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RESEARCH HIGHLIGHT

Ly49 and C-type lectin receptors on dendritic cells regulate T-cell differentiation as co-stimulatory molecules

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The C-type lectin receptors (CLRs) expressed on dendritic cells (DCs) participate in T-cell polarization by recognizing pathogen-associated molecular patterns and activating signaling pathways for cytokine production. In addition, some CLRs expressed on DCs function as co-stimulatory molecules via recognition of endogenous ligands on T cells and regulate proliferation and/or differentiation of T cells. We recently showed that killer cell lectin-like receptor Ly49s3 is expressed in rat thymic DCs and recognizes MHC class I molecules on T cells, for differentiation into naturally occurring regulatory T cells (nTregs). Upon binding to MHC class I molecules on T cells, Ly49s3 seems to stimulate signal transduction pathway(s) leading to up-regulation of the MHC class II genes and then functions as a co-stimulatory molecule. The signaling pathway(s) is supposed to involve Dap12, Syk/Zap70, Lat, Plcγ, PKC, PU.1 and C2ta proteins to attain MHC class II expression. Other than Ly49s3, Ly49Q and Ly49B have been shown to be expressed in myeloid cells including DCs and macrophages, raising the possibility that they may be involved in the regulation of T-cell differentiation through recognition of MHC class I molecules on T cells. In humans, immunoglobulin (Ig)-like receptors binding to MHC class I molecules take the place of Ly49 receptors. Among them, expression of the *KIR2DL4* gene has been reported to be induced in antigen-presenting cells, although its biological significance is obscure, and immunoglobulin-like transcript 4 (ILT4) expressed in DCs has been shown to down-regulate expression of MHC class II molecules on the same cells, upon binding to MHC class I molecules. They may also be involved in regulation of T-cell differentiation. Some other CLRs are expressed on DCs and possibly function as co-stimulatory molecules. For example, dectin-1, dectin-2 and Dcal-1 have been shown to promote T-cell proliferation, Treg differentiation and IL-4 production of T cells, respectively, through binding to unidentified ligands on T cells. DC-Sign, which recognizes ICAM3 on T cells, is also suggested to be involved in T-cell differentiation. Further investigation of the functional roles of CLRs on DCs will provide insight into the regulatory mechanisms of T-cell differentiation, essential processes for regulating immune responses.

Keywords: Ly49s3; dendritic cells; co-stimulatory molecule; T-cell differentiation

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Introduction

The C-type lectin receptors (CLRs) comprise a large family of receptors characterized by the presence of one or more C-type lectin-like domains (CTLDs). Although originally identified as carbohydrate binding receptors through CTLDs, CLRs have since been shown to bind to a

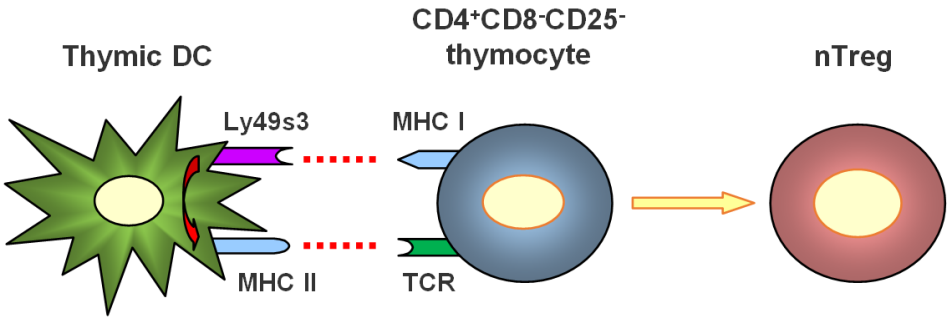

Figure 1. Ly49s3 as a co-stimulatory molecule in the process of nTreg differentiation. From our co-culture experiments, it is suggested that Ly49s3 on thymic DCs binds to the MHC class I molecule on thymocytes, up-regulates expression of MHC class II molecules on DCs and regulates nTreg differentiation in cooperation with MHC class II molecules.

wide range of ligands including proteins and lipids [1-3]. CLRs containing cytoplasmic immuno-receptor tyrosine-based activation motifs (ITAMs) are capable of triggering signaling pathways directly to activate cellular functions, while those without ITAMs trigger signaling pathways through interaction with adaptor molecules containing ITAMs. On the other hand, CLRs containing cytoplasmic immuno-receptor tyrosine-based inhibitory motifs (ITIMs) trigger inhibitory signals to inhibit cellular functions [2,4].

