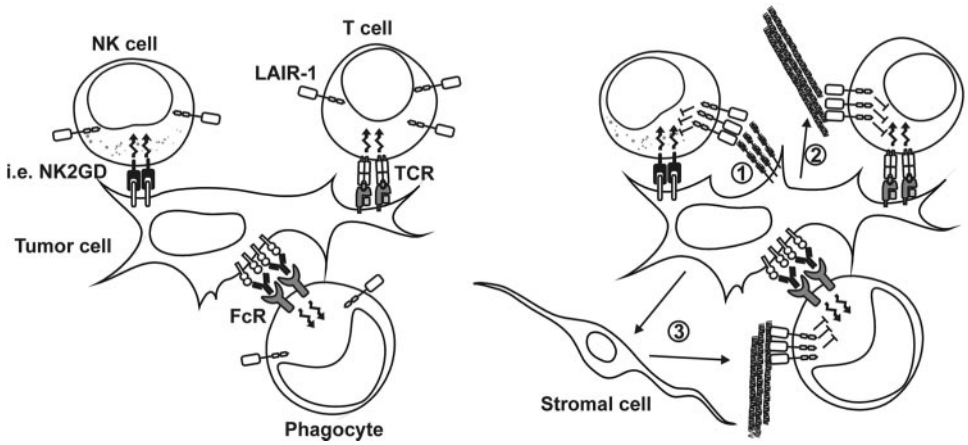

Fig. 1. Increased collagen expression by tumors to evade cellular immunity. Immunity against tumor cells, mediated by NK cells, T cells, and/or phagocytes (left panel), could potentially be inhibited by ligation of LAIR-1 on these effector cells by collagens (right panel). These collagens can be transmembrane collagens (1) or extracellular matrix (ECM) collagens (2), expressed by the tumor cell itself or collagens produced by the stromal cells surrounding the tumor cells (3).

LAIR-1b might be differentially expressed in NK and T cells, but the relevance of this has not been studied extensively [5, 14]. LAIR-1c is identical to LAIR-1b except for a single amino acid change in the extracellular domain, and LAIR-1d lacks part of the intracellular tail [17].

The LRC contains a number of inhibitory receptor families, including the killer cell inhibitory receptors (KIRs) and the leukocyte Ig-like receptors. In addition, inhibitory immune receptor families are encoded in other regions of the human genome, among which include the Siglecs in region 19q13.3 and several c-type lectins in the NK complex on chromosome 12. LAIR-1 is a unique member of the inhibitory receptor family for several reasons. First, although most inhibitory receptors are restricted in their expression, LAIR-1 is expressed on almost all cells of the immune system (**Table 1**). In addition, the LAIR-1 family consists of only two members, and many inhibitory immune receptor families consist of multiple genes encoding inhibitory and activating receptors. Lastly, most known ligands of inhibitory receptors are cell-bound, implying a role in cell–cell interactions. The identification of collagens as ligands for LAIR-1 revealed a novel role for ECM proteins in immune regulation.

TABLE 1. LAIR-1 Expression on Primary Hematopoietic Cells[a]

Cell type	LAIR-1 expression		References (human)
	human	mouse[b]	
CD34+ HPC	+	n.t.	[9, 19]
Thymocytes	+ (on subset)	+ (on subset)	[5, 6]
T cells	+ (on subset)	+ (on subset)	[5, 20, 21]
B cells	+ (on subset)	–	[5, 6, 22]
NK cells	+	+	[5, 6]
Monocytes	+	+	[5, 23]
Dendritic cells	+	+	[23]
Neutrophils	– (induced upon activation)	– (induced upon activation)	[19]
Eosinophils	+	n.t.	[19]
Basophils	+	n.t.	[24]
Mast cells	+	n.t.	[24]
Platelets	–	n.t.	[5]
Erythrocytes	–	n.t.	[5, 6]

[a] Published expression of LAIR-1 on primary hematopoietic cells. References indicate studies about human cells. [b] All mouse data are from one study [18]. n.t., Not tested.

