To the editor:

**Expression of KIR2DL1 on the entire NK cell population: a possible novel immunodeficiency syndrome**

The killer immunoglobulin-like receptor (KIR) family recognizes class I major histocompatibility complex (MHC) molecules and inhibits natural killer (NK) activity. This family is highly polymorphic, and only some of the genes are present in each individual.1 Thus, the frequency of a single inhibitory receptor in a bulk NK population varies between 5% and 50%.2 It was suggested that such diversity of NK receptors enables the killing of infected cells by at least a subset of NK cells.3

A 7-year-old patient from Israel had been hospitalized 12 times due to infections. At the age of 2.5 months, the patient had severe interstitial pneumonitis, hepatosplenomegaly, anemia, and thrombocytopenia. Immunoglobulin M (IgM) antibodies against cytomegalovirus (CMV) were identified, and CMV in the urine was detected. At the age of 2.5 years, the patient had a severe bilateral pneumonia and respiratory failure. Bronchoalveolar lavage recovered CMV from the lungs. In the following years, 8 additional admissions due to lung infections and 1 due to acute gastroenteritis occurred. At the age of 6 years, the child developed chicken pox, with hundreds of skin lesions. Despite acyclovir treatment, a severe pneumonia with bilateral “white lungs” was evident. All laboratory tests at age 7 years were normal, including blood count, blood chemistry (SMA-18), urinalysis, serum antibodies, complement, and hemolytic complement. IgG antibodies for diphtheria, tetanus, pertussis, poliomyelitis, Epstein-Barr virus, and CMV were positive; tests for HIV were negative. Lymphocyte population was as follows: CD3 (approximately 80%), CD4 (approximately 58%), CD8 (approximately 27%), CD19 (approximately 11%), CD16 (approximately 8%), and CD56 (approximately 9%).

Importantly, the observed symptoms were almost identical to those observed in other patients suffering from NK cell deficiency.4 Surprisingly, the bulk NK cultures of the patient were inhibited by HLA-Cw4 (Figure 1A). Expression of KIR2DL1 receptor was detected on all NK cells in the bulk culture, by the HP3E4 or the EB6 monoclonal antibodies (mAbs) (Figure 1B). Never before had we, or others, observed such an unusual expression of KIR2DL1 on the entire NK cell population. Furthermore, all NK clones derived from the patient expressed KIR2DL1 and were inhibited by HLA-Cw4 (data not shown). Expression of other NK receptors, including KIR2DL2, KIR3DL1, NKG2A, CEACAM1, LIR1, and NKp46, was normal (28%, 21%, 25%, 12%, 12.5%, and 100%, respectively). The inhibition observed was the result of KIR2DL1 interaction with HLA-Cw4, as the HP3E4 mAb abolished the inhibition of either the NK clones or the bulk NK cultures (Figure 1C-D). The MHC haplotype of the patient is A26/A72, B51/B53, Cw06/Cw15, with both HLA-C alleles able to interact with KIR2DL1.

Our patient frequently suffers from recurrent infections, mainly CMV. Importantly, the CMV developed many mechanisms to avoid attack by NK cells and by cytotoxic T lymphocytes (CTLs),5 including the down-regulation of HLA-A and -B to avoid CTL attack, while maintaining HLA-C expression to avoid NK attack.6 Since all NK clones in the patient express KIR2DL1, which is able to interact with both HLA-C proteins of the patient, it is possible that in the often observed CMV
infections, all NK activity is inhibited. We suggest that overexpression of an inhibitory NK receptor might lead to a novel immune deficiency associated with primary CMV infection.

