The Expanding Spectrum of Ligands for Leukocyte Ig-like Receptors

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J Immunol 2016; 196:947-955; doi: 10.4049/jimmunol.1501937
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Deborah N. Burshtyn and Chris Morcos

The human leukocyte Ig-like receptor (LILR) family belongs to the superfamily of paired receptors that contain receptors with the potential to transmit stimulatory or inhibitory signals. In general, these receptors regulate the immune system to temper or augment responses by other cells and mark tolerogenic APCs. Paired receptors are sets of receptors with highly similar extracellular domains linked to either activating or inhibitory signaling systems. In many cases, the activating receptors share the same ligands as their inhibitory counterpart, but the interactions are weaker. The LILR receptors were identified as receptors related to the MHC class I (MHC-I)–specific killer cell Ig-like receptors (KIRs) and one as the receptor to a viral MHC-I mimic (1–3). Despite their identification ~20 years ago, understanding of the specific functions of each different receptor and elucidating their ligands has been relatively slow and to a certain degree hindered by the divergence of the human and mouse receptor family. The difference is most pronounced in the number and probable subfunctionalization of the inhibitory receptors with five human and only a single mouse. In contrast, both species encode many activating receptors, and more is known about the binding characteristics for the human. LILR orthologs are found in most mammalian species studied, and highly related receptor families are found in marsupials, with more distantly related receptor systems found in birds, frogs, and perhaps even fish in terms of their Ig domain structure, suggesting that they have arisen from a common ancestral gene (4, 5). In the case of bats, one major lineage lacks the family altogether, whereas the other has it greatly expanded (6). Although the evolutionary plasticity in the receptor family among even closely related species makes it tempting to speculate that the expansion and contraction of the family coincides with emergence and/or extinction of pathogens, the growing list of endogenous ligands suggests the selective pressures go well beyond the direct interaction with MHC-I and evasion strategies of pathogens.

This review will focus on the newly identified and growing list of LILR ligands that are not MHC-I–related along with discussion of the specifics of the LILR interaction with diverse types of MHC-I molecules. Over six distinct ligands have been reported for two of the receptors, and several ligands engage multiple receptors (Fig. 1, Table I). The list includes endogenous molecules involved in development and responses of the immune system, tissue-specific molecules that can be autoantigens as well as binding to intact bacteria, and a member of the flaviviridae. The complex assortment of ligands raises many questions about the functions of the LILR receptors in various cell types and contexts, how the individual receptors can accommodate binding to the range of ligands, and how these ligands collaborate or cross-regulate each other.

General features of LILR

The human LILRs are encoded at chromosome 19q13.4 within the leukocyte receptor complex. The locus encodes genes for six inhibitory receptors, four stimulatory receptors, one secreted receptor, and two pseudogenes. There is considerable polymorphism, and copy-number variation likely also contributes to diversity within the population (7–11).
Monocytes express all but one of the receptors, whereas most immune cell types express at least one member of the LILR family (Table I). In general, what distinguishes the inhibitory and stimulatory forms of the receptors is the presence of ITIMs in the cytoplasmic tail of the inhibitory receptors or a positively charged arginine in the transmembrane region of the activating receptor that couples the receptor to the ITAM-containing adaptor FcR. The inhibitory forms are denoted by “B” in the name and numbered to identify the various receptors, whereas the activating forms are denoted with “A.” The receptors typically have four Ig domains, a stem region, transmembrane domain, and a cytoplasmic tail. The exceptions are LILRB4 and LILRA5, which only have two Ig domains, and LILRA1, for which a two-domain isoform is created by alternative splicing. LILRA3 is the sole secreted form, and even though it has an A in its name, it cannot directly transmit an activating signal. In contrast, paired Ig-like receptor B (PIRB), the single inhibitory receptor in mouse, has six Ig domains. How the PIRB domains relate to the various LILRB domains will be discussed further below.

The human LILR receptors are divided into two groups based on their sequence similarity relative to MHC-I binding (12). As will be covered in the following section, the first group has high similarity with each other within the MHC-I binding regions, and, although most do, they have not all been shown to bind to MHC-I. The remaining receptors differ from the group 1 at the MHC-I contact region and share certain residues at these locations with each other (12); however, their ligands identified to date bear little obvious structural relationship to one another, and they likely use distinct surfaces to engage the array of distinct ligands.