CLRs are expressed in many types of cell including hematopoietic cells. CLRs expressed on dendritic cells (DCs), highly specialized antigen-presenting cells (APCs), are involved in the induction of T-cell differentiation as pattern-recognition receptors (PRRs) [5,6]. After binding to CLRs, highly conserved exogenous pathogen-associated molecular patterns (PAMPs) are internalized by DCs for the purposes of pathogen processing and subsequent presentation to T cells on MHC class II molecules. Concomitantly, upon binding to PAMPs, CLRs trigger intracellular signal transduction pathways, leading to the production and release of cytokines to regulate effector T-cell differentiation. Representative CLRs that function as PRRs and are involved in effector T-cell differentiation are listed in Table 1. In addition, some CLRs on DCs can recognize endogenous ligands on T cells and regulate their proliferation and differentiation. It is, therefore, supposed that they function as co-stimulatory molecules [7].

Natural killer (NK) cell receptors are expressed on NK cells to detect MHC class I molecules on target cells. Upon binding to MHC class I molecules, they transmit stimulatory or inhibitory signals to NK cells to control their functions [8]. NK cell receptors include two large families: one is composed of receptors homologous to CLRs, thus called killer cell lectin-like receptors (KLRs). The other family is composed of receptors with immunoglobulin (Ig)-like domains, called killer cell Ig-like receptors (KIRs). Ly49 receptors belonging to the KLR family function as dominant NK cell receptors in rodents. In humans, KIRs play a parallel function instead of Ly49 receptors [8-11]. In a recent study, we showed that one member of the rat Ly49 receptors, Ly49s3, is expressed in thymic DCs and involved in regulation of the differentiation of naturally occurring regulatory T cells (nTregs) in the thymus [12]. In our study, we also showed evidence suggesting that Ly49s3 binds to MHC class I molecules on T cells [12]. It is, therefore, suggested that Ly49 receptors possess a new functional role as a co-stimulatory molecule in the process of induction of T-cell differentiation.

In this article, we first introduce our study and discuss possible mechanisms through which Ly49s3 induces nTreg differentiation as a co-stimulatory molecule. We next briefly introduce other NK cell receptors and CLRs expressed on DCs that are involved in the regulation of T-cell proliferation and/or differentiation through interaction with endogenous ligands on T cells.

Ly49s3 and nTreg differentiation

Ly49s3 on thymic cDCs is essential for nTreg differentiation

Ly49 receptors are type II transmembrane receptors of rodents originally identified as NK cell receptors for the detection of MHC class I molecules on target cells [9]. A total of 23 potentially functional Ly49 genes are clustered in the natural killer cell gene complex (NKC) on chromosome 6F3 in mouse and 26 on chromosome 4q42 in rat [13]. Upon encountering MHC class I molecules,

