The recent findings on NK activation indicate that these cells are important antitumor effectors. NK cells participate in the graft-vs.-leukemia effect to control the relapse in leukemic patients transplanted with allogeneic hematopoietic stem cells. In various tumors, correlation between NK cell infiltrates and prognosis were reported. However, tumor-infiltrating NK cells are yet poorly characterized. We here summarize our results and the recent studies of the literature on tumor-infiltrating NK cells, and discuss the impact of these novel insights into NK cell responses against tumors for the design of NK cell-based therapies.

**Antitumor Effects of NK Cells**

NK cells were first identified as a distinct sub-population of lymphocytes endowed with the spontaneous capacity to in vitro kill tumor cells. Since then, the increased knowledge of NK cell biology has provided strong arguments for their role in immune response against infections and tumors.

Natural Killer cell activation depends on the intricate balance between activating and inhibitory signals derived from receptors. Most inhibitory receptors (KIR, NKG2A, LIR) are specific for different HLA-I molecules. In normal conditions, the low engagement of activating receptors counterbalanced by high inhibitory signals triggered by HLA-I molecules on normal cells avoids self-reactivity of NK cells (Fig. 1). In the context of tumor, NK cell activation relies on the expression of NK ligands by target cells. To be “seen” by NK cells, cancer cells have to express ligands for activating receptors, while the low expression of HLA-I molecules attenuates the triggering of inhibitory receptors. Cancer cells can also secrete immunomodulating molecules inducing immune cell anergy. Thus, tumor-related parameters strongly control NK cell activation and any factor that modifies the expression of NK ligands on tumor cells may thus affect the activation of NK cells.

Numerous data demonstrate the implication of NK cells in tumor control and support a potential benefit of their usage in cancer immunotherapy. Clinical evidence for the benefit of in vivo NK cell targeting of human tumors has come from allogenic hematopoietic stem cell transplantation (HSCT) to treat the relapse in patients with acute myeloid leukemia (AML). Infusions of donor alloreactive NK cells (presenting at least one KIR/HLA mismatch with the recipient) participate in graft-vs.-leukemia (GvL) effect and correlate with relapse-free survival. An 11 y-follow up of 3625 residents of a Japanese population showed a negative correlation between NK cell cytotoxic activity from blood and cancer incidence. Other arguments for the role of NK cells in tumor control rely on the presence of NK cell infiltrates in diverse solid tumors.

Different strategies aimed at increasing NK cell lytic activity against tumor cells and/or to enhance their homing at the tumor site have been evaluated: cytokine-mediated activation of endogenous NK cells (IL2, IFNz), NK infusions, anti-KIR mAb, ADCC-promoting therapeutic Abs, Bispecific Ab (CD16/CD30) or combined therapies. Preclinical and clinical studies emphasize that NK-mediated immunotherapy would be efficient in treating minimal residual disease. On the other hand, accumulating evidences indicate that, even when conventional therapies apparently result in complete remission, micrometastases of residual tumor cells can lead to tumor relapse. Thus, it is conceivable to associate conventional cancer therapies, reducing tumor size, with immunotherapy treatments for the complete and durable eradication of tumors.
However, different mechanisms concerning the anti-tumor function of NK cells remain partially understood: the in vivo NK cell activation during tumor progression, the influence of tumor microenvironment on NK cells, and how the treatments interfere with NK cell effector functions in cancer patients.

This review summarizes our results on NK cells in metastatic renal cell carcinoma (RCC) and melanoma, and recent studies in other solid tumors. In particular, we discuss the role of some important tumor parameters that interfere with NK cell activation and subsequent recognition of cancer cells. We especially analyze...
the mechanisms involved in tumor immunogenicity and how tumor stage and patient therapies modulate the functional status of NK cells. Finally, we discuss the impact of these novel insights on the design of anti-tumor NK cell-based therapies.

