

## Innate Lymphoid Cells in Cancer

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### Abstract

The world of lymphocytes has recently expanded. A group of cells, innate lymphoid cells (ILC), has been defined. It includes lymphoid cells that have been known for decades, such as natural killer (NK) cells and lymphoid tissue-inducer (LTI) cells. NK cells recognize a vast array of tumor cells, which they help to eliminate through cytotoxicity and the production of cytokines, such as IFN $\gamma$ . Advances in our understanding of NK-cell biology have led to a growing interest in the clinical manipulation of these cells in cancer. The other ILCs are found mostly in the mucosae and mucosal-associated lymphoid tissues, where they rapidly initiate

immune responses to pathogens without the need for specific sensitization. Here, we outline the basic features of ILCs and review the role of ILCs other than NK cells in cancer. Much of the role of these ILCs in cancer remains unknown, but several findings should lead to further efforts to dissect the contribution of different ILC subsets to the promotion, maintenance, or elimination of tumors at various anatomic sites. This will require the development of standardized reagents and protocols for monitoring the presence and function of ILCs in human blood and tissue samples. *Cancer Immunol Res*; 3(10); 1109–14. ©2015 AACR.

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### Learning Objectives

Upon completion of this activity, the participant should understand the classification of innate lymphoid cells, the basic principles of their function, and their contribution to the immune response during cancer.

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### Introduction

The immune system is classically divided into innate and adaptive arms. Adaptive immunity can be defined as the presence of cells (e.g., T and B lymphocytes in higher vertebrates) display-

ing the clonal expression of a colossal repertoire of receptors (i.e., the T-cell and the B-cell antigen receptors), the diversity of which results from somatic DNA rearrangements. Natural killer (NK) cells constitute another type of innate immune system lymphocytes. They were first identified in the 1970s and can both kill an array of target cells and secrete cytokines involved in shaping the adaptive immune and tissue repair responses (1). One key feature of NK cells is their capacity to distinguish normal cells from stressed cells, such as tumor cells, in particular.

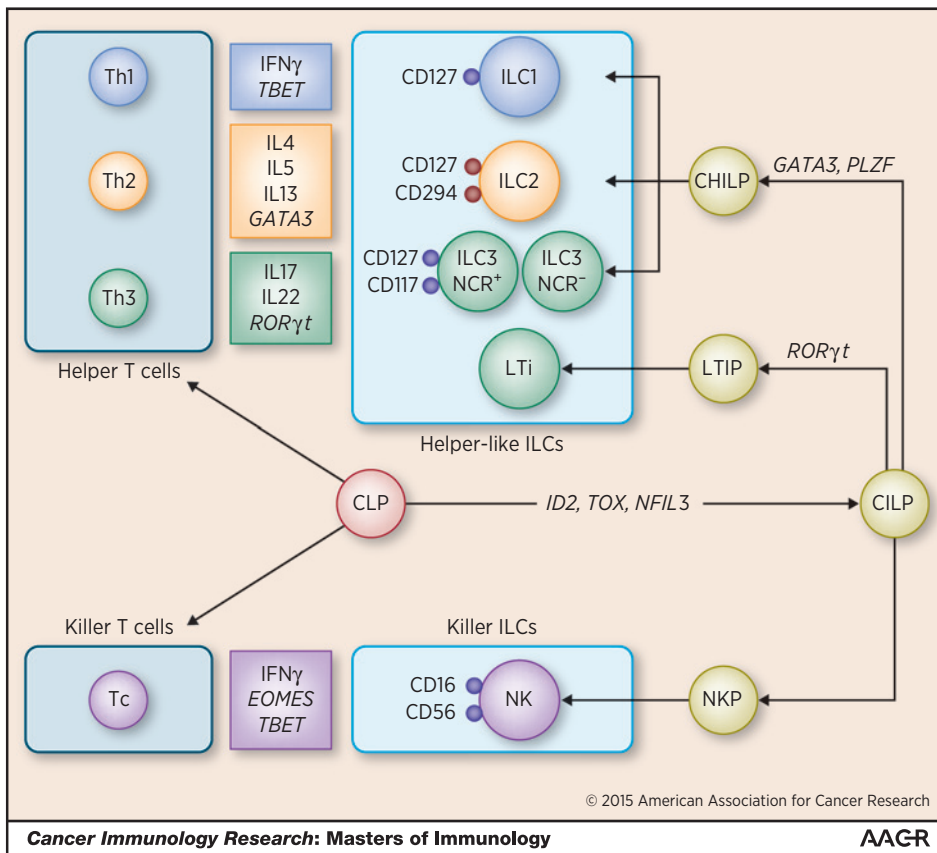
The immune system has been implicated in the control of cancer development. Higher rates of spontaneous cancer development have been observed in mice with deficient immune systems (2). In humans, the role of T cells in the elimination of tumors has been highlighted by the considerable success of mAb treatments that interfere with T-cell checkpoints (checkpoint inhibitors) and chimeric antigen receptor therapy (3, 4, 5, 6). The immune response can thus serve as a barrier to cancer. Adaptive immunity has been shown to play a critical role in