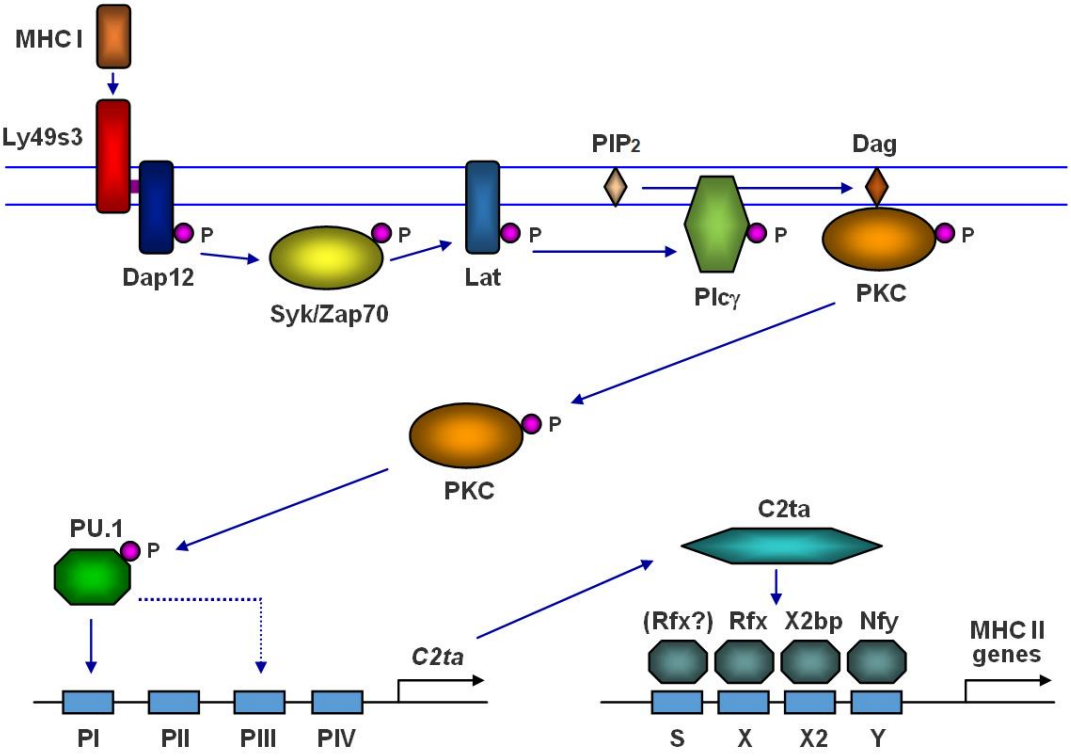

Figure 2. Proposed pathway of MHC class II induction via ligation of Ly49s3. After binding of Ly49s3 to MHC class I molecule, Dap12, Syk/Zap70, Lat and Plcγ are sequentially activated by phosphorylation. Activated Plcγ generates Dag, from PIP_2, which leads to phosphorylation and activation of PKC. PKC, in turn, phosphorylates and activates PU.1, which upregulates expression of the *C2ta* gene through binding to promoter PI (and possibly PIII). C2ta then associates with a multiprotein complex, the MHC class II enhanceosome including Rfx, X2bp and Nfy, on the promoter of the MHC class II genes and upregulates the expression of these genes.

inhibitory members of the receptors transmit inhibitory signals through their cytoplasmic ITIMs to prevent NK cells from mediating cytotoxicity. Stimulatory members transmit stimulatory signals to activate cellular functions through ITAMs contained in adaptor molecules associated with them through a positively charged amino acid in their transmembrane domain [14,15].

nTregs, important for immune regulation and the maintenance of self-tolerance, are characterized by the presence of CD4 and CD25 (interleukin-2 receptor chain) on their surface and Foxp3, a master regulatory transcription factor for nTreg differentiation, in their nuclei [16]. The thymic development of $CD4^+CD25^+Foxp3^+$ nTregs requires interactions of $CD4^+$ thymocytes through their TCRs with self-peptide/MHC complexes present on thymic antigen-presenting cells (APCs) [17,18]. We recently showed that Ly49s3, a stimulatory receptor, is expressed in conventional DCs (cDCs) in the rat thymus and involved in nTreg differentiation [12].

We maintain a mutant strain of rats, the Hirosaki hairless rat (HHR), which was spontaneously derived from the Sprague-Dawley rat (SDR), with a nearly bare phenotype that is inherited in an autosomal recessive manner [19]. HHR shows a small thymus with an underdeveloped medulla and decreased nTreg number. To identify the gene(s) responsible for this phenotype, we performed array CGH analysis and found a deletion of the DNA region containing the *Ly49s3* gene in HHR. As a consequence of this deletion, the expression of the *Ly49s3* gene is lost in HHR thymic cDCs. To examine whether this is the reason for the nTreg deficiency in HHR, we performed a co-culture experiment. When $CD4^+CD8^-CD25^-$ thymocytes were cultured with thymic cDCs, the expression of nTreg marker genes (*Foxp3, Cd25, Ctla4 and Pd-1*) was lower when these cells were from HHRs than from SDRs, suggesting that HHR cDCs are deficient in the ability to induce nTreg differentiation. Expression of the genes was recovered when Ly49s3 was expressed on HHR thymic cDCs by means of transduction with the viral vector of the *Ly49s3* gene. In these co-culture

Table 1. Representative C-type lectin receptors (CLRs) involved in T-cell polarization as pattern-recognition receptors (PRRs).

