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Anti-KIR antibody enhancement of anti-lymphoma activity of natural killer cells as monotherapy and in combination with anti-CD20 antibodies

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Key Points

- Blockade of inhibitory KIRs with MHC class I antigens on lymphoma cells by anti-KIR antibodies augments NK-cell spontaneous cytotoxicity.
- In combination with anti-CD20 mAbs, anti-KIR induces enhanced NK cell–mediated, rituximab-dependent cytotoxicity against lymphoma.

Introduction

Immune checkpoint blockade represents a promising cancer therapy that aims to restore an efficient antitumoral response mediated by endogenous immune cells.1 Antibodies to CTLA-4, an inhibitory receptor that dampens T-cell receptor (TCR) signaling, enhance immune cell function by blocking a negative regulator. CTLA-4 shares CD80 (B7.1) and CD86 (B7.2) as ligands with the TCR costimulatory receptor CD28. The intracellular signals transduced by the TCR, CD28, and CTLA-4 determine the outcome of T-cell activation.2 The therapeutic concept of immunomodulation was validated by the approval of anti–CTLA-4 ipilimumab in metastatic melanoma, thus increasing overall survival.1,3 Other inhibitory receptors of T-cell function, such as PD-1 and LAG-3, are being targeted by therapeutic monoclonal antibodies (mAbs) in clinical and preclinical development.1,4,5

As a corollary to targeting negative regulators of T cells, we hypothesized that the killer cell immunoglobulin-like receptor (KIR) family of natural killer (NK) cell negative regulators would represent a novel and active class of immunotherapy.6 Indeed, NK cells play critical roles in host defense against infections and tumors by secreting immunoregulatory cytokines and by killing infected or transformed cells. The activation of NK-cell effector function is regulated by multiple types of activating and inhibitory receptors, including KIR, that recognize ligands expressed on potential target cells. The balance between positive and negative signals transmitted via these NK receptors determines whether or not a target cell is killed by an NK cell.7 In addition, lack of KIR–HLA class I interactions has been associated with potent NK-mediated antitumor efficacy and increased survival in acute myeloid leukemia (AML) patients upon haplo-identical stem cell transplantation from KIR mismatched donors.8 To exploit this pathway pharmacologically, the fully human mAb anti–KIR 1-7F9 (IPH2101) was first generated,9 and then a recombinant version of this mAb was developed with a stabilized hinge (lirilumab). 1-7F9 and lirilumab mAbs cross-react with KIR2DL1, -L2, and -L3 receptors and impair their inhibitory signaling by preventing their binding to HLA-C. In vitro, anti-KIR mAbs augmented NK-cell-mediated lysis of HLA-C-expressing tumor cells, including autologous AML blasts and autologous CD138+ multiple myeloma cells.9,10 In addition, splenocytes from major histocompatibility complex class I (MHC-I)–deficient mice expressing HLA-Cw3 were rejected in 20 hours from Rag1KO mice
expressing KIR2DL3 with increasing doses of 1-7F9, demonstrating that in vivo blockade of KIR HLA class I interactions could mediate rejection of HLA-C–expressing cells.9,11 In mice, the Ly49 receptors have functions similar to human KIRs and bind to murine H-2 (MHC-I) molecules. We demonstrated a beneficial effect of blocking H-2-Ly49 interactions in vivo in combination with lenalidomide in rejecting MHC-I–positive tumor cells.10 A phase 1 clinical trial in elderly patients with AML was performed with an escalating-dose of 1-7F9. Results demonstrated that the 1-7F9 mAb injections were safe and could block KIR for long periods of time (more than 2 weeks at 1 and 3 mg/kg) with limited adverse effects.12

More than a decade prior to the approval of ipilimumab, a murine–human chimeric immunoglobulin G1 (IgG1) antibody against CD20 called rituximab was approved and has since become a standard treatment for patients with B-cell lymphomas. Although rituximab has multiple mechanisms of action, antibody-dependent cell-mediated cytotoxicity (ADCC) is of particular importance. Neutralizing antibodies that prevent the Fc-FcR–interaction abrogate the B-cell–depleting and antilymphoma activity in vivo13 and in vivo in murine models.14-16 In clinical practice, FcγRIIIA polymorphism with a higher affinity for IgG1 is associated with a higher response rate.17,18 Because the response rate to rituximab among patients with relapsed/refractory lymphoma may be approximately half that of patients previously untreated, we investigated whether NK-cell immunomodulation by combination of blockade of inhibitory KIR by lirilumab and stimulation via FcγRIII by rituximab could enhance antilymphoma efficacy in preclinical models.

