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Stimulatory and Inhibitory Killer Ig-Like Receptor Molecules Are Expressed and Functional on Lupus T Cells

Dhiman Basu,* Ying Liu,* Ailing Wu,* Sushma Yarlagadda,* Gabriela J. Gorelik,* Mariana J. Kaplan,* Anura Hewagama,* Robert C. Hinderer,* Faith M. Strickland,* and Bruce C. Richardson2*†

T cells from lupus patients have hypomethylated DNA and overexpress genes normally suppressed by DNA methylation that contribute to disease pathogenesis. We found that stimulatory and inhibitory killer cell Ig-like receptor (KIR) genes are aberrantly overexpressed on experimentally demethylated T cells. We therefore asked if lupus T cells also overexpress KIR, and if the proteins are functional. T cells from lupus patients were found to overexpress KIR genes, and expression was proportional to disease activity. Abs to the stimulatory molecule KIR2DL4 triggered IFN-γ release by lupus T cells, and production was proportional to disease activity. Similarly, cross-linking the inhibitory molecule KIR3DL1 prevented the autoreactive macrophage killing that characterizes lupus T cells. These results indicate that aberrant T cell KIR expression may contribute to IFN overproduction and macrophage killing in human lupus, and they suggest that Abs to inhibitory KIR may be a treatment for this disease. The Journal of Immunology, 2009, 183: 3481–3487.

Impaired T cell DNA methylation contributes to the development of lupus-like diseases. Injecting experimentally demethylated T cells into syngeneic mice causes lupus-like autoimmunity (1, 2), as does decreasing T cell DNA methyltransferase 1 expression in transgenic mice (3). Similarly, reports that the DNA methylation inhibitors procainamide and hydralazine cause anti-nuclear Abs in most patients receiving these drugs, and a lupus-like disease in a genetically predisposed subset (4), also support a causative role for DNA demethylation in lupus-like autoimmunity.

Methylation is a repressive DNA modification, suppressing genes unnecessary or potentially detrimental to normal cellular function, but for which the cell expresses the requisite transcription factors. Inhibiting DNA methylation in CD4+ T cells causes aberrant overexpression of genes that contribute to the development of autoimmunity in adoptive transfer models. Demethylation of ITGAL (CD11a) causes LFA-1 overexpression, resulting in MHC-specific autoreactivity (5, 6), and demethylation of PRF1 results in perforin overexpression that contributes to autoreactive macrophage (Mφ) killing and release of antigenic nucleosomes (7, 8). Similarly, demethylation of TNFSF7 and CD40LG results in overexpression of the B cell costimulatory molecules CD40L and CD70, contributing to Ab overproduction (9, 10).

Identical changes in DNA methylation, gene expression, and cellular function characterize a CD4+ T cell subset in patients with active lupus, and the degree of demethylation and gene overexpression are directly related to disease activity. ITGAL demethylation results in LFA-1 overexpression on autoreactive T cells (10), PRF1 demethylation in CD4+ T cells results in aberrant perforin expression contributing to autologous Mφ killing (7), and CD40LG demethylation contributes to B cell overstimulation in women with active lupus (9).

The evidence indicating a role for T cells with hypomethylated DNA in lupus pathogenesis suggests that Abs or other recombinant molecules designed to deplete or inactivate this subset may be therapeutic in human lupus, and be more selective and safer than current modalities such as corticosteroids or cyclophosphamide. The ideal therapeutic target would be a gene expressed on demethylated but not normal T cells, and which inhibits autoreactive responses when ligated.

We recently identified the killer cell Ig-like receptor (KIR) gene family as methylation sensitive in human T cells (11). The KIR genes constitute a polymorphic family normally expressed on NK cells but rarely on normal T cells (12). KIR molecules on NK cells recognize class I MHC molecules and possibly other self ligands, and they either stimulate or inhibit killing and secretion of inflammatory cytokines depending on the cytoplasmic domain (13). Therefore, in the present study we investigated whether experimentally demethylated T cells aberrantly express KIR genes, both stimulatory and inhibitory, and whether KIR expression has functional implications by cross-linking stimulatory KIR to induce IFN-γ secretion, and inhibitory KIR to prevent autoreactive Mφ killing. Furthermore, since lupus T cells have hypomethylated DNA and aberrantly overexpress other methylation-sensitive genes, we hypothesized that the KIR genes would be similarly overexpressed in T cells from patients with active lupus. We also hypothesized that Abs to inhibitory KIR molecules might inhibit the autoreactive, cytotoxic responses that characterize this subset in lupus patients. We therefore compared KIR expression and function on experimentally demethylated T cells and on T cells from patients with active and inactive systemic lupus erythematosus (SLE).
Materials and Methods