**Oncogenic Events are Recognized by NK Cells**

Malignant tumors are proliferating cells that have accumulated mutations in genes regulating important biological pathways as, for example, proliferation, apoptosis, angiogenesis and migration. Oncogenic mutations often lead to the aberrant activation of signaling pathways and to important modifications in protein expression by cancer cells. Compared with normal cells, cancer cells can overexpress stress-induced molecules, bear constitutive activation of growth factors, downregulate MHC-I molecules, or express specific tumor-associated antigens. Immune cells detect tumors through receptors that recognize the altered expression of these molecules. Thus, an oncogenic event can influence tumor

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**Figure 2.** Tumors parameters implicated in the activation of NK cells. In RCC, VHL mutations induce constitutive activation and accumulation of Hypoxia-inducible factor (HIF). Certain VHL mutations correlate with low HLA-I molecules expression via a partially HIF-dependent pathway. The low expression of HLA-I molecules by VHL-mutated RCC cells reduces the engagement of NKG2A inhibitory receptor, shifting the balance toward NK cell activation. Membrane HLA-G molecules upregulate inhibitory receptors (NKG2A, and ILT2) on NK cells. Membrane-bound IL15 (Mb-IL15) is involved in NK cell activation and survival. In CML, the oncogenic protein bcr/abl induces the expression of ICAM-1 and NKG2D ligands on myeloid cells favoring NK/target conjugates and lysis. Altered IFNγ signaling in bcr/abl target maintains a low HLA-I molecules expression. Bcr/abl dendritic cells activate NK cells via NKG2D receptor. Imatinib mesylate interferes with NK/leukemic targets. DC: Dendritic cell; IM: Imatinib Mesylate; IRF: Interferon regulatory factor; STAT-1: Signal Transducer and Activator of Transcription factor-1.
immunogenicity when it directly or indirectly modulates the expression of those molecules recognized by immune cells and involved in their activation.

In RCC, we have shown that loss-of-function mutations of Von Hippel Lindau (VHL) gene may be targeted by NK cells (Fig. 2). This oncogenic event is important for the development of these tumors and 80% of RCC bear mutations in VHL gene leading to HIF (Hypoxia-inducible factor)-1 accumulation and increased activation of downstream signaling pathways. Previous studies including ours showed that NK cells lyse RCC cell lines and that LFA-1/ICAM-1 and HLA-I/NKR interactions are important in RCC recognition by NK cells. We have shown that certain loss-of-function VHL mutations correlate with a reduced expression of classical HLA-I molecules via a partially HIF-1α-dependent mechanism and with higher RCC lysis by NK cells. These results corroborate previous findings reporting that VHL controls the constitutive expression of STAT-1 and LMP2, involved in MHC-I dependent antigen presentation, probably via the downregulation of STRA-13. HLA-E molecules, ligands of the inhibitory receptor NKG2A, are also decreased in VHL-mutated cells. HLA-E promoter also contains STAT-1 binding site. HLA-I molecules are often downregulated in tumors and their modulation is considered a common mechanism of tumor escape from T cell immune response. Conversely, low HLA-I expression may shift the balance toward activation in NK cells. In non-tumor pathology and upon hypoxia-dependent HIF accumulation, the expression of MICA/B molecules, stress-induced ligands of the activating receptor NKG2D, was found augmented and correlated with increased NK cytoxicity. In our studies, the expression of NKG2D ligands was not controlled by VHL mutation.

Data on VHL-dependent RCC susceptibility to NK cell lysis are reminiscent of previous studies of the lab on Chronic Myeloid Leukemia (CML), as summarized in Figure 2. We showed that the high expression of bcr/abl oncoprotein in leukemic cells increased NK cell-mediated lysis through the NF-κB activation dependent induction of ICAM-1 expression on tumor cells. In addition, we reported an altered IFN-γ pathway consequent to bcr/abl expression; HLA-I molecules were not induced by IFN-γ treatment, thus preserving leukemic cell susceptibility to NK cell lysis. Finally, we showed that the overexpression of bcr/abl oncogenic protein in DCs promotes DC-mediated NK cell activation via the upregulation of NKG2D ligands.