Here we present results that support the monotherapy activity of lirilumab in a KIR2DL3 transgenic lymphoma model and of anti-Ly49C/I F(ab′)2 in a C57BL/6 syngeneic lymphoma model. In both models tested, combination of either of those with an anti-CD20 mAb significantly improves the antitumor efficacy of anti-CD20 mAb alone. These findings provide rationale for a clinical trial in lymphoma investigating this novel combination of an anti-KIR mAb to tilt the balance of inhibitory and stimulatory NK signals favoring spontaneous cytotoxicity and to further enhance the efficacy of rituximab by augmentation of ADCC.

Material and methods
Cell lines and mice
Human B-cell line LCL 721.221 was transduced with lentiviral particles encoding either HLA-Cw3 (221 HLA-Cw3) or enhanced green fluorescent protein (eGFP) as a control (221), from which sequences were cloned into TripdU3 EF1a plasmid. EL4 murine T lymphoma cells were transduced with human CD20 complementary DNA (EL4-huCD20). Both cell lines were cultured in RPMI-1640 medium (Invitrogen/Life Technologies), 2 mML-glutamine (Sigma-Aldrich), and 1 mM sodium pyruvate (Sigma-Aldrich), with the addition of 50 μg/mL streptomycin (both from Invitrogen/Media Technologies) supplemented with 10% heat-inactivated fetal calf serum (HyClone Laboratories), 2 mM t-glutamine (Sigma-Aldrich), and 1 mM sodium pyruvate (Sigma-Aldrich), with the addition of 50 μM 2-mercaptoethanol (Sigma-Aldrich) for EL-4 only. Cells were grown in suspension culture at 37°C in 5% CO2.

Biological and reagents
Antibodies for flow cytometry
The following mAbs to mouse antigens were used: CD8 fluorescein isothiocyanate (FITC) (Becton Dickinson [BD]/BD Biosciences (San Jose, CA), CD107a FITC (BD), CD44 FITC (BD), CD5 peridinin chlorophyll protein complex (BD), NK1.1 allophycocyanin (BD), and P4/80 allophycocyanin (eBioscience, San Diego, CA). Stained cells were collected on a FACS Calibur

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or an LSRII three-laser cytometer (BD), and data were analyzed by using Cytobank (http://www.cytobank.org).21

Statistical analysis
Prism software (GraphPad) was used to analyze tumor growth and luciferase light units and determine the statistical significance of differences between groups by applying an unpaired Student t test. Kaplan-Meier plots were used to analyze survival. Comparisons of survival curves were made by using the log-rank test. P values <.05 were considered significant. For tumor burdens, comparisons of means were done by analysis of variance.

Results
Anti-Ly49C/I F(ab′)2 increases anti-CD20 mAb-mediated NK-cell degranulation and cytotoxicity

To investigate the effects of blocking inhibitory receptors on NK cells in combination with a CD20-targeting antibody, we first selected a murine lymphoma cell line transfected with human CD20—EL4-huCD20—which was previously shown to be sensitive to anti-Ly49C/I mAb therapy.22 This model allowed targeting the murine homolog of the human KIR, the Ly49 family, using F(ab′)2 fragments of the anti-Ly49C/I mAb concurrently with an anti-CD20 mAb (CAT-13) therapy in an immune competent system. We first assessed whether blocking inhibitory NK-cell receptors by using anti-Ly49C/I F(ab′)2 could enhance anti-CD20–mediated NK-cell function, specifically degranulation and cytotoxicity. By using CD107a expression on murine NK cells as a marker of granule mobilization,23 we found that anti-CD20–induced degranulation could be significantly enhanced by anti-Ly49C/I F(ab′)2 (Figure 1A). IFNγ was also increased by anti-Ly49C/I F(ab′)2 (Figure 1B). We then assessed the effect of anti-Ly49C/I F(ab′)2 on anti-CD20–induced ADCC. Murine NK cells were purified and cultured with 51Cr-labeled EL4-huCD20 cells and anti-CD20 CAT-13 mAb in the presence or absence of anti-Ly49C/I F(ab′)2. The addition of anti-Ly49C/I F(ab′)2 significantly increased anti-CD20–induced ADCC compared with anti-CD20 CAT-13 mAb alone (Figure 1C).