Subjects

Healthy subjects were recruited by advertising. Lupus patients met criteria for lupus (14) and were recruited from the Michigan Lupus Cohort and the inpatient services at the University of Michigan Hospitals. Disease activity was quantitated using the SLE disease activity index (SLEDAI) (15). The protocols were reviewed and approved by the University of Michigan Institutional Review Board.

T cell isolation

PBMC were isolated from peripheral blood by density gradient centrifugation, and T cells were purified using the MACS Pan-T cell isolation kit (Miltenyi Biotec) and instructions provided by the manufacturer. The Pan-T cell isolation kit removes non-T cells, that is, B cells, NK cells, dendritic cells, monocytes, granulocytes, and erythrocytes, using a cocktail of biotin-conjugated Abs against CD14, CD16, CD19, CD36, CD56, CD123, and CD235a (glycophorin A). The non-T cells were labeled with anti-biotin microbeads and magnetically depleted, following the manufacturer’s instructions. Following collection of the unlabeled T cells, CD4+ and CD8+ cells were further isolated by negative selection using CD4+ and CD8+ isolation kits (Miltenyi Biotec). The resultant CD4+ and CD8+ T cells were free of NK and NKT (CD56+) cells, as determined by staining with PE-anti-CD56 Ab (BD Pharmingen) and by flow cytometry.

KIR genotyping

KIR genotypes were determined using a KIR typing kit (Miltenyi Biotec), testing the presence of 15 KIR genes and pseudogenes, using protocols provided by the manufacturer.

Antibodies

Unconjugated and PE-conjugated anti-CD158d (KIR2DL4) were purchased from R&D Systems, and unconjugated and PE-conjugated anti-NKB1 (KIR3DL1), anti-perforin Abs, and isotype-matched control Abs were obtained from BD Pharmingen. Anti-CD4-Cy5, anti-CD8-FITC, and PE-conjugated Abs to KIR2DS2 (anti-CD158a/h) and KIR3DL1/3DS1 (CD158e1/e2) were from Beckman Coulter, and 2DL1/2DL3/2DS2 (anti-CD158 b1/b2/j) (GL183) was purchased from R&D Systems. Ten micrograms of each PE-conjugated KIR Ab was mixed to form a “cocktail” used to stain the cells. All labeling procedures were performed on ice in PBS containing 10% horse serum and normal human AB serum (Intrvitrogen) and sodium azide. Intracellular staining for perforin was performed on cells permeabilized for 20 min on ice with Cytofix/Cytoperm solution (BD Pharmingen). Following staining, the cells were fixed in 1% paraformaldehyde and kept at 4°C until analyzed.

Flow cytometric analysis

Multicolor flow cytometry was performed using previously published protocols (16).

IFN-γ stimulation

Anti-KIR2DL4 or isotype-matched control Abs were diluted in PBS, then allowed to bind to flat-bottom 96-well microtiter plates (Costar; Corning) for 3 h at 37°C. The plates were then washed and 2 × 10⁶ T cells were added per well in RPMI 1640 supplemented with 10% FBS (Invitrogen) and express KIR genes following treatment with the DNA methylation inhibitor 5-azaC. PBMC from 11 healthy subjects were stimulated with PHA, treated with 5-azaC, and then KIR expression was measured on untreated and treated CD4+ and CD8+ cells using a “cocktail” of anti-KIR Abs and flow cytometry as described in Materials and Methods. Fig. 1 confirms that 5-azaC