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**Figure 1.** The diversity of ILCs mirrors the diversity of T cells. Italicized labels indicate the gene producing the main transcription factors driving the function and differentiation of helper T cells, helper-like ILCs (ILC1, ILC2, and ILC3 cells), cytolytic T cells (Tc), and cytolytic ILCs (NK cells). All ILCs develop in an *Id2*-dependent way from a CLP which can differentiate into a common ILC precursor (CILP, also referred as to  $\alpha$ LP). CILPs differentiate into the NK-cell precursor (NKP), lymphoid tissue-inducer precursor (LTIP), or common helper innate lymphoid precursor (CHILP). CHILPs that acquire promyelocytic leukemia zinc finger (PLZF) can lead to ILC1, ILC2, and ILC3 subsets. ILC3 are divided into two groups:  $NCR^-$  ILC3 and  $NCR^+$  ILC3. There are three NCRs in humans: NKp46, NKp44, and NKp30, and only one in the mouse: NKp46. Some cell surface molecules of human ILCs are also indicated (CD127, CD294, CD117, CD56, CD16).

eliminating tumors, but we still know little about the role of innate lymphocytes in this process, except for NK cells, which can kill tumor cells both directly (natural cytotoxicity) and after the tumor cells have been coated with antibodies (antibody-dependent cell cytotoxicity or ADCC). These properties of NK cells have increased the interest in their clinical manipulation in cancer, in adoptive therapy, and in treatments based on checkpoint inhibitors that can target NK cells, such as the mAb to KIR, lirilumab (7, 8). The role of NK cells in cancer, and their manipulation in the treatment of this disease, has recently been reviewed elsewhere (9–11). We review here the role of ILCs other than NK cells in cancer.

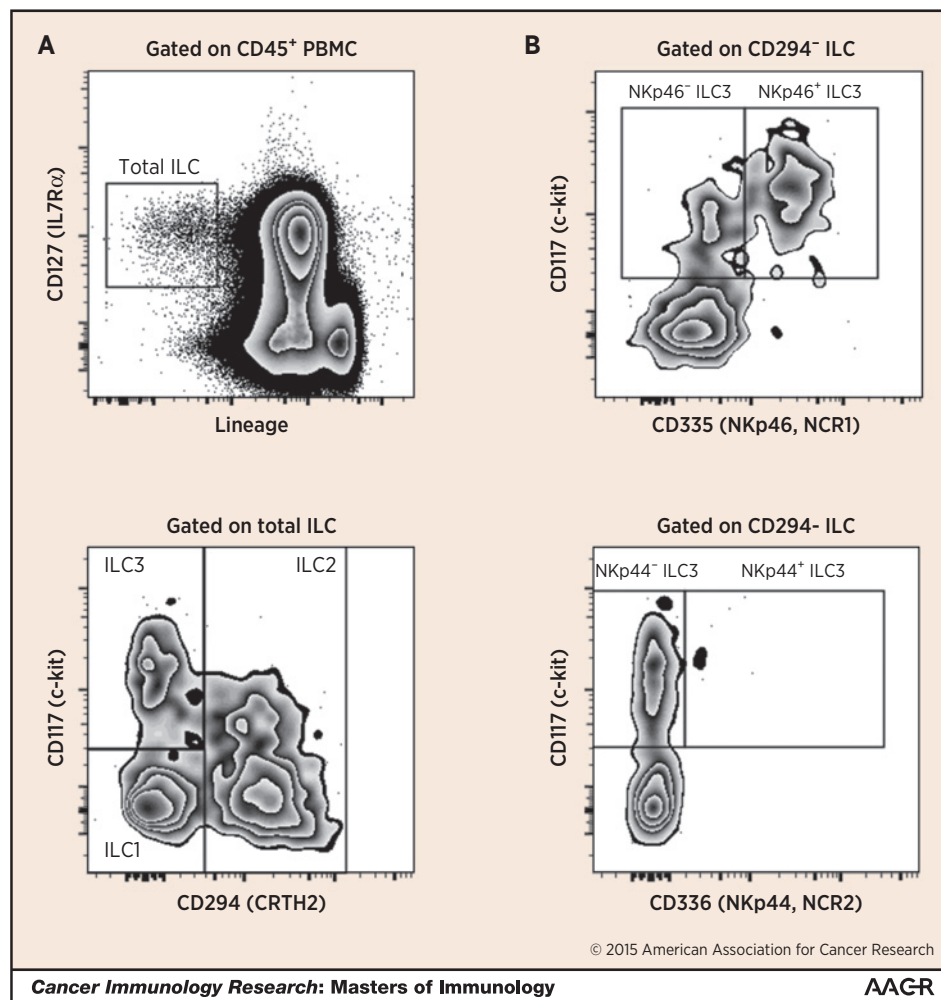
### From NK Cells to Innate Lymphoid Cells

