Human natural killer (NK) cells are functionally regulated by killer cell immunoglobulin-like receptors (KIRs) and their interactions with HLA class I molecules. As KIR expression in a given NK cell is stochastically established, KIR repertoire perturbations reflect a dominance of discrete NK-cell subsets as the consequence of adaptation of the NK-cell compartment to exogenous agents, more often represented by virus infection. Although inhibitory interactions between KIR and their cognate HLA class I ligands abrogate effector responses of NK cells, they are also required for the functional education of NK cell. The biology and molecular specificities of the activating KIRs are less well defined, and most interactions with NK cells, they are also required for the functional education of NK cell. The biology and molecular specificities of the activating KIRs are less well defined, and most interactions with NK cells, they are also required for the functional education of NK cell. The biology and molecular specificities of the activating KIRs are less well defined, and most interactions with NK cells, they are also required for the functional education of NK cell. The biology and molecular specificities of the activating KIRs are less well defined, and most interactions with NK cells, they are also required for the functional education of NK cell. The biology and molecular specificities of the activating KIRs are less well defined, and most interactions with NK cells, they are also required for the functional education of NK cell. The biology and molecular specificities of the activating KIRs are less well defined, and most interactions with NK cells, they are also required for the functional education of NK cell. The biology and molecular specificities of the activating KIRs are less well defined, and most interactions with NK cells, they are also required for the functional education of NK cell. The biology and molecular specificities of the activating KIRs are less well defined, and most interactions with NK cells, they are also required for the functional education of NK cell. The biology and molecular specificities of the activating KIRs are less well defined, and most interactions with
KIR expression (22). A typical feature of these patients is the pref-
either by a dominant expression of a relevant KIR, or by a lack of
has usually been reported in these patients, which is characterized
(21). As indicated above, a restricted pattern of KIR expression
related to the detection in these patients of type B
susceptibility for this disease has been suggested and has been
progressive increase of peripheral blood NK cells and with organ
volve. In rare cases, the disease transforms to aggressive NK
cell leukemia (13). These EBV positive patients usually suffer from
chronic active EBV infection and should carefully be monitored
for the emergence of clonal cells (11). Several cases with a sponta-
neous complete remission have been reported (14). Patients with
CLPD-NK usually have an indolent clinical course and respond to
immunosuppressive therapy with low doses of methotrexate (usu-
ally 10 mg/m²/week) or cyclophosphamide (50 or 100 mg/day) or
cyclosporin (3–5 mg/kg/day) with or without inclusion of low
doses of steroid (15). Because of the potential long-term side
effects of immunosuppressive therapy, limiting specific therapy
only to patients with symptomatic disease is recommended.

CLPD-NK EXPRESS ACTIVATING KIR
In recent years, several studies have been published focusing on
the pathogenetic mechanisms of this disease (9, 16–20). A genetic
susceptibility for this disease has been suggested and has been
related to the detection in these patients of type B KIR gene reperto-
ire, which is characterized by a high number of activating genes
(21). As indicated above, a restricted pattern of KIR expression
has usually been reported in these patients, which is characterized
either by a dominant expression of a relevant KIR, or by a lack of
KIR expression (22). A typical feature of these patients is the pre-
ferential expression of the KIR activating receptors isoforms (10,
23). Together with a bias toward activating KIR expression, a deep
silencing of inhibitory KIR through increased gene methylation
has been demonstrated by our group (19). More specifically, we
showed the complete lack of KIR3DL1 expression in most anal-
yzed patients, being the receptor expressed in 13% of patients as
compared to 90% of controls (p < 0.01). Interestingly, the results
of methylation patterns of KIR3DL1 promoter showed a signifi-
cantly higher methylation status (0.76 ± 0.12 SD) in the patients
with respect to the healthy subjects (0.49 ± 0.10 SD, p < 0.01).
These data suggest that together with the increased expression of
activating receptors, the lack of the inhibitory signal could also
play a role in the pathogenesis of disease (19). Only few studies
addressed the expression of NCR, NKG2D, and other activating
receptors. We investigated the expression of these receptors in a
series of 18 cases of LDGL patients and showed that, among NCR
antigen expression, Nkp30 was strongly down regulated in all but
one of the cases analyzed. Similarly the Nkp46 receptor in most
instances was detected only in small fractions of NK cells (10).
These peculiar phenotypic results in these patients suggested the
occurrence of a defect in NCR expression that was reminiscent of
that reported in acute myeloid leukemia patients (24). Regarding
Nkp44, which is normally expressed only in activated NK cells,
this receptor was not expressed at significant levels on LGL sur-
face of the patients analyzed. A completely different pattern was
observed for NKG2D, Nkp80, and 2B4 molecules that were homo-
geneously present on NK cells in the majority of the patients. All
together, these data indicate that in most cases patients’ NK cells
express normal levels of NKG2D while NCR molecules are gener-
ally present at low density. In addition, although in most patients
NK cells were characterized by the CD94/NKG2A+ phenotype, a
minor fraction of cases (nearly 20%) expressed CD94+/NKG2C+
phenotype (10).