LAIR-1 FUNCTIONS AS AN INHIBITORY RECEPTOR ON MANY IMMUNE CELLS

As summarized in Table 1, LAIR-1 is expressed on almost all immune cells, including NK cells, T cells, B cells and monocytes [5, 6], monocyte-derived dendritic cells [23], eosinophils [19], and basophils and mast cells [24]. Besides being expressed on differentiated peripheral blood cells, the receptor is also present on $CD34^+$ hematopoietic progenitor cells [9, 19] and on the majority of thymocytes [5, 6]. In mice, LAIR-1 has a similar cellular distribution; it is expressed on the majority of cells of the immune system, including T cells, NK cells, monocytes, and dendritic cells but unexpectedly, not on splenic and blood B220+ B cells [18].

The inhibitory potential of LAIR-1 was initially demonstrated by cross-linking the molecule via mAb in vitro. Cross-linking of LAIR-1 on human NK cells delivers a potent inhibitory signal that is capable of inhibiting target cell lysis by resting and activated NK cells [5, 6, 9, 25]. Furthermore, LAIR-1 can inhibit the cytotoxic activity of effector T cells upon CD3 cross-linking [5, 14, 20, 25] or antigen stimulation [21]. The inhibitory capacity of LAIR-1 in T cell clones correlates to surface density expression [26]. In primary B cells, LAIR-1 cross-linking leads to decreased BCR-induced calcium mobilization [22] and down-regulation of Ig and cytokine production [27]. Furthermore, cross-linking of the receptor inhibits FcγRII-induced calcium mobilization in U937 cells [28] and FcεR-induced degranulation of RBL-2H3 cells [29].

Next to inhibition of signals relayed by ITAM-bearing receptors, LAIR-1 has been reported to inhibit cytokine-mediated signals. LAIR-1 inhibits the differentiation of peripheral blood precursors toward dendritic cells in vitro [23, 28] and GM-CSF-dependent proliferation and protein kinase B activation in primary leukemias [30]. Lastly, it was reported that the receptor prevents proliferation and induces apoptosis in human myeloid leukemia cell lines [31].

LAIR-1 RECRUITS Src HOMOLOGY REGION 2-CONTAINING TYROSINE PHOSPHATASE-1 (SHP-1), SHP-2, AND C-TERMINAL Src KINASE (Csk)

Upon cross-linking of the receptor with mAb, the tyrosines in the cytoplasmic ITIMs of LAIR-1 become phosphorylated [5, 17, 29], and both ITIMs of LAIR-1 are required for full inhibition of cellular responses [29]. LAIR-1 phosphorylation is inhibited by PP1, a Src kinase inhibitor, although the identity of the responsible kinase is not known [17]. Differential recruitment of downstream effectors by inhibitory receptors might contribute to their nonoverlapping function. ITIM-bearing receptors classically recruit one or more of the phosphatases SHIP, SHP-1, or SHP-2 (reviewed in ref. [32]). Indeed, hLAIR-1 recruits SHP-1 and SHP-2 [5, 28] but not SHIP [33]. Originally, SHP-1 was described as the major LAIR-1-interacting protein [17], and LAIR-1 constitutively associates with SHP-1 in Jurkat cells [34]. However, mLAIR-1 does not interact with SHP-1 and still is a functional inhibitory receptor [12]. This may be explained by the recruitment of SHP-2, which could be sufficient for the inhibitory capacity of mLAIR-1 [35]. On the other hand, additional signaling molecules are involved, as LAIR-1 can still function in a cell line deficient for both phosphatases [33]. hLAIR-1 and mLAIR-1 recruit C-terminal Csk [33], a known negative regulator of immune cell function that inactivates Src family kinases [36]. Csk association is also reported for other ITIM-bearing receptors, including signal regulatory protein-α, Ig-like transcript-2, and FcγRIIB [33, 37, 38] but not KIR3DL1 [39]. Thus, LAIR-1-mediated inhibition is not solely dependent on phosphatases, and Csk may be the key downstream effector of LAIR-1 in cells where phosphatase activity is limited [33].