Interaction with native classical MHC-I

To date, five LILRs have been shown to bind to classical MHC-I proteins. LILRB1, LILRB2, and LILRA3 bind a spectrum of classical class I alleles. The interaction between LILRB1 and LILRB2 and classical MHC-I proteins has been well characterized through structural studies (13–16). Both these receptors have four Ig domains and use the two membrane distal domains (D1 and D2) to contact conserved features of the α3-domain and β2-microglobulin subunit of the MHC-I proteins. The interaction with these highly conserved regions of the MHC-I explains how both receptors bind the range of MHC-I subtypes and alleles, but there are details of the interaction that differ between the two receptors. Specifically, LILRB2 has a larger interaction interface with the α3-domain, whereas LILRB1 is highly dependent on the interaction with β2-microglobulin (β2m) to form a stable complex.

Why there are two LILRs with such similar binding capabilities for MHC-I is not clear, but perhaps is related to differential expression by cell types or the variety of non-MHC-I ligands that the two receptors have evolved that are distinct that will be covered in subsequent sections. Although the LILRB1 and LILRB2 both bind to all HLA-A, -B, and -C tested, sequence differences of the MHC-I molecules do impact the strength of the binding. Jones et al. (17) performed the most comprehensive comparative assessment examining the interaction of two receptors with >90 alleles of MHC-I.

FIGURE 1. LILR interactions. The known LILR interactions are illustrated for the receptors depicted on a generic APC interacting with cell-surface and soluble ligands. The shaded LILR domains indicate those domains have been mapped as important for the interaction with the ligand. The dashed lines of the MHC-I free H-chains (FHC) and B27 indicate their altered α1 and α2 conformation compared with the full complex. The receptor labels lack the LILR for clarity of the figure. The receptors that lack known ligands are illustrated for completeness. DC, dendritic cell; LTA, lipoteichoic acid.
using Luminex technology. Their study indicates a polymorphism in the \( \alpha_3 \) domain influences LILRB1 binding (17). The change involves a proline at position 193 that is in tight linkage disequilibrium with an isoleucine/valine dimorphism at position 194, a residue that makes direct contact with LILRB1 (14). In contrast, LILRB2 binds A, B, C and only weakly binds a few of HLA-B alleles, including the disease-associated HLA-B*2705 (17). In contrast to the regions that influence LILRB1, MHC-I polymorphisms that influence LILRB2 binding are restricted to the MHC-I \( \alpha_1 \) domain. Insensitivity to the \( \alpha_3 \) domain polymorphisms likely relates to the differences in how the LILRB2 interacts with the \( \alpha_3 \) with a more extensive interface that can accommodate the changes in \( \beta_2m \). However, an interaction by the D3D4 domains could explain the LILRB2 sensitivity to differences in \( \alpha_1 \). Such an interaction was proposed by Nam et al. (18), who solved the structure of the two membrane proximal domains independent of the rest of the receptor. These authors suggested that the D3D4 domains could wrap over the top of the \( \alpha_1\alpha_2 \) domains of the class I in a manner reminiscent of the KIR3DL1–MHC-I interaction (19), but there is no known influence of peptide on the interaction of LILRs with MHC-I.

The remaining group 1 LILRs are LILRA1, LILRA2, and LILRA3. LILRA1 and LILRA3 also broadly bind classical MHC-I, and, as is characteristic of paired receptors, the interaction is of lower affinity than that of the inhibitory receptors (17, 20). Curiously, these receptors also bind HLA-C better than HLA-A and -B, which is opposite to LILRB2. The preference for HLA-C could indicate function in a specialized tissue, such as placenta that expresses HLA-C, but not -A or -B (reviewed in Ref. 21) or the ability to respond in scenarios in which HLAs are differentially manipulated by a virus such as HIV (reviewed in Ref. 22). There are no studies indicating a functional interaction of LILRA1 with MHC-I with cells naturally expressing LILRA1, but it would be expected to counterbalance LILRB1 and -B2 signals in cells that coexpress the receptors, such as monocytes/macrophages and dendritic cells. LILRA3 is constitutively expressed by monocytes at low levels and upregulated in response to inflammatory states and in response to IL-10 in vitro (23) as detected in serum, suggesting it might provide feedback control on inflammatory responses. Purified LILRA3 can suppress TNF-\( \alpha \) production by LPS-stimulated PBMC, implying a regulatory role (24). However, the latter study did not determine if MHC-I was the necessary ligand in this context. In fact, Lee et al. (24) showed preferential binding to monocytes over other lymphoid cells that have high levels of MHC-I, suggesting LILRA3 has another ligand and also that the binding to monocytes requires native glycosylated LILRA3. LILRB3, LILRB4, and LILRA5 appear not to bind MHC-I, as they have been tested using assays with soluble receptors and class I on cells and/or surface plasmon resonance (16, 25, 26).