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To the editor:

Imatinib mesylate impairs Flt3L-mediated dendritic cell expansion and antitumor effects in vivo

Appel et al.1 reported in January that the paradigmatic KIT, PDGFR, ABL tyrosine kinase inhibitor imatinib mesylate (STI571/Gleevec), known to induce potent antitumor effects in chronic myeloid leukemia (CML) and gastrointestinal stromal tumors, acts on nonmalignant hematopoietic cells, inhibiting the differentiation and maturation of CD34+ progenitors into functional dendritic cells (DCs) in vitro. Indeed, DCs can be propagated from mobilized human CD34+ progenitors to micromolar ranges of STI571 affects the development of DCs and their capacity to induce primary cytotoxic T-lymphocyte (CTL) responses in vitro.1 Extending Appel et al’s observation to in vivo settings, we report here that the FL capacity (10 μg/mouse administered intraperitoneally for 10 days) to promote in vivo DC expansion in mice is abrogated when STI571 is concomitantly administered (oral feeding of mice with 150 mg/kg STI571 twice a day from day 5 to day 10 leading to antitumor effects in patients with melanoma.3 The DC growth factor Flt3L (FL) also has been used to propagate DCs from progenitors in vivo in mice, healthy volunteers, and patients with cancer, leading to organomegaly and antitumor effects. In the January 15, 2004, issue of Blood, the authors demonstrate that in vitro exposure of CD34+ progenitors to micromolar ranges of STI571 affects the development of DCs and their capacity to induce primary cytotoxic T-lymphocyte (CTL) responses in vitro.1 Extending Appel et al’s observation to in vivo settings, we report here that the FL capacity (10 μg/mouse administered intraperitoneally for 10 days) to promote in vivo DC expansion in mice is abrogated when STI571 is concomitantly administered (oral feeding of mice with 150 mg/kg STI571 twice a day from day 5 to day 10 leading to residual plasmatic concentrations of about 1 μM). Indeed, the spleen weight in BL6 mice receiving FL alone reached 215 ± 12 mg at day 12, while reaching 157 ± 8 mg in the combination of FL plus STI571 (P < .001, Mann Whitney 2-sample t test). Accordingly, the number of splenic DCs was dramatically reduced when STI571 was added to FL in both C57BL/6 and SWISS nu/nu mice (35 × 106 ± 6 [BL6] and 45 × 106 ± 6 [nu/nu] with FL alone versus 9.5 × 106 ± 5 [BL6] and 26 × 105 ± 5 [nu/nu]) with FL plus STI571, P < .05 in both strains, whereas control BL6 and nu/nu spleens contained 5 × 106 ± 5 and 3.6 × 105 ± 4 DCs, respectively. No significant differences were seen between the groups concerning CD11b, CD11c, IAb, CD80, CD40, and CD86 expression on spleen DCs. Consequently, we demonstrate that the FL-mediated antitumor effects are severely hampered when FL is combined with STI571 in such a setting (Figure 1). In 2 tumor models (the RMA-S lymphoma and the MCA 102 fibrosarcoma), although FL could significantly prevent tumor growth, the coinadministration of STI571 at early stages of therapy with FL abrogated tumor regressions (P < .01 in both settings, Kruskall Wallis one-way analysis of variance [ANOVA]). Here again, STI571 inhibits FL bioactivity by preventing DC expansion in vivo, thereby reducing

References


Figure 1. STI571 abrogates FL-mediated antitumor effects. Twice the minimal tumorigenic dose of RMA-S (A) or MCA102 (B) cells was inoculated into the abdominal flank of C57BL/6 mice at day 0. From day −4 to day +5, FL (10 μg/mouse) or phosphate-buffered saline (PBS) only (200 μL) was injected intraperitoneally. From day +1 to day +5, STI571 (150 mg/kg per gavage) or H2O (200 μL) was administered twice a day by oral feeding. Tumor size was monitored with a caliper twice a week, and the product of largest perpendicular diameters is reported for individual time points as mean ± SEM. *Significantly lower than PBS plus H2O, PBS plus STI571, and FL plus STI571; P < .05. Each experiment was performed 3 times with similar results and involved 5 to 7 animals per group. A representative experiment is depicted.
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