NK cells were long considered the only lymphocytes of the innate immune system. However, lymphoid tissue-inducer (LTi) cells were subsequently defined as another subset of innate lymphoid cells (ILC), required for the formation of secondary lymphoid organs (12). In 2008, several laboratories independently identified previously unknown subsets of cells of lymphoid origin, which they referred to as ILCs (13–20). The study of ILCs is an emerging field in immunology that is having a major effect on our understanding of immune responses (21–27). Since their discovery, ILCs have been shown to contribute to defense against infection and wound healing, and recent studies have revealed critical aspects of their differentiation (21–27). Unlike adaptive immune cells, ILCs lack rearranged antigen-specific receptors, but react rapidly to a

wide range of innate signals (21–25, 28). ILCs constitute a large family of different subsets, mirroring those of T cells (21–27). Indeed, the striking similarities between ILC and T-cell subsets, in terms of the transcription factors governing their differentiation and the cytokines they produce, led to the suggestion that ILCs are the innate counterparts of T cells (Fig. 1). ILCs differentiate from common lymphoid progenitors (CLP). CLPs give rise to common helper ILC progenitors (ChILP), leading to the generation of all ILCs other than NK cells and LTi (Fig. 1; refs. 29, 30). ILCs can be classified into cytotoxic ILCs, such as NK cells, and helper-like ILCs, such as the ILC1, ILC2, and ILC3 subsets (Fig. 1).

All helper-like ILCs belong to a subset of lin-lymphocytes that express CD127 (IL7Ra). ILC1 and NK cells are subsets of ILCs that express T-bet and produce IFN $\gamma$ . NK cells are also dependent on Eomes and can be seen as an innate counterpart of CD8<sup>+</sup> T cells, whereas ILC1 are more like Th1 CD4<sup>+</sup> T cells. In humans and mice, ILC1 are best defined in the liver as CD127<sup>+</sup>NKp46<sup>+</sup>TRAIL<sup>+</sup>CD49a<sup>+</sup>CD49b<sup>-</sup> non-T, non-B lymphocytes (31, 32). In other organs, they remain ill-defined, and their link to NK cells remains a matter of debate (33). Nevertheless, a minimal phenotypic definition of ILC1 would be lin<sup>-</sup>CD127<sup>+</sup> cells that do not express c-Kit (CD117) and CRTH2 (CD194). ILC1 subsets may contribute to inflammatory bowel disease (34, 35).

ILC2 (Lin<sup>-</sup>CD127<sup>+</sup>CRTH2<sup>+</sup>) maturation is dependent on the transcription factor GATA-3, and these cells produce mostly IL5 and IL13 (18, 20). They can be seen as the innate counterparts of Th2 CD4<sup>+</sup> T cells. They are characterized by the dependence on



**Figure 2.** Flow cytometry gating strategy for the identification of human peripheral blood ILCs. ILCs are defined as  $lin^{-}CD127^{+}$  cells with a lineage cocktail containing antibodies directed against CD3, CD19, CD14, TCR $\alpha\beta$ , TCR $\gamma\delta$ , CD94, CD16, Fc $\epsilon$ R1, CD34, CD123, and CD303. Within the ILC gate, ILC2 are CD294 $^{+}$ , whereas ILC1 and ILC3 are CD294 $^{-}CD117^{-}$  and CD294 $^{-}CD117^{+}$ , respectively. This example illustrates the much lower frequency of NKp44 $^{+}$  ILC3 cells than of NKp46 $^{+}$  ILC3 in the peripheral blood of healthy individuals.

ROR $\alpha$  of their development and functions (36). ILC2 are induced systemically by helminth infection, but they also sustain metabolic homeostasis and contribute to tissue repair. Recent studies have described two subtypes of ILC2: the so-called inflammatory ILC2 (or iILC2) and natural ILC2 (nILC2), which are responsive to IL25 and IL33, respectively (37). Unlike nILC2, iILC2 express the nuclear hormone receptor ROR $\gamma$ t, enabling them to synthesize IL17. However, our understanding of this plasticity and the environmental influences affecting ILC2 development remains incomplete.