### Table I. Summary of LILR family ligands

<table>
<thead>
<tr>
<th>Receptor</th>
<th>No. of Ig Domains</th>
<th>Expression</th>
<th>Ligands</th>
</tr>
</thead>
<tbody>
<tr>
<td>LILRB1</td>
<td>4</td>
<td>Mo, Mac, DC, HSC, T-subset</td>
<td>HLA-A, -B, -C, -F, and -G, HLA-B27 H-chain dimer? CMV UL18 S100A9 Dengue virus</td>
</tr>
<tr>
<td>LILRB3</td>
<td>4</td>
<td>Mo, DC, Gran</td>
<td>S. aureus Angiopoietin-like protein 2 and 5</td>
</tr>
<tr>
<td>LILRB4</td>
<td>2</td>
<td>Mo, Mac, DC, plasmablast</td>
<td>?</td>
</tr>
<tr>
<td>LILRB5</td>
<td>4</td>
<td>Mo, Mac</td>
<td>HLA-B7 HLA-B27 H-chain dimer Angiopoietin-like protein 2 and 5</td>
</tr>
<tr>
<td>LILRA1</td>
<td>4 or 2</td>
<td>Mo, Mac, DC</td>
<td>HLA-B27 HLA-B27 H-chain dimer HLA-C free H-chain</td>
</tr>
<tr>
<td>LILRA2</td>
<td>4</td>
<td>Mo, Mac, DC, Gran, T, NK</td>
<td>?</td>
</tr>
<tr>
<td>LILRA3</td>
<td>4</td>
<td>Mo, Mac, DC, B, T-Subset</td>
<td>HLA-C? HLA-A, HLA-G</td>
</tr>
<tr>
<td>LILRA4</td>
<td>4</td>
<td>pDC</td>
<td>BSA2</td>
</tr>
<tr>
<td>LILRA5</td>
<td>2</td>
<td>MO, PMN</td>
<td>?</td>
</tr>
<tr>
<td>LILRA6</td>
<td>4</td>
<td>Mo</td>
<td>?</td>
</tr>
</tbody>
</table>

DC, dendritic cell; Gran, granulocyte; HSC, hematopoietic stem cell; Mac, macrophage; Mo, monocyte; pDC, plasmacytoid dendritic cell; PMN, polymorphonuclear neutrophil.

### Nonconventional MHC-I ligands

A few of the LILRs interact with classical class I molecules in a more allele-specific manner than LILRB1 and LILRB2 or prefer the semidenatured free H-chains. LILRA1 and LILRA3 share preferential binding to HLA-C (17), but the significance...
LILRB1 and LILRB2 both interact with HLA-G (36). HLA-G expression is normally found on placental trophoblasts but it is also expressed by a variety of cancers. LILRB1 and LILRB2 are expressed on cell types that are important during placentaion such as NK cells and monocytes, suggesting the interaction of HLA-G and the LILRs could be highly selected for in humans (21). The affinity of LILRB1 and LILRB2 for HLA-G is above that for classical MHC-I, suggesting HLA-G might be a more potent ligand, and better functional recognition of HLA-G relative to classical MHC-I has been shown using NK cells that express LILRB1 (35–37). The ability of HLA-G to form dimers further enhances the binding. There remain many questions regarding when HLA-G acts through LILRs, including during tumor progression in which deviation of the inflammatory response by macrophages is pivotal. HLA-F is one of the least well understood of the nonclassical MHC-I proteins. LILRB1 and LILRB2 can bind to HLA-F (38). However, as HLA-F remains largely intracellular in normal conditions (38), the physiologic consequence of the binding by the LILRs is unclear. It is worth noting that HLA-G and HLA-F are thought to be more recent additions to the class I–like than HLA-E (39). In relation to this, when directly tested, no binding of LILRB1 can be detected to HLA-E (40, 41). It is curious that these receptors do not bind HLA-E because the α3 domain is so highly conserved (as illustrated in Ref. 30) (36). To our knowledge, binding to the HLA-E and HLA-G has not been tested for other types of LILRs, but given the conservation of the α3 domain, it is likely to follow the same pattern as for the classical molecules.