Table I. KIR genes in lupus patients and controls

<table>
<thead>
<tr>
<th>KIR</th>
<th>SLE (%) (N = 35)</th>
<th>Control (%) (N = 35)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2DL4</td>
<td>35 (100)</td>
<td>35 (100)</td>
</tr>
<tr>
<td>2DL2</td>
<td>35 (100)</td>
<td>23 (66)</td>
</tr>
<tr>
<td>3DL2</td>
<td>33 (94)</td>
<td>35 (100)</td>
</tr>
<tr>
<td>3DL3</td>
<td>30 (86)</td>
<td>34 (97)</td>
</tr>
<tr>
<td>2DL3</td>
<td>30 (86)</td>
<td>32 (91)</td>
</tr>
<tr>
<td>2DL1</td>
<td>30 (86)</td>
<td>29 (83)</td>
</tr>
</tbody>
</table>

Statistical analyses

The significance of differences between means was determined using Student’s t test, and the relationship between disease activity and measured parameters were determined by linear regression and ANOVA using Systat software.

Results

5-Azacytidine (5-azaC) induces KIR expression on T cells

The KIR gene family is highly polymorphic, containing up to 14 genes and pseudogenes, and multiple alleles exist, resulting in extensive variability between individuals (18). We therefore genotyped a panel of 35 lupus patients and 35 healthy controls. Both the lupus and control subjects were primarily (>85%) Caucasian. Table I shows the most common alleles observed in the lupus patients compared with controls. 2DL4 was present in everyone, as reported (18), and the frequencies of the other alleles shown resemble those reported by others for Caucasians (19). Other alleles were variably present at a lower frequency in the lupus patients and controls, but given the limited number of subjects studied the significance of the variability is uncertain.

We then confirmed that CD4+ and CD8+ T cells demethylate and express KIR genes following treatment with the DNA methylation inhibitor 5-azaC. PBMC from 11 healthy subjects were stimulated with PHA, treated with 5-azaC, and then KIR expression was measured on untreated and treated CD4+ and CD8+ cells using a “cocktail” of anti-KIR Abs and flow cytometry as described above.

FIGURE 1. KIR expression on 5-azaC-treated CD4+ and CD8+ T cells. PBMC from 11 healthy subjects were stimulated with PHA, treated with 5-azaC, then 72 h later stained with anti-CD4-CyChrome, anti-CD8-FITC, and a cocktail of PE-conjugated Abs to KIR 3DL1, 2DS2, 2DL1, and 2DL1/2DL3/2DS2 and then analyzed by flow cytometry. Dark hatched bars represent PHA-stimulated, untreated T cells, and the light hatched bars represent PHA-stimulated, 5-azaC-treated T cells.

Mφ killing assays

Monocytes were purified from PBMC by adherence to round-bottom microtiter wells and labeled with 51Cr as previously described (17). Purified anti-KIR3DL1 or isotype-matched control Abs were added where indicated. Purified T cells were then cultured with the Mφ for 18 h at 37°C in room air supplemented with 5% CO2, and 51Cr release was measured as described (17). Results are presented as the means ± SEM of three to four determinations per data point.
significantly increases KIR expression on both CD4⁺ and CD8⁺ T cells.

KIR is functional in 5-azaC-treated T cells

Stimulatory and inhibitory KIR functions were tested in 5-azaC-treated CD4⁺ and CD8⁺ T cells. mAbs are available for some but not all KIR gene products, and some of the Abs are cross-reactive with multiple KIR genes. However, Abs reactive with CD158d (KIR2DL4), a stimulatory molecule present in all donors, and CD158e1/2 (anti-NKB1, KIR3DL1), an inhibitory molecule present in most but not all individuals (19), are available. PBMC from three healthy individuals were stimulated with PHA and treated with 5-azaC as before. CD4⁺ and CD8⁺ T cells were isolated using magnetic beads and then stimulated with immobilized anti-KIR2DL4 or an equal concentration of isotype-matched control Ig. IFN-γ release was measured by ELISA. Fig. 2A confirms that anti-KIR2DL4, but not the control Ab, stimulates IFN-γ synthesis by 5-azaC-treated CD4⁺ and CD8⁺ T cells.