LAIR-1 IS A COLLAGEN RECEPTOR

The identification of collagens as ligands for LAIR-1 was unexpected and revealed a novel function for ECM components as potential immune regulatory proteins [40]. The interaction of LAIR-1 with collagens is of high affinity and dependent of the presence of hydroxyproline, as post-translational modification that is uniquely present in Gly-Pro-Hyp collagen repeats. Given that LAIR-1 recognizes a common collagen motif, it is not surprising that hLAIR-1 and mLAIR-1 interact with all collagens tested [18, 40].

Collagens are mostly studied for their role in thrombosis and hemostasis. Mammalian collagen receptors include discoidin domain receptors, integrins, mannose receptor family members, and glycoprotein VI (GpVI) [41]. These receptors selectively recognize different structural aspects of the collagen molecules, and many play a role in cell adhesion [42]. LAIR-1 is most related to the activating collagen receptor GpVI, also encoded in the LRC, which plays a central role in collagen-induced platelet activation leading to thrombus formation [43]. Similar to LAIR-1, the interaction of GpVI with collagens is dependent on the conserved Gly-Pro-Hyp collagen repeats [44]. When LAIR-1 and GpVI are coexpressed in cell lines, collagen-mediated activation signals through GpVI are prevented by coengagement of LAIR-1 [45].

Collagens are functional ligands for LAIR-1 and directly inhibit immune cell activation in vitro in cell lines and primary cells [18, 21, 40]. It should be noted that in these experiments, collagen was coated on plastic plates together with the activating stimulus, resulting in cocross-linking of activating and inhibitory receptors. Whether this represents how immune cells interact with collagen in vivo is debatable. The response of immune cells to soluble antigens in the presence of ECM collagens or transmembrane collagens needs to be studied in detail to elucidate this.

Still, the in vitro experiments suggest that through LAIR-1, collagens can set a threshold for activation for cells that have migrated into (damaged) tissue. In addition, collagens could play a role in the regulation, differentiation, and proliferation of CD34+ progenitor cells, which highly express LAIR-1 and are present in the collagen-rich environment in the bone marrow [9, 19].

An interesting implication of the discovery of LAIR-1 as an inhibitory collagen receptor is that tumor cells, known to up-regulate collagen expression, may use this interaction to down-regulate anti-tumor responses. ECM collagens and transmembrane collagens have been reported to be produced by tumor cells and/or tumor stroma. This could lead to down-regulation of responses directed against the tumor by various effector cells (Fig. 1). Lastly, its high affinity for collagen implicates a possible, additional role for LAIR-1 as an adhesion molecule.

REGULATION OF THE COLLAGEN/LAIR-1 INTERACTION

LAIR-1 is a widely expressed receptor with abundantly available ligands, suggesting that this interaction must be regulated to ensure balanced immune responses. First, the strength of the activation signal(s) given to the cell will determine whether collagen-induced cross-linking of LAIR-1 will result in inhibition of this signal. In addition, the interaction between LAIR-1 and collagens can be regulated at the level of the receptor but also by soluble LAIR-1 and LAIR-2 molecules (**Fig. 2**).

In B lymphocytes, LAIR-1 expression decreases upon cell activation in vitro [22]. Naïve B cells express high levels of LAIR-1, but the expression is absent in 50% of the memory B cells and in plasma cells [22]. In T cells, LAIR-1 expression is high on naïve cells but lower and more heterogeneous on memory cells [20, 21]. The effect of stimulation on LAIR-1 by T cells differs between reports. Human T cells stimulated with aCD3 and CD28 mAb down-regulate LAIR-1 expression [21], and cells stimulated with aCD3 with IL-2 up-regulate the molecule [20]. In mice, stimulation with aCD3 and CD28 mAb does not alter LAIR-1 expression, and aCD3 alone induces increased expression [18]. It is tempting to conclude from these findings that triggering T cells without CD28-mediated costimulation leads to up-regulation of LAIR-1, and full costimulation can result in down-regulation of receptor expression. Indeed, ex vivo analysis of $CD127^-$ and antigen-specific T cells