CD1. LILRB2 interacts with CD1d and CD1c, class I–like proteins that are more divergent than HLA-F or -G from the classical class I forms (42, 43). CD1 molecules associate with β2m and are involved in lipid Ag presentation to specialized NKT cells. Li et al. (42, 43) have shown that the contact site between LILRB2 and CD1d involves the two membrane distal Ig domains of LILRB2 and the Ag-binding domains of CD1d and can occur in cis. The interaction blocks the loading of lipid Ags onto CD1d and inhibits NKT activation. CD1c upregulation can apparently inhibit the regulatory effects of the LILRB2–CD1d interaction on Ag presentation by titrating away the LILRB2 (42, 43). There is some specificity on the side of the LILRs, as LILRB1 does not recognize CD1c or CD1d, but to our knowledge, other LILRs nor the mouse counterpart PIRB have not been tested in this regard. The studies published to date did not assess if LILRB2 interacts with CD1 in trans, and it is not clear when a trans interaction would occur naturally. The different expression patterns of the CD1 molecules could mean that LILRB2 regulates the CD1 pathway in cells such as dendritic cells that express LILRB2, but not typical B cells that express LILRB1. Perhaps B cells that are involved in lipid Ag presentation to NKT cells (44) use LILRB2 to regulate their function. The idea that LILRB2 binds to CD1 is remarkable because CD1 is an ancestral MHC-like molecule (39), and the interaction with the LILR family could predate the evolution of interactions with classical MHC-I, forcing the receptor to find the conserved regions of β2m and the α3 domain.

Pathogen-derived ligands

UL18. LILRB1 was first identified as the receptor for the MHC-I mimic in human CMV (1). The interaction with the
viral molecule is similar to the interaction with the endogenous MHC-I, except that the interface is much larger with more extensive contacts, which explains the 1000-fold higher affinity with UL18 (15, 45). The ability of UL18 to inhibit NK cells has been documented, suggesting that the primary function of UL18 is to subvert the NK response (46). However, LILRB1 is expressed on a range of cells that are involved during the response to CMV such as T cells, and there it has been shown in one report to costimulate the T cells by a yet-undefined signaling mechanism and may also stimulate NK cells that lack LILRB1 (46, 47). Another possibility is that UL18 could impact virus mechanism and may also stimulate NK cells that lack LILRB1 to costimulate the T cells by a yet-undefined signaling to CMV such as T cells, and there it has been shown in one follow-up study with mutant strains of S. aureus implicates lipoteichoic acid as important for the interaction of S. aureus with PIRB, but as there is no interaction with other bacteria that have lipoteichoic acid in their cell wall, lipoteichoic acid is not sufficient (51). Further studies are required to determine if lipoteichoic acid is the moiety involved in LILRB1 and B3 binding bacteria as well. Although the functional consequences of the bacteria binding to human LILRs in vivo remains unclear, the physiologic consequence of the PIRB–S. aureus interaction in mice suggests engaging PIRB provides immune evasion for bacteria, as PIRB-deficient mice have enhanced clearance of S. aureus. The situation with S. aureus is in contrast to an earlier report of an enhanced susceptibility to Salmonella in PIRB-deficient mice, which is thought to be a defect in control of replication within macrophages (52). Whether or not PIRB can bind Salmonella is not known, and it is also possible that the situation varies for bacteria such as Salmonella that replicate inside cells that express PIRB. In addition, prevention of lipoteichoic acid formation for the cell wall enhances bacterial virulence, perhaps suggesting a role for the stimulatory PIRA1 interaction as important to contain the infection in addition to other pattern recognition receptors known to sense lipoteichoic acid. Therefore, future studies should address defining the structure that the LILRs and PIRs interact with to explain the specificity for bacterial species and whether there is benefit to disrupting the interactions for treatment of sepsis. One important point relevant to how these interactions could be targeted is that MHC-I was not competing for the interaction with S. aureus, suggesting interactions with MHC-I in cis or trans are not regulating the interaction.