Inhibitory KIR function was tested by culturing 5-azaC-treated, magnetic bead-purified T cells from a KIR3DL1-positive subject with ⁵¹Cr-labeled autologous Mφ, with or without graded amounts of anti-KIR3DL1 or isotype-matched control Ig. IFN-γ release was measured by ELISA. Fig. 2B shows that demethylated T cells spontaneously kill autologous Mφ, as we previously reported (17), and that the killing is inhibited with anti-KIR3DL1 but not control Ig. Similar results were seen in a confirming experiment (37 ± 8% vs 66 ± 6% cytotoxicity (mean ± SEM), KIR3DL1 vs control, p = 0.016). Taken together, these results indicate that stimulatory and inhibitory KIR function is intact in KIR-expressing, demethylated T cells.

Lupus T cells express KIR

We then asked if KIR is expressed on lupus T cells. Fig. 3A shows T cells from a lupus patient stained with anti-CD4 and the cocktail of anti-KIR Abs, and Fig. 3B shows cells similarly stained with anti-CD8 and the anti-KIR mixture. KIR is expressed on a subset of T cells. Fig. 3C compares the percentage of KIR⁺CD4⁺ and KIR⁺CD8⁺ T cells in PBMC from 16 lupus patients and 16 age- and sex-matched controls. There is a significant increase in KIR expression on both subsets in T cells from the lupus patients, with a somewhat greater percentage of CD8⁺ T cells expressing KIR relative to CD4.

Previous studies demonstrated that CD11a, perforin, and CD40L overexpression is directly proportional to disease activity. We therefore compared KIR expression with disease activity in the 16 lupus patients studied in Fig. 3. Fig. 4A shows

FIGURE 2. 5-azaC-induced KIR molecules are functional. T cells were stimulated with PHA and treated with 5-azaC as in Fig. 1. A. The 5-azaC-treated T cells were fractionated into CD4⁺ and CD8⁺ cells using magnetic beads, then cultured with immobilized anti-KIR2DL4 or an isotype-matched IgG and IFN-γ release was measured by ELISA. The light hatched bars represent 5-azaC-treated cells and the dark hatched bars untreated cells. B, the treated T cells were cultured with ⁵¹Cr-labeled autologous monocytes/Mφ and the indicated concentrations of anti-KIR-3DL1 or isotype-matched control IgG, and ⁵¹Cr release was measured 18 h later. Results are presented as the means ± SEM of three determinations.

FIGURE 3. Lupus T cells express KIR molecules. A, PBMC from a representative lupus patient were stained with anti-CD4-CyChrome and the cocktail of PE-conjugated anti-KIR Abs and then analyzed by flow cytometry. The percentage CD4⁺KIR⁺ is shown in the upper right quadrant. B, PBMC from the same subject were similarly stained and analyzed for CD8 and KIR. The percentage CD8⁺KIR⁺ is again shown in the upper right quadrant. C, PBMC from 16 lupus patients (light hatched bars) and 16 age- and sex-matched controls (dark bars) were stained for CD4, CD8, and KIR as in A and B. Results are represent the percentage KIR⁺CD4 or CD8 cells and are presented as the means ± SEM of the 16 determinations.
the relationship between the percentage of CD4 \(^{+}\) KIR\(^{+}\) T cells and lupus disease activity as measured by the SLEDAI, and Fig. 4B similarly compares the percentage of CD8 \(^{+}\) KIR\(^{+}\) T cells with the SLEDAI. The number of KIR\(^{+}\) T cells is proportional to disease activity, similar to other methylation-sensitive genes (\(p = 0.059\) for CD4 \(^{+}\) KIR\(^{+}\) cells, and \(p = 0.016\) for CD8 \(^{+}\) KIR\(^{+}\) cells).