ILC3 ( $Lin^{-}CD127^{+}CD117^{+}$ ) comprise two subsets of cells defined on the basis of their cell surface expression of natural cytotoxicity receptors (NCR). It is almost 20 years since NCRs were first shown to be involved in the activation of NK cells by tumor cells (38). The NCR family consists of three molecules: NKp30 (NCR3, CD337) and NKp44 (NCR2, CD336) in humans, and NKp46 (NCR1, CD335), the only NCR conserved in all mammals (1). NKp46 was the first NCR to be identified and is expressed on NK cells regardless of their activation status

and location (1). ILC3 include NCR $^{-}$ ILC3 (including LTI-like cells after birth) and NCR $^{+}$ ILC3 cells. LTI cells were originally found in the fetus and are required for the development of lymph nodes and Peyer's patches (12). Expression of the nuclear hormone receptor ROR $\gamma$ t is necessary for the generation and function of ILC3, which secrete IL17 and IL22. Early experiments in mice showed that ILC3 played a critical role in controlling commensals and pathogenic bacteria, through their secretion of IL22 (13), whereas human studies revealed a higher proportion of NCR $^{+}$ ILC3 in the skin of psoriasis patients than in that of healthy controls (39). It has been suggested that human NCR $^{+}$  ILC3 should be defined on the basis of the cell surface expression of NKp44. However, this proposal is contentious, as NKp44 is an activation marker in NK cells and is not conserved in the mouse, making it difficult to compare ILC3 between humans and mice. We thus suggest that NCR $^{+}$  ILC3 should be defined on the basis of their cell surface expression of NKp46 (Fig. 2), which is conserved in mammals, facilitating more direct comparisons between species.

The immune system has a dual role in cancer development. On the one hand, several immune mechanisms, including natural cytotoxicity, ADCC, antibody-dependent cell phagocytosis, and complement activation, can directly attack the tumor, and others, such as the cytokine-mediated inhibition of tumor angiogenesis (e.g., via the secretion of IFN $\gamma$ ), can lead to its indirect elimination (2, 40, 41). On the other hand, immune responses may be deleterious, through the provision of an immunosuppressive environment that supports tumorigenesis and promotes tumor growth (42, 43). The factors and pathways important for wound healing may therefore also promote tumorigenesis, as demonstrated for IL22 in the gut (44, 45).

## ILCs and Gastrointestinal Tumors

### Colorectal cancers

In the intestine, chronic inflammatory responses have been shown to be associated with an increase in susceptibility to cancer; for example, inflammatory bowel disease has been shown to lead to a higher risk of colon cancer (46). The immune cells and cytokines mediating the transition from colitis to colon cancer are yet to be identified, but IL23 receptor signaling has been correlated with inflammatory bowel disease pathogenesis, and with the promotion of tumor growth. ILC3 may also play a key role in this process. Indeed, the production of IL22 by NCR<sup>+</sup> ILC3 is a key factor underlying cancer maintenance in a mouse model of colon cancer induced by bacteria (47). These data are supported by others showing that IL23 transgene expression induces the rapid development of intestinal adenomas, independently of carcinogens, *Helicobacter*, or tumor-suppressor gene mutations (48). In this model, tumorigenesis was shown to require the secretion of IL17 by ILC3, even before the development of inflammatory infiltrates. Thus, in the colon, NCR<sup>-</sup> ILC3 contribute, via their production of IL22 and IL17, to the inflammation responsible for sustaining colorectal cancer, suggesting that these cells and the cytokines IL23, IL17, and IL22 may be considered to be potential treatment targets in colon cancer.

### Gastric cancers

A predominant Th2 phenotype is correlated with a poor prognosis in patients with gastric cancer (49). In these tumors, an immunosuppressive microenvironment is maintained by the interaction between Th2 cells, myeloid-derived suppressor cells, and M2 macrophages (50). The frequency of circulating ILC2 has been shown to be high in gastric cancer patients, suggesting that these cells might contribute to the immunosuppressive microenvironment (51).

### Hepatic carcinoma

Excessive IL22 production is observed in some cases of hepatic carcinoma. This production of IL22 in humans and mice has been associated with tumorigenesis and tumor growth, the inhibition of apoptosis, and the promotion of metastasis due to STAT3 activation (52). These results suggest that it would be useful to analyze the presence and function of the ILC3 subset in liver cancers.