Host immunomodulatory proteins

Bone marrow stromal Ag 2 (BST2) was the first endogenous non–MHC-I–related ligand identified for an LILR family member and the first ligand defined for a family member that is activating (53). As its name suggests, BST2 is expressed on bone marrow stromal cells, but it is also on plasma cells and induced by type I IFN on a variety of cells. BST2 also goes by the name tetherin for its ability to prevent release of a wide range of enveloped viruses, although many viruses have methods to circumvent it (reviewed in Ref. 54). BST2 binds LILRA4, which is expressed on monocytes, immature dendritic cells, plasmacytoid dendritic cells, and plasmablasts. Counterintuitively for an activating receptor, LILRA4 interaction with BST2 decreases TLR7/9–mediated production of type I IFN and other proinflammatory mediators (53). However, DAP-12–coupled receptors also limit the TLR responses, and DAP12 signals through the same pathway as the LILRA4–associated FcRy chain (55). The molecular details of the physical interaction between LILRA4 and BST2 remain to be resolved, and BST2 has no obvious relationship to other LILR ligands except an overall coiled-coil structure seen in the envelope protein of dengue virus. BST2 is composed of a coiled-coil dimer that loops out from the membrane and is localized to lipid rafts by a GPI anchorage at the C terminus. Clarification of how LILRA4 binds to BST2 will be required to predict if this function is conserved in any other species and may provide insight into putative ligands of the related LILRs. Angiopoietin family. LILRB2 was identified as the receptor for all seven angiopoietin-like proteins through an expression-cloning
approach to identify receptors for these orphan secreted proteins (56). These were the first soluble ligands to be identified for LILRs, and binding is quite strong, with a dissociation constant in the nanomolar range for angiopoietin-like protein 5. The high $K_d$ is in keeping with signaling by a soluble ligand, although still not as high as many cytokine or chemokine interactions. A weaker interaction with LILRB3 and LILRB5 with angiopoietin-like protein 2 and 5 was also reported, and the interaction is specific, as several other LILRs tested did not display detectable binding, although LILRA3, -5, and -6 were not tested. In this case, the details of the binding have been characterized. The interaction involves the first and fourth Ig domains of the receptor and maps to short stretches in each with a similar motif GRY/GTY and critical glycine and tyrosine residues (57). The interaction extends to mouse PIRB and can be exploited to promote proliferation and maintenance of human and mouse hematopoietic stem cells in mouse models (56, 57). The effect of angiopoietins through LILRB2 illustrates the context-dependent signaling of these receptors because the binding of the soluble angiopoietins increases phosphorylation of CAMK-2, a signaling cascade that is important for stem cell maintenance. It is worth noting that defects in hematopoiesis have not been described for PIRB-deficient mice and that angiopoietin-like proteins are made by a wide range of cell types and in response to various stimuli, making it hard to predict the full physiologic implications of the binding to LILRBs in humans. However, it might be possible to exploit the pathway for purposes of long-term reconstitution of the immune system (56).

**S100A.** One recent study has implicated an interaction of LILRB1 with a damage-associated molecular pattern protein, S100A9. The interaction was found in a study to identify non-MHC-I ligands of LILRB1 on HIV-infected dendritic cells, because LILRB1 upregulation is associated with enhanced function in this context (58). The two other known receptors for S100A9 are TLR4 and receptor for advanced glycation end products (RAGE), and they are generally thought to promote inflammation. The findings of the interaction between LILRB1 and S100A9 await confirmation by other studies, as does better characterization of interaction. However, S100A9 can also act as a soluble tetramer, and stimulating LILRB1+ NK cells with exogenous tetrameric S100A9 marginally increases TNF-α production and produces some enhanced anti-HIV activity compared with unstimulated NK cells (58). The S100A9 protein can be held on the surface of an APC and could regulate other cells through LILRB1 in that context, too. It is tempting to speculate that LILRs could be important for transducing signals from these or other damage-associated molecular patterns to control inflammation, and further studies with other cell types expressing LILRB1 could be informative as well as exploring the possibility that other LILRs bind to S100A9.