KIR genes are also expressed on “senescent” CD4\(^{+}\)CD28\(^{-}\) T cells (20). Cells in this subset have shortened telomeres, decreased replicative potential, express large amounts of proinflammatory molecules such as IFN-\(\gamma\) and perforin (21), and are found in the elderly (22) as well as in patients with chronic inflammatory diseases such as rheumatoid arthritis (23). Interestingly, these cells are cytotoxic for endothelial cells, and they have been cloned from ruptured atherosclerotic plaques in patients dying from myocardial infarctions (21). We therefore addressed the possibility that KIR was primarily expressed on CD4\(^{+}\)CD28\(^{-}\) T cells in lupus, similar to rheumatoid arthritis. Fig. 5 compares KIR expression, again measured with the anti-KIR cocktail, on CD4\(^{+}\)CD28\(^{-}\) and CD4\(^{+}\)CD28\(^{-}\) T cells from six lupus patients and six healthy age- and sex-matched controls. The healthy controls had small numbers (about \(\leq 1\%\)) of KIR\(^{+}\) T cells in both subsets. In contrast, KIR was expressed on significantly \((p < 0.05)\) greater numbers of CD4\(^{+}\)CD28\(^{-}\) as well as CD4\(^{+}\)CD28\(^{-}\) T cells from lupus patients relative to the controls. There was a trend for greater KIR expression on CD4\(^{+}\)CD28\(^{-}\) T cells relative to the CD4\(^{+}\)CD28\(^{-}\) subset in the lupus patients, but was of borderline significance \((p = 0.078)\).

**KIR2DL4 is demethylated in lupus T cells**

Our earlier report on T cell DNA methylation and KIR expression demonstrated demethylation of 7 CG pairs, located between bp −158 and −126 relative to the start site, in the 2DL4 promoter of 5-azaC-treated CD4\(^{+}\) and CD8\(^{+}\) T cells. MS-PCR was used to compare methylation of CG pairs located −158 and −26 in T cells from 5 lupus patients and age- and sex-matched controls (Fig. 6). There was significantly \((p = 0.006)\) less methylation of the KIR2DL4 promoter in the lupus T cells relative to controls, thus resembling T methylation patterns observed in normal T cells demethylated with 5-azaC (24).
FIGURE 4. For each of the nine lupus patients. Reduced is plotted against the SLEDAI.

FIGURE 7. KIR2DL4 on lupus T cells is functional. A, T cells from nine lupus patients and nine age- and sex-matched controls were stimulated with immobilized anti-KIR2DL4 (light hatched bars) or isotype matched control IgG. B, The amount of IFN-γ produced is plotted against the SLEDAI for each of the nine lupus patients. Regression analysis was performed as in Fig. 4.

FIGURE 8. KIR3DL1 inhibits autoreactive monocyte/Mϕ killing by lupus T cells. T cells from six lupus patients were cultured with 51Cr-labeled autologous Mϕs alone, with anti-KIR3DL1, or with isotype-matched IgG. Results are presented as the means ± SEM of the nine determinations. B, The amount of IFN-γ produced is plotted against the SLEDAI for each of the nine lupus patients. Regression analysis was performed as in Fig. 4.

Discussion
KIR genes are expressed on a small subset of CD4⁺ and CD8⁺ T cells in healthy individuals, and on a somewhat larger senescent CD28⁻ subset found in patients with acute coronary syndromes (unstable angina and acute myocardial infarctions), chronic inflammatory diseases such as rheumatoid arthritis, and in the elderly (20–23). This report describes KIR expression on both CD28⁺ and CD28⁻ T cells from patients with active lupus. The mechanism appears to involve demethylation of regulatory elements, and it confers INF-γ secretion and cytotoxic function on the cells affected.

The distribution of KIR genes was similar in lupus patients and controls, although the number of subjects studied was relatively small. However, a larger study from Germany also failed to find an association of specific KIR genes with SLE (25). We found a somewhat different distribution of KIR genes in lupus patients and controls relative to this report (25), likely reflecting a different ethnic makeup of the two populations (19) and/or the smaller number of subjects studied in the present report.