Anti-Ly49C/I F(ab′)2 potentiates antilymphoma activity of anti-CD20 mAb in vivo

To test whether treatment with anti-Ly49C/I F(ab′)2 would enhance the antilymphoma activity of anti-CD20 mAb in vivo, we used a mouse lymphoma transfected with human CD20. Anti-Ly49C/I F(ab′)2 monotherapy has previously been shown to prolong survival against the murine lymphoma cell line EL4.22 Therefore, the EL4-huCD20 murine model provides an opportunity to test whether the combination of anti-Ly49C/I F(ab′)2 and anti-CD20 mAb elicits an enhanced efficacy in a therapeutic tumor model.

Although anti-CD20 mAb and anti-Ly49C/I F(ab′)2 both had antitumor activity when used as single agents, their combination significantly enhanced survival (Figure 2A-B). To determine activity against well-established tumors, therapy was delayed 1 week until day 10 resulting in decreased efficacy of both single agents and the combination. Anti-CD20 mAb and anti-Ly49C/I F(ab′)2 as monotherapy on day 10 minimally prolonged survival whereas combination of both on day 10 resulted in prolonged survival (Figure 2E).

Antilymphoma activity of combination therapy requires NK cells

To further investigate the mechanism of action of anti-CD20 mAb and anti-Ly49C/I F(ab′)2 and to confirm the role of NK cells in the therapeutic effect, we next performed a depletion experiment. We found that NK-cell, and not macrophage, CD4, or CD8 T-cell depletion, abrogated the therapeutic efficacy of anti-CD20 mAb and anti-Ly49C/I F(ab′)2 combination therapy (Figure 2C-D).

Blockade of KIR2DL3/HLA-C interaction induces tumor cell killing by NK cells in vitro

To study the therapeutic effect of KIR-targeting antibody in preclinical models, we generated transgenic mice for human KIR2DL3