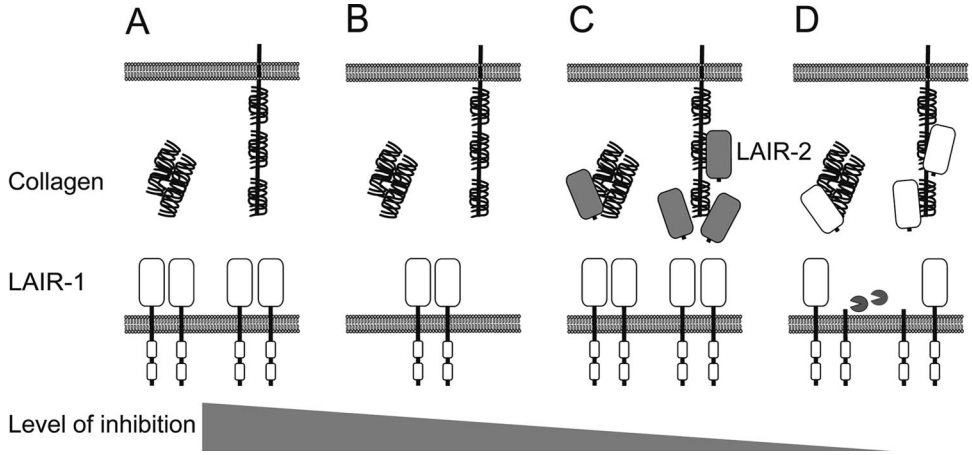

Fig. 2. Regulation of LAIR-1-mediated inhibition. LAIR-1 can interact with transmembrane and/or ECM collagens, resulting in an inhibitory signal (A). This signal can be regulated by down-regulation of LAIR-1 (B), the production of LAIR-2 (C), and/or shedding of LAIR-1 (D), which will result in a less-potent inhibitory signal.

suggested that activation-induced down-modulation of LAIR-1 also occurs in vivo [21].

Differentiation of $CD14^+$ peripheral blood precursors toward dendritic cells is associated with a decrease in LAIR-1 cell surface expression [23]. Furthermore, whereas $CD34^+$ progenitor cells and immature neutrophils isolated from the bone marrow highly express LAIR-1, the surface expression is lost in peripheral blood neutrophils [19]. Thus, in several types of immune cells, a high cell-surface expression of LAIR-1 is associated with a less-differentiated or naïve phenotype, and LAIR-1 expression on memory and terminally differentiated cells is more heterogeneous.

An alternative level of regulation might be provided by soluble LAIR molecules. hLAIR-1 can be detected in the supernatant of stimulated lymphocytes, suggesting the receptor is shed upon cellular activation [46]. This could potentially block the interaction of the transmembrane receptor with its ligands. Highly interesting in this respect is the protein encoded by the *hLAIR-2* gene, which is also capable to bind to collagens and can efficiently block the LAIR-1–collagen interaction [47].

Altered expression of LAIR proteins can also be observed in several pathological conditions. Soluble LAIR-1 can be detected in sera of patients with renal disease [46], and LAIR-2 is present in the synovial fluid of rheumatoid arthritis patients [47], indicating that these proteins are present in increased amounts in conditions associated with inflammation. Transmembrane LAIR-1 expression has been studied in a few pathological conditions. In one case report from a boy with chronic active EBV infection, decreased expression of LAIR-1 on NK cells was found [48]. In chronic and primary HIV-1 infection, down-regulated expression of LAIR-1 on B cells was interpreted as a sign of hyperactivation [49, 50].

CONCLUDING REMARKS

LAIR-1 is a distinctive receptor in the immune inhibitory receptor family because of its broad expression pattern and the unique ligands. Potentially, the interaction of LAIR-1 with collagen could play a role in controlling immune cells in various phases of the immune response. Additionally, LAIR-1 could mediate cell adhesion to ECM collagens. Although the literature reviewed here represents major progress in the understanding of this receptor, the biological role of LAIR-1 in vivo awaits clarification. With the recent identification and characterization of mLAIR-1, in vivo studies are possible and clearly, the next step in this line of research.

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