CLRs	T-cell subsets	Refs
Dectin-1	Th1, Th2 (suppresses Th2 response), Th17, $CD8^+$ CTL	[62-65]
Dectin-2	Th2, Th17	[54-56]
CLEC-1	Th17 (suppresses Th17 response), Treg	[66]
DCAL-2	Th1	[67]
Mincle	Th1, Th17	[68]
DC-SIGN	Treg	[69]
DEC-205	Treg, $CD8^+$ CTL	[70]

experiments, expression levels of MHC class II genes (*Rt1-Bα* and *Rt1-Bβ*) from cDCs were up-regulated in parallel with those of nTreg marker genes. This is consistent with the theory that thymocytes receive strong signals through MHC class II-TCR interaction to differentiate into nTregs. However, when an anti-MHC class I antibody was added to the co-culture to block interaction between Ly49s3 and MHC class I molecules, the expression of the MHC class II genes was up-regulated while that of the nTreg marker genes was down-regulated. Taken together, our results suggest a unique scenario in which Ly49s3 contributes to nTreg induction along with MHC class II molecules as an essential co-stimulatory molecule in thymic cDCs (Fig. 1), and loss of Ly49s3 from thymic cDCs is the reason for the nTreg deficiency in HHR.

Possible functional roles of Ly49s3 as a co-stimulatory molecule

In our co-culture experiments, enforced expression of Ly49s3 in HHR thymic cDCs resulted in up-regulation of the MHC class II expression in the cells (Fig. 1). Given that the ligands of Ly49s3 were strongly suggested to be MHC class I molecules on T cells, an intriguing possibility arises that MHC class I binding of Ly49s3 leads to enhanced expression of the MHC class II genes.

A possible signaling pathway is shown in Figure 2. Since Ly49s3 is a stimulatory receptor with a positively charged amino acid, arginine, in its transmembrane domain, it is likely that ITAM-containing adaptor molecule Dap12 is associated through its transmembrane negatively charged amino acid aspartic acid [14,15]. It is known that, upon binding of stimulatory Ly49 receptors to MHC class I molecules, Dap12 is transiently tyrosine-phosphorylated and then recruits the Syk/Zap70 proteins and phosphorylates their tyrosine residues. This Syk/Zap70 activation leads to substantial activation of several downstream cascades. One of them is tyrosine-phosphorylation and activation of the scaffolding molecule, linker for activation of T cells (Lat) [14,15]. Activated Lat then recruits phospholipase Cγ (Plcγ) and leads to its tyrosine-phosphorylation. Then, activated Plcγ generates from phosphatidylinositol 4,5-bisphosphate (PIP_2) the secondary messenger diacylglycerol (Dag), which leads to activation of protein kinase C (PKC) [14].

MHC class II molecules are heterodimeric proteins composed of α and β chains [20]. In the upstream regulatory region of each of the α and β genes, four cis-acting elements (S, X, X2 and Y boxes) are present and expression of the genes is regulated by transactivating proteins associated with these elements [21]. The configuration of the promoter is conserved in many species including rodents and humans. The first event of activation of the MHC class II genes is the binding of Rfx (a trimeric complex of Rfxank, Rfxap and Rfx5) to the X box, which facilitates the binding of other factors to other elements, X2bp (Creb) to the X2 box and Nfy to the Y box, and formation of a complex for assembly of these DNA-binding proteins, called the MHC class II enhanceosome [21]. Class II transactivator (C2ta), a coactivator showing no DNA-binding activity but containing a transcription activation domain, is then recruited to the enhanceosome through protein-protein interaction, which leads to activation of the genes [21]. C2ta is the master regulator of expression of the MHC class II genes.