Figure 1. Anti-Ly49C/I F(ab′)2 increases anti-CD20 mAb-mediated NK-cell degranulation and cytotoxicity. (A) NK cells isolated and purified from C57BL/6 mice were analyzed for degranulation by CD107a mobilization after 24-hour culture with 5 conditions: medium alone; human CD20–murine lymphoma cell line (EL4-huCD20) at a 1:1 ratio of tumor:NK cells; tumor and anti-CD20 mAb (CAT13; 10 μg/mL); tumor and anti-Ly49C/I F(ab′)2 (5E6; 10 μg/mL); or tumor, anti-CD20 mAb (10 μg/mL), and anti-Ly49C/I F(ab′)2 (10 μg/mL). *P = .0109. (B) Enzyme-linked immunosorbent assay (ELISA) results measuring IFN-γ following a 4-hour culture of purified murine NK cells in medium alone; EL4-huCD20 at a 1:1 ratio of tumor:NK cells; tumor and anti-CD20 mAb (CAT13; 10 μg/mL); tumor and anti-Ly49C/I F(ab′)2 (10 μg/mL); or tumor, anti-CD20 mAb (10 μg/mL), and anti-Ly49C/I F(ab′)2 (10 μg/mL). *P = .001. (C) Supernatant was harvested and analyzed by ELISA for IFN-γ. NK-cell cytotoxicity on EL4-huCD20 tumor cells was analyzed in a chromium-release assay. NK cells were purified before being incubated with 51Cr-labeled EL4-huCD20. (C) Percent lysis of target cells by chromium release at varying effector (purified murine NK cells):target (EL4-huCD20) cell ratios cultured with (●) medium alone; (▲) anti-Ly49C/I F(ab′)2 (10 μg/mL); (●) anti-CD20 mAb (10 μg/mL); or (▲) the combination of both antibodies. *P = .019.
Figure 2. Anti-Ly49C/I F(ab’)2 enhances the anti-lymphoma activity of anti-CD20 mAb in vivo and is NK-cell–dependent. (A) C57BL/6 mice were inoculated retro-orbitally with 0.5 × 10⁶ EL4-huCD20 lymphoma tumor cells. (B) After tumor inoculation, mice received (●) rat IgG control, (●) 250 μg of anti-CD20 mAb (CAT-13) on day 3 and once per week for 3 weeks, (▲) 200 μg of anti-Ly49C/I F(ab’)2 (SE6) on day 3 and 2 weeks, (♦) 200 μg of anti-Ly49C/I F(ab’)2 on day 3, or (▼) the combination of both antibodies. Mice were then monitored for overall survival. *P = .042. (C) C57BL/6 mice were inoculated retro-orbitally with 0.5 × 10⁶ EL4-huCD20 lymphoma tumor cells. (D) After tumor inoculation, mice received (●) rat IgG control on day 3; (●) 50 μL of anti-Asialo-GM1 on days 1, 0, 5, 10, 15, 20, and 25 with 250 μg of anti-CD20 mAb and 200 μg anti-Ly49C/I F(ab’)2 on day 3; (▲) 200 μL liposomal clodronate on day 2 followed by 100 μL of liposomal clodronate on days 0, 4, 8, 12, 16, 20, and 24 with 250 μg of anti-CD20 mAb and 200 μg of anti-Ly49C/I F(ab’)2 on day 3; (●) 500 μg anti-CD8 mAb on days 1, 0, 5, 10, 15, 20, and 25 with 250 μg of anti-CD20 mAb and 200 μg anti-Ly49C/I F(ab’)2 on day 3; or (▼) 250 μg of anti-CD20 mAb on day 3 and 200 μg of anti-Ly49C/I F(ab’)2 on day 3 with 250 μg of anti-CD20 mAb repeated once per week for 3 weeks and 200 μg of anti-Ly49C/I F(ab’)2 repeated biweekly for 3 weeks. Mice were then monitored for overall survival. *P < .001.

All in vivo models were piloted with 5 mice per group and repeated with 10 mice per group. Isotype controls included 5% normal mouse serum and 250 μg of 4D11 (Ly49G2) on day 3 and biweekly for 3 weeks in addition to rat IgG with no effect on tumor growth or survival (representative control, rat IgG, shown). (E) Survival with identical treatment groups but with treatment delayed until day 10 after tumor inoculation. Mice received (●) rat IgG control, (●) 250 μg of anti-CD20 mAb (CAT-13) on day 10 and once per week for 3 weeks, and (▲) 200 μg of anti-Ly49C/I F(ab’)2 (SE6) on day 10 and biweekly for 3 weeks, or (▼) the combination of both antibodies. *P = .005.

KIR2DL3 engagement on NK cells by tumor MHC-I mediates tumor escape in vivo

Rag1KO-Tg KIR mice lacking T and B cells can be engrafted with various human tumor cell lines, allowing the evaluation in a murine model of anti-KIR antibody that targets NK cells. When Rag1KO-Tg KIR mice were injected intravenously with 221 cells, the majority rejected the tumor and did not show any clinical signs of disease over a 100-day period (Figure 3A-B). The depletion of NK cells in these mice induced the death of mice in a median of 31 days (range, 25 to 38 days), demonstrating that NK cells are involved in 221 tumor growth control in Rag1KO-Tg KIR mice. When 221 HLA-Cw3 cells were injected intravenously into Rag1KO-Tg KIR mice, these cells induced death in a median of 29 days (range, 27 to 32 days). The engagement of KIR2DL3 by HLA-Cw3 is therefore sufficient to inhibit NK cell control of 221 tumor cells in vivo.