**CNS-derived ligands**

**Nogo receptor inhibitors.** The Nogo receptor limits axonal growth through interactions with several components of myelin, and studies with Nogo receptor–deficient mice indicated there are other receptors involved in the process. In a screen for the additional receptors for Nogo, Atwal et al. (59) identified LILRB2 using an expression-cloning strategy. They also found that LILRB2 binds two additional known Nogo receptor ligands, myelin-associated glycoprotein (MAG) and oligodendrocyte myelin glycoprotein (OMgp), and the binding is very strong, with a nanomolar range dissociation constant for MAG (59). PIRB binds all three known Nogo receptor ligands derived from myelin, Nogo, MAG, and OMgp, illustrating the conservation of the interaction and suggesting it is biologically important. Characterization of the functional consequences and details of the interaction have only been studied for PIRB, and it is unclear what can be extrapolated to the human system at this point. Nonetheless, PIRB is expressed on particular neurons, and subsequent studies by the Shatz group and others (60–63) have shown that PIRB regulates axon regeneration in a SHP-dependent manner and even neural stem cell survival. PIRB has six Ig domains, and, similar to LILRB2, the first two Ig domains mediate the interaction with mouse MHC-I molecules (64). In contrast, the third to sixth domains mediate the strongest binding with Nogo, but the first two alone also interact but with a 10-fold lower dissociation constant (64). Takai et al. (64) used surface plasmon resonance to define binding constants with Nogo and PIRB that are submicromolar. Furthermore, they found that Nogo competes with MHC-I for binding to PIRB (64). Interestingly, Takai et al. (64) also found expression of Nogo inhibitor proteins in immune cells outside the CNS and that deletion of Nogo impacts the response of mast cells to LPS. The latter observation suggests a *cis* interaction between PIRB and endogenously produced Nogo regulates TLR signaling. Nogo-B is also expressed by mouse and human endothelial cells, and a recent report shows that endothelial-derived Nogo-B is important in downregulating macrophage-mediated vascular remodeling through PIRB (65). Furthermore, PIRA also binds to Nogo, although the binding strength is 10-fold less and only detected for the third to sixth domains. The functional importance of the interaction with PIRA with Nogo has not been determined, but some functions of PIRA are known, such as regulating cytokine-driven maturation of eosinophils (66), providing some idea of the possibilities. The measured interaction with PIRA also begs the question of which other LILRs might interact with the NogoR ligands as well. The difference in domain organization between PIRB and LILRB2 makes it hard to predict how LILRB2 interacts with Nogo, MAG, and OMgp, but it is most likely that the interaction would compete with MHC-I as well. Whether or not LILRB2 is also expressed by human neurons is unclear, but there is expression within the CNS that is likely due at least in part to immune cells within the CNS such as microglia cells and would also be present on infiltrating monocytes during disease states. Moreover, it will be very interesting to determine if the myelin inhibitors of the Nogo pathway are also expressed in human cells outside of the CNS. It is also possible that when the myelin sheath is being destroyed in demyelinating diseases such as multiple sclerosis, interactions of LILRB2 on immune cells within the CNS play a regulatory role through this axis.

**β amyloid.** Soluble oligomeric β amyloids are known to damage neural synapses and impair synaptic plasticity. Based on earlier studies that implicated PIRB in regulating synaptic plasticity, Kim et al. (67) tested if PIRB was a receptor for β amyloids and found that the oligomeric form of β amyloid peptide Aβ42 is a PIRB and LILRB2 ligand. The binding is specific in that there is no detectable interaction with two PIRA receptors tested, rat PIRB, LILRB1, or LILRB3. The interaction maps to
the first and second Ig-like domains of both LILRB2 and PIRB, suggesting it would compete with MHC-I as well. PIRB-deficient mice were spared damage to synaptic plasticity in the mouse Alzheimer model, providing a functional consequence for loss of PIR-B revealed in a murine Alzheimer model that generates β amyloids (67). In this case, the damage is suggested to be directly through stimulation of a coflin-linked pathway in cortical neurons that express PIRB. Although follow-up studies that confirm LILRB2 is expressed in neurons and not just resident APCs are required, the study generates an obvious target to protect neurons in such types of neurodegenerative disease. Other questions remain, such as if any of the LILRs not tested share the specificity for amyloid proteins and whether there are functions for the interaction outside the CNS.