Expression of the *C2ta* gene itself is regulated by four upstream promoters (PI, PII, PIII and PIV). Of these promoters, PI is mainly used in DCs and PIII in B cells [22,23]. Recent studies revealed that myelomonocyte- and B-cell-specific transcription factor PU.1 binds to PI as a monomer in murine bone marrow-derived DCs and to PIII as a heterodimer with coactivator IRF-4 in human B-cell lines [23,24]. PU.1 may transactivate PIII also in DCs because PIII is known to be used in DCs as well as in B cells [24]. It has been recently reported that PKCδ phosphorylates the transactivation domain of PU.1 and enhances its transactivation activity in cDCs differentiated from human $CD34^+$ hematopoietic stem cells [25]. It is, therefore, interesting to speculate that activated PKCδ downstream of the Dap12 signaling pathway phosphorylates PU.1 and it, in turn, activates expression of the *C2ta* gene in our system. Taking together the features described so far in this section, it is suggested that there is crosstalk between MHC class I molecules on T cells and MHC class II molecules on cDCs via Ly49s3.

Since the anti-MHC class I antibody used in our study to interfere with binding between Ly49s3 and MHC class I molecules recognizes the non-polymorphic region of the

Table 2. CLRs expressed on DCs recognize ligands on T cells and possibly function as co-stimulatory molecules for proliferation and/or differentiation of T cells.

CLRs	Ligands on T cells	Effector (target) T cells	Refs
Dectin-1	Unidentified	Thymic T cells	[48,49]
Dectin-2	Unidentified	Treg	[57]
Dcal-1	Unidentified	Th2	[58]
Ly49s3	MHC class I	nTreg	[12]

latter, it is suggested that Ly49s3 recognizes the non-polymorphic region, like Ly49A, which has been shown to interact with β2 microglobulin and the α3 domain of MHC class I molecules [26-28], but not the polymorphic region and/or peptide antigens. However, it is not completely ruled out that Ly49s3 recognizes the polymorphic region and/or peptide antigens, which are likely self-antigens in this case, together with the non-polymorphic region. If this were the case, T cells expressing self-antigens with stronger affinity to Ly49s3 may take advantage of this for differentiation into nTregs. This is an interesting point to be elucidated.

On the basis of the hypothesis described above, it is speculated that blockage of Ly49s3-MHC class I interaction results in down-regulation of MHC class II expression. In our experiments, however, the expression of the MHC class II genes was not reduced, but was rather enhanced upon addition of the anti-MHC class I antibody to the co-culture. The actual reason for this is unknown at present, but it is hypothesized that negative signaling pathway(s), suppressing MHC class II gene expression, antigen processing, and loading and/or recycling of MHC class II molecules, may also be activated for precise tuning of MHC class II levels after the stimulation of Ly49s3 by MHC class I molecules. The negative pathway(s) may require stronger stimulation from Ly49s3 to be activated than the positive one(s), and may be selectively inactivated in the presence of the anti-MHC class I antibody. Since a considerable proportion of thymic cDCs express CD8α molecules [29-31], the possibility raises that thymic cDCs and T cells interact via binding of CD8α and MHC class I molecules, and this interaction may be affected by the antibody. It is also supposed that there is direct binding of the antibody to MHC class I molecules on cDCs, in addition to binding to the molecules on T cells. These features may affect MHC class II expression levels in cDCs. Further investigation is required to assess these possibilities.

While most Ly49 receptors recognize classical MHC class Ia molecules, Ly49s3 on NK cells has been reported to recognize nonclassical MHC class Ib molecules [32]. The antibody used in this study was for detection of classical MHC class Ia molecules, suggesting that Ly49s3 can also recognize classical MHC class Ia molecules under certain conditions such as in the case expressed on DCs. This also remains to be determined.

Other Ly49 receptors expressed in DCs

Ly49Q

Some members of the Ly49 receptors are expressed in myeloid, but not NK, cells. Murine Ly49Q with ITIM is exclusively expressed in myeloid cells and plasmacytoid DCs (pDCs), a subset of DCs producing a high level of type I interferon (IFN) [33-35]. Ly49Q is involved in regulation of the polarization and migration of neutrophils, and maturation and cytokine (IFN-α and IL-12) production of pDCs [36,37]. A low level of Ly49Q expression is also found on cDCs induced by GM-CSF from murine BM cells and this expression is enhanced by IFN-α treatment, suggesting that Ly49Q plays some functional roles in cDCs [38]. Since pDCs as well as cDCs govern T-cell differentiation [39,40], Ly49Q on DCs may be involved in the regulation of T-cell differentiation through recognition of MHC class I molecules on T cells in some situations.