Triggering of NK cell activation by oncogenic-induced changes in the expression of NK ligands on tumor cells may be a common phenomenon. In melanoma, BRAF is frequently mutated in tumor tissue and new therapies targeting the activation of its signaling pathway have been recently developed for the treatment of patients. Moreover, other genes implicated in the familial occurrence of melanoma (i.e., germline mutations of CDKN2A) were identified. It will be interesting to study whether mutations in BRAF, or in other genes involved in melanoma development and progression, determine changes in melanoma immunogenicity (expression of NK ligands), thus modulating NK activation.

Whether NK cells are able to indirectly target oncogenic defects, or to recognize the constitutive overactivation of membrane receptors in tumors, are important issues and may contribute to develop complementary targeted therapies based on these cytotoxic cells.

**NK Cell Alterations in Cancer Patients: What are the Direct and/or Indirect Effects of Tumor Cells?**

The interactions between NK and tumor cells could be influenced by the site of their encounter. Well characterized in blood, NK cells are also present in various tissues and different sites of NK development and maturation have been discovered. On the other hand, cancer cells develop from and disseminate to distinct sites depending on tumor type and on the course of the disease. Thus, when studying tumor-infiltrating NK cells, it is important to consider the tissue resident NK cells and the site of metastases.

1. **Circulating NK cells.** The first ex vivo evaluation of anti-tumor NK function was done on circulating NK cells from leukemia patients. Due to the easier access, NK cells from blood are also the best characterized in patients with solid tumors. However, in these patients, blood is probably not the most relevant compartment for the investigation of NK cells. Numerous studies have reported functional defects of blood NK cells from most cancer patients and the severity of these deficiencies varies among different types of tumor. Profound alterations of NK differentiation and function were found in CML, AML and myelodysplastic patients, whereas in patients with solid tumors defects on blood NK cells are generally mild and often associated with advanced tumor stage.

In patients with invasive cervical carcinoma and premalignant lesions, the expression of Nkp30 and Nkp46 was found downregulated on blood NK cells and correlated with a reduced cytolytic activity and with the clinical stage of patients. In invasive cervical carcinoma, the expression of NKG2D was also decreased. We recently showed that circulating NK cells from stage IV melanoma patients present a unique Nkp46low/NKG2Aα expression profile that correlates with high lytic efficiency toward melanoma cell lines. Our preliminary results indicate that NK cells from stage III melanoma patients are less affected, suggesting that NK alterations may change during disease progression (unpublished data). Other groups also reported a reduced expression of NKG2D and NCR receptors in NK cells from melanoma patients. Moreover, altered activating NK receptors and dysfunctions of circulating NK cells were recently reported from a large series of patients with breast cancer; the severity of the defects was clearly increased with the progression of the disease.

2. **Tumor-infiltrating NK cells.** Numerous reports show that NK cells infiltrate tumors of different origins. However, the detection of NK cells has been done using different antibodies. In some cases, double staining with CD3 and CD56 or CD57 specific antibodies have been performed, whereas more recent studies used the direct staining with anti-NKp46 antibody. Several groups (including ours), reported that NK cells infiltrate clear-cell RCC. NK cells were described in melanoma, non small cell lung cancer, gastrointestinal stromal tumors.
In several tumors, NK cell infiltration has been associated with clinical outcome. A positive correlation was reported in RCC between the numbers of tumor-infiltrating NK cells (NK-TILs), the expression of CD16 receptor and NK cytotoxic activity. In a study including 150 patients, the count of intra-tumor NK cells (anti-CD57 staining) in resected lung adenocarcinomas was associated with the control of tumor progression, representing a likely prognostic marker in patients with lung adenocarcinoma. Correlation between intra-tumor NK cell counts and tumor control was also reported in patients with squamous cell lung cancer. The prognostic value of CD57⁺ NK-TILs was observed in gastric carcinoma and colorectal carcinoma. In prostate cancer, elevated counts of CD56⁺ NK cells were associated with a lower risk of progression. Moreover, a recent study showed a positive association between numbers of NK-TILs (anti-CD56 staining) and regression of melanocytic lesions.