## ILCs and Melanoma

IL12 acts as a powerful mediator of melanoma rejection. However, it fails to repress tumor growth in *Il2rgc*-deficient mice, which lack ILCs and T cells (53). In contrast, IL12 restricts the

growth of B16 melanoma cells in Rag-deficient mice, which lack T and B cells (54). These results suggest that ILCs may be involved in the antitumor function of IL12. Consistent with this hypothesis, NCR<sup>+</sup> ILC3 cells have been shown to respond to IL12 and to contribute to the elimination of B16 melanoma cells, by upregulating adhesion molecules in the tumor vasculature, leading to greater leukocyte invasion and tumor elimination in the B16 melanoma model (55).

## ILCs in Hematologic Malignancies

The analysis of ILCs in hematologic malignancies is still in its infancy. One study reported changes in the circulating ILCs at the onset of acute myeloid leukemia (AML) in a cohort of adult patients (56). This study showed the production of cytokines by ILCs to be impaired in these patients. Furthermore, ILC1 counts increased with decreasing ILC3 counts. Bidirectional plasticity between ILC1 and ILC3 has been described in the gut, in response to various environmental changes (35). This suggests that environmental factors may also affect the plasticity of ILCs during AML. Interestingly, the percentage of ILC3 was restored in patients responding to chemotherapy. Clearly, additional longitudinal studies on large cohorts of cancer patients are required to dissect the role of ILCs in hematologic malignancies, and to determine whether it is useful to monitor circulating ILC numbers in patients during treatment.

## ILCs and Cancer Treatment

Cancer treatments include surgery, radiotherapy, chemotherapy, and hematopoietic stem cell transplantation (HSCT). Given the roles of ILCs in shaping the immune response and in the development of tumors, it will be critical to monitor the impact of cancer treatments on ILCs. The generation of ILCs during HSCT is also a matter of great interest. In a longitudinal cohort of AML patients, a slow, weak reconstitution of ILCs of donor origin was observed 12 weeks after transplantation, but no data are currently available concerning long-term reconstitution (57). In addition, two studies have suggested that further investigations into the links between ILCs and graft versus host disease (GvHD) should be carried out. GvHD is an adverse effect of HSCT characterized by tissue damage in cancer patients undergoing allogeneic HSCT. GvHD classically affects the skin and gut mucosa, leading to clinical signs that can be life-threatening. IL22 is a critical regulator of tissue sensitivity to GvHD and it also protects intestinal stem cells against inflammatory intestinal damage, such as that caused by radiotherapy/chemotherapy (58). As ILC3 can produce IL22 in mucosal tissues, it will be critical to investigate whether this subset of ILCs can protect against GvHD in cancer patients undergoing allogeneic HSCT. Consistent with this hypothesis, an association between counts of circulating Nkp44<sup>+</sup> ILC3 and an absence of GvHD has been reported in AML (57).

## Concluding Remarks

The role of ILCs in infection was investigated shortly after the identification of this new type of lymphocyte. The role of ILCs in cancer has been little studied (59), but the results of several studies suggest that more detailed investigations of this aspect should be carried out. This is true not only for gastrointestinal tumors, melanoma, and hematologic malignancies, but also for cutaneous T-cell lymphoma (mycosis fungoides and Sezary syndrome),



in which IL22 contributes to shape the tumor microenvironment (60), ovarian cancers, in which IL17 may contribute to protective tumor immunity (61), and breast cancer, in which the IL33/ST2 axis promotes cancer growth and the accumulation of ILCs (62).

Most studies on the newly identified subsets of ILCs have been focused on mice. The next major step in ILC research will be to dissect the role of ILCs in humans and to determine the extent to which these cells can be manipulated. ILCs are involved in many homeostatic processes and diseases, but no ILC-based treatments, other than those involving NK cells (10, 11), have yet been proposed. By harnessing the activity of ILCs, we may be able to improve immunotherapy and vaccines. Research programs should be designed to decipher these new immune pathways, taking into account, in particular, the unique tropism of ILCs subsets, such as ILC3, in the mucosa. ILCs may thus provide a target for new avenues of therapeutic intervention in cancer. Finally, about 4% of all cases of acute leukemia are of ambiguous

lineage (63), including acute undifferentiated leukemia expressing no lineage-specific markers and mixed-phenotype leukemia coexpressing antigens of the myeloid and lymphoid lineages (64). ILC cancers may exist and may belong to these ill-defined leukemia categories. The development of standardized reagents and protocols for monitoring the presence and function of ILCs in human blood and tissue samples is thus urgently required to address these questions.

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