Ly49B

Another example of a Ly49 receptor expressed in myeloid cells is murine Ly49B, with atypical ITIM, which has been shown to be expressed in granulocytes and monocytes/macrophages [41]. Since macrophages are APCs, Ly49B may also be involved in the regulation of T-cell differentiation through recognition of MHC class I molecules on T cells.

Further investigation is required to elucidate the functional roles of Ly49Q and Ly49B in APCs for T-cell differentiation induction.

Human NK cell receptors expressed in DCs

KIR2DL4

In humans, in contrast to the case in rodents, a limited number of genes for KLRs to recognize MHC class I molecules are present in NKC on chromosome 12p13, namely, four *NKG2* and one *CD94* genes for NKG2/CD94 heterodimers and one *hLy49L* gene, which is thought to be a pseudogene [42]. Instead, MHC class I recognition of NK cells in humans is mediated mainly by KIRs [8]. Fifteen potentially functional genes for KIRs, either stimulatory or inhibitory, are clustered on chromosome 19q13 [10,11]. Among them, only KIR2DL4 has so far been reported to be expressed in APC [43]. KIR2DL4 possesses

characteristics of both stimulatory and inhibitory receptors and has been shown to transduce activating signals through association with FcRγ containing ITAM. It was reported that expression of the *KIR2DL4* gene was induced in APC cell lines (lymphoblastoid cells and promyelomonocytic KG1a cells) when its ligand, nonclassical MHC class I molecule HLA-G, was expressed in the same cells. However, the physiological significance of the upregulation of the gene is not clear because expression of KIR2DL4 protein was not detected on the surface of the cells [43].

ILT2 and ILT4

Another group of human genes for Ig-like receptors, Ig-like transcripts (ILTs), are clustered near the KIR gene cluster on chromosome 19q13 [10]. Some members of the ILTs are expressed in DCs and recognize MHC class I molecules as well as other ligands from bacteria and viruses [44]. It has been reported that ligation of ILT4 with its ligand HLA-G on human monocyte-derived cDCs leads to maturation/activation arrest of the cells associated with diminished expression of MHC class II molecules and co-stimulatory molecules, CD80 and CD86 [45]. The following mechanism is proposed to explain the down-regulation of MHC class II expression [45]. Binding of HLA-G induces phosphorylation of ITIM of ILT4 and recruitment of SHP-2 protein tyrosine phosphatase to it. Recruited SHP-2 activates downstream signaling to enhance NF-kB activity, which leads to up-regulation of expression of the *Il-6* gene and IL-6 production. Secreted IL-6, next, binds to its receptor on the surface of the same cell and induces STAT3 activation. Activated STAT3 enhances the activity of cathepsin S, which lowers intracellular MHC class II levels, leading to diminished expression of surface MHC class II molecules. This is an interesting example of negative crosstalk between MHC class I and class II molecules and raises the possibility that ILT4 on DCs is involved in the regulation of T-cell differentiation through interacting with MHC class I molecules on T cells.

It has been demonstrated that ILT2 and ILT4 bind to MHC class I molecules on the same DCs in a *cis* configuration as well as the molecules on T cells in *trans*. They are suggested to influence the polarization of $CD8^+$ T cells through this *cis*-association, that is, competition with CD8 molecules on T cells for MHC class I binding [46,47].

CLRs expressed in DCs and functioning as co-stimulatory molecules

Several CLRs expressed on DCs recognize endogenous ligand on T cells and potentially function as co-stimulatory molecules.

Dectin-1

Dectin-1 is a type II transmembrane receptor having a single CTLD and an intramolecular ITAM-like motif and expressed in myeloid cells, such as monocytes/macrophages, DCs and neutrophils but not in lymphocytes. It is expressed in the spleen, lymph nodes, thymus and skin [48]. As a PRR, dectin-1 recognizes beta1,3-linked glucan in cell walls of fungi, plants and some bacteria [49,50]. Upon binding to ligands, dectin-1 induces ligand uptake and activation of spleen tyrosine kinase (Syk) through its ITAM-like motif. Activated Syk, in turn, mediates signaling, through Card9/Bcl10/Malt1 complex, leading to the activation of NF-kB and subsequent production of cytokines and chemokines, including TNF, CXCL2, IL-23, IL-6 and IL-10. These cytokines and chemokines are thought to drive Th1 and Th17 polarization of $CD4^+$ T cells and cytotoxic responses of $CD8^+$ cells [50] (Table 1).