Compared with blood NK cells, only a limited amount of information is available on tissue infiltrating NK cells. NK-TILs usually present more severe phenotypic and functional alterations compared with circulating or non-cancerous tissue-infiltrating NK counterparts. There is a marked decreased expression of Nkp30 receptor in GIST. Furthermore, NK cells show tissue specific patterns of expression. In few studies, NK-TILs and non-cancerous tissue specific NK cells were analyzed in parallel. In non small cell lung cancer (NSCLC), Carrega and colleagues showed that although peritumoral NK cells were similar in phenotype and function to blood NK cells, intratumoral NK cells were CD56⁺/CD16⁻, expressed Nkp44 and HLA-DR, lacked perforin, expressed high levels of inhibitory receptors and were impaired in cytoxic function but secrete cytokines (IFNγ, TNFα). A recent study further showed profound reduction in the expression of a cluster of NK receptors (Nkp30, Nkp80, DNAM-1, CD16 and ILT-2) and functional anergy in intratumoral NK cells compared with blood and lung-derived NK cells. Moreover, a distinct NK cell distribution was shown between malignant (MLTA) and non malignant lung tissues (NMLTA). NK cells were abundant in non malignant lung tissues and displayed high cytotoxic activity compared with NK cells in MLTA. A similar alteration in NK cell distribution was also recently found between normal liver tissue and liver metastasis of CRC. In breast cancers, the number of NK cells in malignant tissue is reduced and includes a higher percentage of CD56⁺ compared with healthy mammary tissue. These NK-TILs display reduced activities compared with paired circulating NK cells.

In RCC tumors, NK-TILs differ from autologous blood NK cells regarding the expression of inhibitory receptors, which may contribute to functional deficits within tumor tissues. However, in some RCC highly infiltrated by NK cells, NK function could be restored after stimulation with low-dose IL2 and the cytotoxic activity of NK-TILs resided in the CD16⁻/NKG2A⁺ NK cell population. In RCC, NK cells undergo a specific phenotype and function to blood NK cells, intratumoral NK cells lack perforin, express high levels of inhibitory receptors and secrete cytokines.

An open question concerns the origin of the NK-TILs for which several hypotheses may be proposed. The activation of tissue resident NK cells could occur although the marked differences between peri- and intratumoral NK cells do not favor this hypothesis. Moreover, NK precursors are present in certain tissues, like lymph nodes (LN), and within these sites, tumor cells may interfere with NK maturation and contribute to the altered phenotype observed in blood NK cells. Our preliminary results indicate that, compared with normal LNs, NK cells from melanoma metastatic LNs are functionally defective and displayed a co-reduced expression of a pattern of activating receptors (CD16, NKG2D, DNAM-1 and Nkp30) close to that described in NK-TILs from ovarian carcinoma and NSCLC. Alternatively, NK-TILs may be recruited from the circulation through chemokine gradients produced by the tumor.

These different hypotheses are not exclusive and the source of NK cells may vary as a result of changes in the tumor microenvironment (Fig. 3). The determination of the transcription factors and/or the immune related genes expressed by NK cells from different compartments will be a valuable strategy to precise the origin of NK-TILs. For instance, in the case of metastatic LNs, it will be likely useful to compare the transcriptional profiles of NK cells derived from metastatic LNs from diverse cancers (i.e., breast cancer, melanoma).

Mechanisms Underlying Alterations of NKs in Cancer Patients

In cancer patients, the defects of blood NK cells depend of the tumor type and are more severe in advanced stages, and NK TILs are more affected than peritumoral NK cells.