KIR molecules on NK cells have stimulatory or inhibitory functions, depending on the length of the cytoplasmic domain. KIR molecules with short cytoplasmic tails, designated by the “S” in the name, are stimulatory, while molecules with longer (“L”) cytoplasmic domains are inhibitory, with the exception of 2DL4, which stimulates IFN-γ secretion (13). KIR molecules on T cells serve similar functions. Others have confirmed that KIR molecules on the senescent CD4⁺ CD28⁻ subset have similar stimulatory function, as measured by IFN-γ secretion (26), or as measured by redirected killing assays (20). KIR function on 5-azaC-treated T cells appears to serve similar functions. We find that cross-linking KIR2DL4 stimulates IFN-γ secretion, and that cross-linking KIR3DL1 inhibits autoreactive cytotoxic responses to autologous Mϕs. Thus, the necessary signaling pathways are present in the demethylated T cells to permit KIR function analogous to those found in NK cells. However, since the Mϕ killing we used in this report is an autologous system, one would expect that inhibitory KIR molecules recognizing self ligands on the Mϕs would prevent the killing. It is possible that a stronger interaction between anti-KIR Abs and the KIR molecules than between KIR and its ligands would result in a stronger inhibitory signal.

T cell DNA demethylates in lupus in proportion to disease activity, and we have found that genes activated by 5-azaC in T cells, including ITGAL (CD11a), PRF1 (perforin), TNFSF7 (CD70), and CD40LG (CD40L) are similarly demethylated and expressed in CD4⁺ T cells from lupus patients with active disease (5, 8–10). The KIR gene family appears to be similarly affected in lupus, with expression directly proportional to disease activity. To the best of our knowledge, this is the first report of T cell KIR expression in lupus. The observation that expression is increased on both CD28⁺ and CD28⁻ T cells in lupus is potentially interesting. KIR expression on senescent CD28⁻ cells is well described in the literature (20, 21, 23). However, the KIR genes were also overexpressed on the CD28⁻ subset in lupus relative to age- and sex-matched controls. We have reported that inhibiting DNA methylation in...
otherwise normal cloned or polyclonal CD4+ T cells induces autoreactivity (27), and that the demethylated T cells in lupus demonstrate similar autoreactivity (17). It is possible that the autoreactivity in lupus results in chronic stimulation leading to senescence. This is consistent with in vitro models where KIR expression appears on chronically stimulated T cells, correlating with loss of CD28 expression (28).

Expression of KIR molecules on T cells may contribute to lupus pathogenesis. IFNs contribute to inflammatory processes in SLE. While type I IFN overproduction plays an important role (29), KIR+ T cells responding to self class I MHC or other self molecules may also contribute through IFN-γ production (30). Furthermore, autoreactive Mø killing by demethylated T cells results in increased amounts of antigenic apoptotic material contributing to autoantibody responses in murine systems and likely in human lupus (31). This autoreactive response may be mediated at least in part by stimulatory KIR molecules. The observation that cross-linking inhibitory KIR molecules prevents this killing suggests a potential therapeutic approach to lupus, based on recombinant Abs to inhibitory KIR molecules. Prevention of Mø killing may decrease antigenic apoptotic material, helping to decrease the autoantibody response. Furthermore, since demethylated T cells are sufficient to cause lupuslike autoimmunity, anti-KIR Abs may deplete the demethylated subset also ameliorating the disease. NK cells would also be depleted, but this subset may be functionally impaired in human SLE (32). Furthermore, KIR genes are clonally expressed on NK cells (33), so it is possible that only a subset would be affected. Inhibiting DNA methylation also induces expression of suppressed KIR genes in NK cells (33), but whether DNA methylation is impaired in lupus NK cells is unknown. Interestingly, NK and NKT cells are stimulated by hypomethylated DNA to secrete IFN-γ (34, 35), and immune complexes containing hypomethylated DNA can be found in the peripheral circulation of patients with active lupus (36). However, this NK response is diminished in lupus patients (37), and NK cell numbers are reduced and have impaired function in lupus (38), so the relevance of this response to lupus pathogenesis is unclear.

In summary, KIR molecules are aberrantly overexpressed in T cells from patients with active lupus. They may contribute to disease pathogenesis by promoting killing of Mø and release of IFN-γ. Since KIR+CD4+CD28− T cells have been implicated in the pathogenesis of acute coronary syndromes, the KIR molecules may also play a role in the cardiovascular complications of human SLE. Importantly, KIR expression may serve as a marker for pathologic T cells in lupus, and that recombinant Ab approaches designed to target and deplete this subset, and potentially inactivate it as well, may be useful therapeutically.

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Disclosures
The authors have no financial conflicts of interest.

References