On the other hand, in experiments using the extracellular domain of dectin-1, it was shown that dectin-1 binds to unidentified ligands on T cells and promotes their proliferation in the presence of anti-CD3 antibody, leading to the notion that it functions as a co-stimulatory molecule [48,50]. In immunohistochemical analysis, dectin-1 was found in the medullary and corticomedullary regions in the murine thymus, implying its functional roles in the regulation of T-cell differentiation, although no obvious T-cell abnormalities have been observed in dectin-1-deficient mice [51].

Dectin-2

Dectin-2 is a type II transmembrane receptor expressed in myeloid cells, such as monocytes/ macrophages, DCs and neutrophils. It is expressed in the spleen, lymph nodes, thymus and skin [52]. Dectin-2 recognizes high-mannose structures of a wide variety of pathogens [53]. Dectin-2 is associated with ITAM-containing adaptor molecules, FcRγ, and activates intracellular signaling through the Syk-Card9 pathway to produce cytokines and chemokines, which induce Th2 and Th17 responses [53-56] (Table 1).

Ultraviolet radiation-induced immunosuppressive status in the skin is known as ultraviolet radiation-induced tolerance, which can be transferred to recipients by injection of T cells from such treated donors. Aragane et al. [57] demonstrated that injection into mice of a soluble form of dectin-2 containing only the extracellular region (sDec2) interfered with interactions between dectin-2-expressing cells and target cells, not only inhibiting the

induction of ultraviolet radiation-induced hapten-specific tolerance but also breaking the already established tolerance in the skin, and the ransfer of T cells from sDec2-injected mice did not transfer the tolerance. Furthermore, they indicated that T cells from tolerized mice, which could transfer the tolerance, were bound to sDec2 and showed the phenotype of $CD4^+CD25^+$ Tregs [57]. From these elegant experiments, they postulated that dectin-2 expressed on DCs, Langerhans cells, in the skin binds to unidentified ligands on T cells and promotes their differentiation into $CD4^+CD25^+$ Tregs, leading to ultraviolet radiation-induced tolerance. Dectin-2 is another example of a CLR expressed in DCs that regulates Treg differentiation via recognition of ligands on T cells.

Dcal-1

Dcal-1 is a type II transmembrane receptor isolated from human tonsillar B cells [58]. Dcal-1 is expressed in mDCs, pDCs and B cells, but not in myeloid or T cells. It is expressed in the spleen, lymph nodes, tonsil, peripheral blood, bone marrow and colon, but not in the thymus [58]. It has been demonstrated that ligand of Dcal-1 is expressed on $CD4^+CD45RA^+$ T cells and soluble Dcal-1 enhances proliferation and IL-4 production of $CD4^+$ T cells stimulated by an anti-CD3 antibody [58]. Dcal-1 expressed on DCs, therefore, is suggested to function as a co-stimulatory molecule for Th2 polarization.

DC-Sign

DC-Sign is a type II transmembrane receptor containing a single extracellular CTLD [59]. DC-Sign is expressed on immature DCs, macrophages and endothelial cells as a tetramer because it interacts with other copies of it through its stalk region located between CTLD and the transmembrane domain [59]. It recognizes high-mannose and fucosylated structures of a wide variety of pathogens, including mycobacteria and fungi [60]. DC-Sign is supposed to be a co-stimulatory molecule because it can recognize ICAM3 on T cells. However, the precise function of DC-Sign is still unclear [59,61].

Conclusion

Accumulating evidence, including our report on Ly49s3, has revealed functional roles of CLRs, and human KIRs and related molecules that are expressed on APCs. At least some of them recognize ligands on T cells and possibly function as co-stimulatory molecules for regulation of the proliferation and/or differentiation of T cells (Table 2). Identification of ligands and elucidation of signaling events in APCs and T cells elicited after ligation will lead to better understanding of the functional roles of these receptors and regulatory mechanisms of T-cell differentiation.

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Conflict of interests

The authors declare that they have no Conflicting interests.

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