Several mechanisms may contribute to the alterations of NK cells in cancer patients depending on where NK and tumor cells encounter (Fig. 3). Circulating tumor cells (CTC) have been detected in melanoma and other tumors and could directly modulate blood NK cells. It would be interesting to evaluate whether the alterations in blood NKs correlate with CTC quantity.

It can be postulated that NK cells are modulated at the tumor site and then recirculate to peripheral blood. Little is known about NK cell recirculation, but chemokine receptors and selectins are considered good candidates for the orchestration of NK trafficking. While NK recruitment at site of inflammation was described, the data concerning a possible recirculation of these cells to blood are scarce.

Independently of the site, tumor cells may affect NK functions in a direct or indirect manner, involving membrane and/or soluble factors expressed and released by tumor cells. The functional consequences will depend on the nature and the density of NK ligands expressed by tumor cells. Cancer cells express ligands for activating NK receptors and in solid tumors, NKG2DL, DNAM-1L, as well as adhesion molecules are important determinants. Thus, in situ, the downregulation/shedding of activating NK receptors may be caused by the constitutive expression of NK ligands or through the release of soluble factors by tumor cells in the microenvironment. Soluble MICA/B molecules were shown to downregulate NKG2D. However, in our study, there was
no correlation between the phenotype of NK cells (NKG2D) and seric levels of MICA/B in patients.

On the other hand, MHC-I molecules control the activation of NK cells. Membrane HLA-G is expressed by RCC and melanoma cells and participates in immune surveillance escape. In particular, HLA-G has been described to upregulate inhibitory receptors on NK cells. Soluble forms of non classical HLA-I molecules were also implicated in tumor evasion from immune response. We have detected elevated seric levels of HLA-E in melanoma patients.
In RCC, prostate cancer and melanoma, a membrane-bound IL15 has been described. Endowed with particular properties on tumor cells, tumor IL15 is involved in NK cell activation and survival (Fig. 2). It can exert reverse signaling and favor tumor progression.

TGFβ is a major immunosuppressive molecule, known to downregulate the expression of NKp30 and NKG2D. TGFβ expression was upregulated in metastatic LN from patients with cervical cancer and anti-TGFβ restores NK cell reactivity in breast cancer patients. Supporting the hypothesis of a modulation of NK status by soluble factors, changes in immune function were shown to precede metastasis in melanoma draining LN.

In addition, the particular phenotype of NK cells in cancer patients may be the result of NK cell interactions with other tumor-modulated cells (DC, T cell subsets, fibroblasts) present at the sites of NK maturation, and/or tumor microenvironment. In melanoma, tumor-associated fibroblasts have been described to directly suppress the function of IL2-activated blood NK cells and to inhibit the cytokine-induced expression of NKp44, NKp30 and DNAM-1 via cell-to-cell contacts.

Developing from different tissues and expressing specific pattern of molecules, each tumor type is unique and characterized by the capacity to metastasize in preferential sites. Differences observed in NK cells (blood NKs vs. NK-TILs) from patients with different cancers likely reflect intrinsic characteristics of the tumor that must be taken into account in the investigation of NK cells in cancer patients.

**Treatments Affect NK Cell Phenotype and Functional Status**

Another important issue from our recent studies is that conventional chemotherapy affects circulating NK cells in melanoma patients. Post-chemotherapy NK cells displayed an induced expression of NKG2A and NKp46 receptors compared with pre-chemotherapy patients and donors. This profile is compatible with a less mature phenotype, and was associated with a reduced NK activation toward melanoma cells. The treatment-induced modulation of NK cell status was not direct because blood samples were collected at least four weeks after the last course of chemotherapy. In addition, using global transcriptome analysis and immunohistochemistry, we showed that dacarbazine induced stromal and immune related genes in responsive cutaneous metastatic lesions. These data further indicate that cytotoxic drugs, in addition to their direct cytotoxicity to tumor cells, may also influence changes in the tumor microenvironment. Thus, in vivo, chemotherapy acts on tumor cells and on other immune cells causing the release of cytokines or soluble factors that in turns modulate NK status.