CLPD-NK AND VIRAL INFECTIONS
Natural killer cell activation in response to an unknown stim-
ulus, likely of viral origin, is postulated to play a role in the
initial steps of CLPD-NK by selecting NK clones (Figure 2) (25).
Although no prototypical HTLV infection was demonstrated in
these patients, the evidence that in 73% of cases sera from a series
of patients from Europe and USA reacted with the recombinant
HTLV env protein p21E suggests that exposure to a protein con-
taining homology to BA21 may be important in the pathogenesis
of this lymphoproliferative disorder (16, 26).

In contrast with other mature NK cell neoplasms, EBV DNA
is not usually detected within affected lymphocytes in USA and
Europe countries (27) (6/16 NK LGL positive for EBV DNA),
whereas a significative high incidence has been reported in Japan-
ese patients, usually correlating with a more aggressive clinical
behavior (11). Anyway the link between EBV infection and LGL
disease is sustained by the observation that spontaneous resolution
of KIR restricted LGL associated with disappearance of EBV DNA
(28). Among Herpes viruses, Human CMV has been reported to
be crucial in influencing NK receptor expression in NK cells (29).
Remarkably, elevated numbers of CD94/NKG2C+ NK cells, pre-
viously shown to expand in association to CMV infection (30),
were preferentially found in Vbeta13.1+/ CD4+ T-LGLL, further
supporting its role in the pathogenesis of a subset of T-LGLL (31).
It is believed that bone marrow, which is frequently involved in CLPD-NK patients, represents the setting where the putative inciting antigen could reside and dendritic cells (DCs) have been suggested to represent the target of infection in these patients (17). Interestingly, analysis of bone marrow biopsies of patients demonstrated a topographic distribution of DCs and NK cells that indicates a close contact between the two cell types (17). DCs are also likely to represent the source of IL-15, which is crucial in the mechanisms sustaining the maintenance of NK proliferation. IL-15 has been found to mediate its activity by altering Bcl-2 family members, and more specifically by modulating Bid expression (18).

**ACTIVATING KIR AND VIRAL PROTECTION: IS IT TRUE IN CLPD-NK?**

Epidemiologic studies link activating KIR genes to resistance against numerous virus infections (32). Beziat et al. showed that infection with human CMV induce expansion and differentiation of KIR-expressing NK cells, causing as stable imprints in the repertoire (33). Interestingly, these authors showed that NK education by inhibitory killer cell immunoglobulin-like receptors (KIRs) was associated with a unique contribution of activating KIRs (KIR2DS4, KIR2DS2, or KIR3DS1), in addition to NKG2C, in the expansion of human NK cells. Interestingly, CMV-associated factors have been suggested to specifically influence KIR gene expression by regulating epigenetic expression of KIR genes (34). In addition, in allogeneic bone marrow transplantation setting, donor KIR2DS1 has been reported to protect against human CMV reactivation (35). KIR3DS1 in conjunction with HLA-Bw4 with an isoleucine at position 80 has been reported to be associated with slower progression of HIV infection to AIDS (36). Pelac et al. demonstrated that NK cells from individuals with multiple copies of KIR3DL1, in the presence of KIR3DS1 and the appropriate ligands inhibit HIV-1 replication (37). This is frequently associated with a significant expansion of KIR3DS1+, but not KIR3DL1+, NK cells in HIV positive patients’ peripheral blood. Epidemiological studies have indicated a protective effect for the activating KIR2DS1 and KIR3DS1 genes also in patients with EBV-associated Hodgkin’s lymphoma, although there is as yet no direct evidence for the involvement of these receptors in the recognition of EBV-transformed cells (38). KIR3DS1 genotype has been shown to exert a positive effect on HCV viral clearance during the first weeks of treatment in HCV/HIV infected patients (39).