The discovery by Atwal et al. (59) and Kim et al. (67) of interactions of LILRB2 and PIRB with these different types of proteins important to the pathophysiology of neurodegenerative and inflammatory diseases within the CNS is provocative. To date, the studies have focused on the role of these interactions in neurodevelopment and synaptic function as opposed to roles in the immune response. Future studies that extend to immune regulation will likely provide very interesting information.

**Implications and future questions**

The LILR family continues to emerge as a very complex and pleiotropic receptor system. The broad expression of LILRs on sentinel cells of the immune system suggest that the individual receptors play diverse and specific roles in immune responses in a context-dependent manner. Although first appreciated for their interaction with MHC-I proteins, it is becoming obvious that the importance of the interaction with MHC-I relative to the emerging list of diverse ligands needs to be clarified as well as their physiological roles. The newly described functions include modulating Ag processing, growth, and differentiation. The interplay between soluble immunomodulatory proteins such as S100A9 or angiopoietin-like proteins and ligands that are cell-surface proteins will require further investigation. The potential to interact in cis should also be considered in investigating the function of other family members, particularly for those with lower affinity for MHC-I as well as the many disparate ligands. The wide variety of endogenous non-MHC LILRB2 ligands and the expression pattern of the receptor raise several questions with regards to its functions and its potential involvement in physiological processes other than immunomodulation. Given the range of molecules identified to date of the other members of the family, it should/would be beneficial to cast a wide net in searching for the ligands for the members of the family that remain without known ligands (Table I).

The interaction of LILRB1 with bacterial pathogens suggests they are under evolutionary pressures from these pathogens, but also suggests additional potential function as receptors that assist in monitoring and perhaps internalization of bacteria. This has been observed for parallel receptor families in humans as well as other species such as FcRs and the carinoembryonic Ag-related cell adhesion molecule family that is targeted by bacteria (reviewed in Ref. 68) and even the distantly related catfish receptors that mediate phagocytosis (69). In particular, there is a potential parallel with carinoembryonic Ag-related cell adhesion molecules, as these ITIM-bearing receptors are important in the handling of bacteria by innate immune cells, and one bacteria, *Neisseria gonorrhoeae*, has exploited a receptor to promote its infection of the genital tract (70). Given the propensity for genetic diversity within the receptor family, it seems likely that some of the diversity will impact the interactions with the growing list of non–MHC-I ligands. It is also possible that polymorphisms in LILR could alter interaction with the microbiome and exert an influence on autoimmune disease, an area of tremendous general interest of late. The recent studies suggest there are many potential areas for therapeutic intervention in infection, such as blocking LILRB1 in dengue virus–infected patients.

The discovery of PIRB expression in mouse neurons and NogoR1 inhibitor expression outside the CNS strengthens overlap between immune and CNSs, two systems that underwent parallel diversification in the same evolutionary window of vertebrate radiation. It will be exciting to determine which LILRs are expressed in human neurons and the affiliated developmental and repair processes as well as how their expression in the Ag-presenting and immunomodulatory cells within the CNS relates to neuroinflammation. The binding to amyloid proteins also tempts speculation that these receptors have properties of scavenger receptors. PIRB/LILRB2 in CNS appears to use different downstream effectors in addition to SHP-2 in response to β-amloid, illustrating that the cellular context influences the signaling properties of the LILRs. There are a few examples in which receptors with ITIMs promote inflammatory responses or those with ITAMs limit them, although some of these areas warrant further studies to solidify the results.

Cancer therapy is another area to be considered in the context of LILRs. HLA-G expression has emerged as a marker of poor prognosis, and altered LILR expression within a tumor context has been reported (reviewed in Ref. 71). There is already a report that LILRB1 can limit the NK-mediated Ab-dependent cellular cytotoxicity response associated with Ab-based therapies to treat cancer (72). Therefore, targeting the LILR interactions with classical and nonclassical MHC-I proteins may provide another avenue to reprogram the immune response akin to the successful checkpoint blockade strategies employed to restore tumor-specific T cells responses.

**Conclusions**

In conclusion, the growing list of ligands for the LILR family provides much fodder for future investigation, and time will reveal the extent to which the new information can be exploited for understanding and treating disease.

**Acknowledgments**

We thank Drs. Mary Carrington, James Stafford, and Kathy Magor and the members of the Burshyn and Stafford laboratories for many helpful discussions and Kang Yu for comments on the manuscript.

**Disclosures**

The authors have no financial conflicts of interest.

**References**