It is likely that compared with chemotherapy, “targeted therapy,” which consists of a novel group of antibodies or small kinase inhibitors targeting specific growth signaling pathways in cancer cells, will exert slight effects on immune cells. However, certain targeted therapies have shown to affect pathways implicated in the activation of immune cells. A recent study has compared the effects of sunitinib and Sorafenib, two kinase inhibitors adopted for the treatment of RCC, on circulating NK cells. They showed that NK cell function in RCC patients is inhibited by Sorafenib as a consequence of an impaired phosphorylation of PI3K and ERK, which directly control NK cell reactivity. In contrast, pharmacological doses of Sunitinib do not affect NK cell function. Thus, new therapies when targeting signaling pathways shared by NK cells (and in general in immune cells) can likely affect their function. In melanoma, BRAF inhibitors have been developed for the treatment of patients. It will be interesting to evaluate their effect on NK cells. Another promising therapeutic approach in melanoma uses anti-CTLA4 mAb to block an inhibitory receptor expressed by activated immune cells (T cells). The effect of such mAbs on NK cells deserves precise investigation.

NK cell activation by cancer therapy does occur and the underlying mechanisms have been investigated. In GIST, gain-of-function mutations of c-kit are found in 85% of tumors and treatment by Imatinib, a c-kit inhibitor, is highly effective. In certain patients, the efficacy of Imatinib was not associated with c-kit mutation in tumor, but dependent on IFNγ production by NK cells upon DC-mediated activation.

Treatments can also modulate the expression of NK ligands on tumor cells. Cisplatin and 5-fluorouracil were described to induce the expression of NKG2D ligands, likely augmenting tumor cell susceptibility to NK lysis. IFNα, used as adjuvant for the treatment of melanoma and RCC, increases the expression of HLA molecules, thus inhibiting NK cell activation toward cancer cells.

All together these studies indicate that anti-cancer therapy (conventional, targeted therapies) can exert important effects on the innate immune response and particularly affect NK cell activation. When NK-based adjuvant therapies are planned to be used, it is important to evaluate whether and how they will be compatible with the first line treatment. A clear example concerns breast cancer patients for which responses to adjuvant therapy by trastuzumab (a Her2-targeting monoclonal Ab) positively correlate with NK cell activity and for which chemotherapy was shown to affect NK function.

**Conclusion**

In melanoma and RCC patients, complete responses have been obtained by high doses of IL2 and first trials of allogenic NK cell infusions in these patients demonstrated that the treatment is safe. These clinical evidences indicated that NK-based immunotherapy approach may represent a good strategy for the adjuvant treatment of cancer. However, only limited objective responses have been achieved using the different NK-based protocols thus far developed. These approaches were aimed at boosting the NK lytic potential but neither the tumor compartment, nor the previous therapies of patients were considered.

The recent findings on NK cell activation in cancer patients indicate that several important parameters require consideration for the choice of a NK-based therapy: immunogenicity and tumor...
capacity to modulate NK function, phenotype of circulating/tumor-infiltrating NK cells and the effect of the treatment on NK function.

Additional studies are necessary to characterize NK-TILs in patients with solid tumors of different origins, tumor stages and evolution in response to treatments. In solid tumors, the study of NK cells from normal vs. tumor tissue is fundamental to understand the modulation exerted by the tumor on NK functional status. Moreover, some tumors like melanoma or breast cancers mainly metastasize through lymphatic vessels thus affecting LNs, important sites of NK cell development and maturation. All these parameters have to be considered for the development of new more effective NK-based therapies.

All in all, these recent findings indicate that it is justified to reconsider immunotherapy not as a competitive treatment but as a complementary approach that can be integrated in therapeutic strategies at different stages of the disease. In particular, NK-based therapies would be probably more effective for the treatment of minimal residual disease when associated to therapy inducing NK ligands on tumors and enhancing the NK recruitment to tumor sites.

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