Although many of the above reported viral infections are at least in part controlled by activating KIRs, a direct proof of the role of these NK receptors in controlling a putative viral infection in patients with CLPD is not available. This is likely due to the fact that not a single, specific agent is responsible for the NK proliferation, which perhaps represents the expression of an abnormal processing of different foreign antigens.

**ARE CLPD-NK CELLS LICENSED?**

It is well known that NK functions are regulated by the integration of signals received from activating and inhibitory receptors. To prevent inadvertent activation against normal tissues, NK must be educated to tolerate self, this process, termed “licensing,” acting through an MHC-dependent mechanism requiring interaction between inhibitory KIR and cognate MHC class I ligands (40). Up to date, two models have been proposed to describe NK cell
education (41): “arming” model and “disarming” model. In “arming” model, which is the best-known model proposed by Raulet and Vance (42), NK cells acquire functional competence after ligation of inhibitory receptors by self MHC class I molecules, while NK cells lacking these inhibitory receptors for self MHC enter in an “anergic” state. In this way, engagement of inhibitory receptor by self MHC during NK cell maturation guarantees NK cells to acquire “license to kill” and to become fully functional competent.

Natural killer licensing involves not only inhibitory KIRs but also activating KIRs have probably an underestimated role in this process, which is complementary but with different outcome, since it has been reported that education via activating KIRs decreases NK cells response (43). However, “unlicensed” NK are not so “anergic” but seem to have a crucial role in discrete settings. As an example, in murine model, unlicensed NK cells were the main mediators of NK cell-mediated control of mouse cytomegalovirus infection in vivo. In fact, depletion of unlicensed NK cells impaired control of viral titers, but depletion of licensed NK cells did not. Furthermore, the transfer of unlicensed NK cells was more protective than the transfer of licensed NK cells, indicating that unlicensed NK cells are critical for protection against viral infection (44).

As stated above, in CLPD-NK, proliferating NK cells are characterized by skewed KIR expression and selection and expansion of NK subset expressing activating KIRs, instead of the more common NK cells expressing inhibitory KIRs, represent a crucial step in the development of this disorder (10). Based on the recent insights in NK cell education and function, in CLPD-NK, we can suppose that expansion of long-lived NK cells involves “unlicensed” NK equipped with activating KIRs, which have a predominant role during viral infections, in accordance with the hypothesis that viral stimulation may be the starting trigger of the disorder. According with this suggestion, we performed HLA genotyping analysis in 29 CLPD-NK patients showing that in 93% of cases, a KIR/HLA-I mismatch was present indicating that NK cell proliferation in CLPD is mostly represented by unlicensed cells (21). Considering that in healthy individuals, KIR/HLA-I genetic mismatch has been detected in nearly 50% of cases, our results point to a role of the KIR/HLA-I mismatch in the pathogenesis of the disease.

CONCLUSIVE REMARKS

Chronic lymphoproliferative disorders of NK cells are characterized by the expression of a restricted pattern of activating KIR receptors on proliferating NK cells. It is believed from indirect evidence that exogenous agent(s), likely of viral origin, might contribute to the initial steps of disease. Recent knowledge on the mechanisms of NK cell function and different contribution of NK cell receptors against viral infections might help in the comprehension of the mechanisms leading to selection of a discrete NK cell population. A possible inciting role of the putative antigen within DCs in the bone marrow can be suggested. The inability of antigen clearance and/or the occurrence of new events might contribute to the persistence of NK clone. In this way, the identification that STAT3 SH2 somatic mutations (45, 46), which can be found in a fraction of CLPD-NK patients, might indicate that an acquired genetic mutation could contribute to the immortalization of NK proliferation.

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