KIR-HLA interaction blockade induces Tg KIR mouse protection from HLA+ tumor challenge

First, we tested the effect of a single injection of lirilumab given the same day as a tumor challenge with the HLA+ cell line 221...
When mice were pretreated with lirilumab (15 mg/kg) a few hours before injection of tumor cells (Figure 3C), 6 of 7 mice survived over a 100-day period (Figure 3C), whereas untreated or IC-treated mice all died in a median of 29 and 27 days, respectively (range, 22 to 32 days). This protection conferred by KIR-MHC-I blockade is at least partly mediated by NK cells, since the depletion of this cell population in lirilumab-treated mice induced the death of 5 of 6 of the mice in a median of 41.5 days (range, 35 to 46 days).

**Therapeutic efficacy of anti-KIR administration in vivo**

A KIR occupancy study with lirilumab was carried out in Rag1KO-Tg KIR mice to define the dose of lirilumab to be injected into mice according to the required KIR saturation duration (supplemental Figure 2). We then tried to delay mouse treatment with lirilumab 5 days after HLA-Cw3 tumor engraftment. Several doses of anti-KIR mAb were tested in single injections (supplemental Figure 3A) and at 0.5 mg/kg, corresponding to 1-day complete KIR saturation on NK cells (supplemental Figure 2); a significant prolongation in survival was observed compared with mice who did not receive lirilumab (supplemental Figure 3B). Here, we showed that in vivo KIR-HLA interaction blockade with a suboptimal dose of 0.5 mg/kg of lirilumab, even 5 days after HLA-Cw3 tumor-cell injection, significantly improved the outcome of the disease in KIR Tg mice. The role of NK cells in tumor control was investigated by depleting this population just before tumor cell injection (Figure 4A). When NK cells were depleted, lirilumab treatment did not have any beneficial effect on mouse survival compared with untreated mice (Figure 4B).

**Therapeutic efficacy of anti-KIR and anti-CD20 combination in vivo**

Having shown that lirilumab treatment 5 days after tumor challenge could significantly improve mouse survival, we then asked whether this treatment could be combined with rituximab. The 221 HLA-Cw3 cells are of human B-cell origin, and they express CD20 at their cell surface (supplemental Figure 1C). We assessed the efficacy of suboptimal doses of rituximab or lirilumab alone (Figure 5A). Median survival of mice challenged with 221 HLA-Cw3 cells and treated with both ICs was 31.5 days (range, 21 to 48 days) and increased to...
and not CD20 expression has been shown to correlate with rituximab efficacy and NK-cell capacity for ADCC.29 Increased expression of HLA class I molecules results in a masked tumor cell appearing as “self” and in inhibition of NK-cell cytotoxicity through KIR interactions.26 More recently, the therapeutic activity of an ADCC-dependent mAb targeting the disialoganglioside GD2 in neuroblastoma was shown to be mediated by KIR-mismatched NK cells.30 In this study, ADCC from KIR-positive NK cells was shown to be inhibited by HLA cognate interaction, but this inhibition was reversible by the addition of anti-HLA Abs in vitro,30 supporting the rationale of blocking KIR to enhance the ADCC effect of therapeutic antibodies.31 Furthermore, in human patients, lirilumab targets several KIRs—KIR2DL1, -L2, -L3, -S1, and -S2—expressed on half of the total NK-cell population. The inhibitory KIRs targeted by lirilumab collectively recognize virtually all HLA-C alleles, and the blockade of all three KIR2DLs allows treating all patients without prior HLA or KIR typing.9,12,32

Therefore, we investigated the efficacy of a treatment regimen that included lirilumab-mediated KIR blockade and the therapeutic mAb rituximab in the hope that such a combination would augment ADCC and improve response rates and prevent resistance and tumor escape.

We developed two CD20-7 lymphoma models to evaluate the combination of anti-KIR and anti-CD20 mAb therapy. By transfecting a murine lymphoma (EL-4) with human CD20, we could assess in vitro and in vivo the efficacy of the combination of anti-CD20 mAb and blockade of the murine homolog of human KIRs (the Ly49 family) by using F(ab’)2 fragments of the anti-Ly49C/I mAb22 in an immune competent system. To study the therapeutic effect of blocking KIR2Ds with lirilumab, we used KIR2DL3 Tg mice on a Rag1KO background.9,10 To investigate combination therapy with anti-CD20 mAb, we generated 221 HLA-Cw3 cells, a human B-cell lymphoma transfected with HLA-Cw3 (one of the ligands for KIR2DL3). The 221 HLA-Cw3 cells express high levels of HLA molecules at their surface as well as CD20 and therefore are targeted by both anti-KIR and anti-CD20 mAbs.

Our findings in vitro confirm prior studies on human cells showing enhancement of anti-CD20 mAb-mediated lysis of CD20-expressing lymphoma cell lines by KIR blockade.33,34 The results reported here illustrate that, when combined in vivo, treatment with rituximab plus
lirilumab or anti-Ly49C/I mAbs augments NK cell activity. Depletion of NK cells abrogated the benefit of combination therapy. It was also previously reported that KIR inhibition enhanced cytotoxicity in an autologous system by using effector NK cells and Epstein-Barr virus–transformed B cells as target cells from the same donor.9 Combined with our findings, this supports that KIR-Ly49 blockade enhances both murine and human NK-cell ADCC.33

Our approach supported here is one of several strategies to improve the innate immune response following Fc receptor activation by an mAb.35 Focusing on NK cells as a major effector cell responsible for ADCC, initial investigation tested the hypothesis that increasing NK-cell numbers ex vivo could enhance the antitumor activity of an mAb. Adoptive transfer of lymphokine-activated killer cells in a cohort of patients with rituximab-refractory lymphoma improved NK-cell counts in peripheral blood and ADCC and even induced clinical responses in some patients.36 In contrast to our approach, adoptive transfer of NK cells is labor- and cost-intensive. It has possible biologic limitations resulting from the removal, isolation, and transfer of NK cells which can lead to NK exhaustion as a result of downregulation of transcription factors such as eomesodermin and T-cell-specific T-box transcription factor.37

Cytokine-based approaches to enhance NK-cell number and function in vivo without adoptive transfer have been investigated clinically, although few combination trials with mAbs have demonstrated superiority to monotherapy.38 Likely a result of the systemic, generalized immune stimulation, most cytokine therapies are accompanied by systemic toxicity. Another possibility for enhancing rituximab-induced killing by NK cells is the combination with lenalidomide, an immunomodulatory drug approved for the treatment of multiple myeloma and myelodysplastic syndrome, which enhances ADCC against CD20-expressing B-cell chronic lymphocytic leukemia primary cells through increased granzyme B and Fas ligand expression.39

As an alternative to enhancing ADCC, lenalidomide was also combined with anti-KIR mAb strategy, and it potentiated NK-cell cytotoxicity toward autologous myeloma cells in vitro.40 This combination is currently being investigated in a phase 1 clinical trial in multiple myeloma patients (NCT01217203).40

In contrast to the anti-KIR combination mAb strategy, which removes an inhibitory checkpoint, we have recently reported use of an agonistic NK-cell–targeted mAb to augment ADCC. Following FcR triggering during ADCC, expression of the activation marker CD137 is increased.41 Agonistic antibodies targeting CD137 in preclinical models, both in vitro and in vivo, augment NK-cell function, including degranulation, secretion of IFN-γ, and antitumor cytotoxicity.42-44 The combination of anti-CD137 antibody approach...
with rituximab is currently being evaluated in a phase 1 trial in patients with lymphoma (NCT01307267).42,43,45,46

Multiple efforts to enhance mAb efficacy, including adoptive NK-cell therapy, systemic cytokine, or immunomodulatory drug administration, and agonistic antibody combinations are currently in active clinical investigation. A first-in-class therapy capable of augmenting ADCC has yet to be successful in late-stage clinical trials. We present here preclinical evidence supporting another novel approach to enhancing mAb antitumor efficacy. Our findings provide a rationale for the combination of an anti-KIR mAb to “remove the brakes” from NK cells and further enhance the efficacy of rituximab among other mAbs by augmentation of ADCC. A clinical trial investigating this strategy is needed.

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References


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