HHS Public Access

Author manuscript

Semin Immunol. Author manuscript; available in PMC 2020 March 21.

Published in final edited form as:

Semin Immunol. 2019 February ; 41: 101269. doi:10.1016/j.smim.2019.03.001.

Tissue-Resident Cytotoxic Innate Lymphoid Cells in Tumor Immunosurveillance

Efstathios G. Stamatiades, **Ming O. Li***

Immunology Program, Memorial Sloan Kettering Cancer Center, New York, NY 10065, USA

Abstract

Innate lymphocytes play an important role in maintaining tissue homeostasis at steady state and during inflammation. The population of innate lymphocytes is incredibly diverse and heterogeneous with the successive identification of new subsets including innate lymphoid cells that arise from progenitors distinct from those of natural killer cells. Although generally considered as T helper-like lymphocytes, innate lymphoid cells with cytotoxic potential can be identified in many tissues. The tissue-resident cytotoxic innate lymphocytes derived from innate lymphoid cell and/or natural killer cell lineages are well positioned in sensing malignant transformation and initiating antitumor immunity. This review provides an overview of innate lymphocyte biology and discuss their roles in tumor immunosurveillance.

Keywords

Innate lymphoid cells; NK cells; tumor immunosurveillance; cytotoxicity

1. Introduction

The vertebrate immune system has evolved to exquisitely distinguish self from non-self. Cell transformation presents a unique challenge to the immune system, since malignant cells are self-derived, but also an invasive, sometimes infectious, entity[1]. The original cancer immunosurveillance hypothesis was proposed in the 1950s to postulate the function of adaptive immune cells in eliminating transformed cells[2]. Since then, studies have revealed both protective and promoting effects of the immune system on transformation[3]. Several studies investigating carcinogen-induced, virally associated, and oncogene-induced models of cancer have demonstrated a role for antigen-specific $CD8^+$ T cells in mediating a host-protective immune response[4–7]. The clinical success of anti-PD1 and anti-CTLA4 checkpoint blockade therapy further supports a role for adaptive lymphocytes in some

*Correspondence: lim@mskcc.org.

Author Contributions

EGS and MOL conceived the ideas. EGS wrote the manuscript, and MOL edited it.

Declarations of Interest

None.

cases[8]. However, many cancers do not express non-self antigens and exposure to tumor-associated antigens in oncogene-induced cancers may fail to induce host-protective T cell responses[9, 10]. Still, evidence for the necessity of immune effector molecules indicates a role for cytotoxic lymphocytes in immunosurveillance, even if antigen-specific adaptive immune responses are not engaged[11–14]. There is an accumulation of evidence that tissue-resident innate lymphocytes are critical in anti-tumor immunity. In this review, we discuss the current understanding of how the lineage, localization, and effector programs of resident innate lymphocytes dictate their tumor immunosurveillance function.

2. Innate lymphocyte subsets and their characteristics

Innate lymphocytes represent a heterogeneous group of cells derived from a common lymphoid progenitor in the bone marrow, but lack genetically rearranged antigen receptors. Based on their effector programs, innate lymphocytes have been grouped into three types, type 1 innate lymphocytes that include NK cells and innate lymphoid cells 1 (ILC1s), type 2 (ILC2s), and type 3 (ILC3s)[15], with innate lymphoid cell subsets largely viewed in the context of helper T cell biology.

Type 1 innate lymphocytes are characterized by the expression of the transcription factor T-bet (encoded by the T-box 21 gene, *Tbx21*) and by the production of type 1 cytokines, including IFN-γ and TNFα. NK cells recirculate throughout the body, express cytotoxic molecules (e.g. granzymes and perforin) and were the first member of innate lymphocytes to be reported in the 1970s[16–18], while type 1 ILCs express similar surface markers like NK cells and have been identified in many organs (e.g. liver and salivary gland)[19]. Yet, their exact function is less well defined. Due to their resemblance to NK cells at the phenotypic level, studies that deplete NK marker-expressing populations (e.g. through antibodies or diphtheria toxin system) inadvertently eliminated type 1 ILCs as well. New emerging genetic tools are needed that target specifically type 1 ILCs but not NK cells. For instance, by using *Zfp683*$^{-/-}$ (Hobit-deficient) mice, which have reduced liver ILCs but not conventional NKs, it was proposed that liver ILCs are important for the early response to mouse cytomegalovirus, because *Zfp683*$^{-/-}$ mice had increased viral load[20].

Type 2 innate lymphocytes (ILC2s) require the transcription factors GATA3 and RORα and produce type 2 cytokines (e.g. IL-5 and IL-13)[21, 22]. ILC2s are the most homogenous among the innate lymphocytes. They are helper cells that control normal immune responses through cross-talk between stroma and other immune cell types, e.g. in helminth infection[23] and allergic inflammation[24, 25].

Type 3 innate lymphocytes (ILC3s) can be defined as IL-17 and IL-22 producing cells that require the transcription factor RORγ for their development and function[26]. ILC3s help maintain intestinal homeostasis by producing IL-22, which in turn triggers antimicrobial peptide production by intestinal epithelium[27–29]. In the lung it was shown that IL-17 produced by ILC3s is required for monocyte-mediated clearance of *Klebsiella pneumoniae*, demonstrating a critical role for ILC3s in maintaining lung homeostasis[30].

Innate lymphocytes are derived from the common lymphoid progenitor (CLP) in mice[31]. A common progenitor for all ILCs, termed innate lymphoid cell progenitor (ILCP) has been identified in the bone marrow, which has lost NK cell differentiation potential and expresses both the transcription factor PLZF and the surface marker PD1 (Table 1)[32, 33]. Indeed, cell fate-mapping and adoptive cell transfer experiments convincedly demonstrated that circulating conventional NK cells and tissue resident

ILCs are distinct lineages of lymphocytes[32, 34]. Conventionally, ILCs are defined as helper cells capable of producing cytokines but lacking cytolytic activity. Nevertheless, recent studies have identified populations of tissue-resident innate lymphocytes that express perforin, granzymes, and death receptors (e.g. TNF-related apoptosis-inducing ligand, TRAIL), suggesting their cytolytic potential. These populations have been named tissue-resident NK cells in the liver[35]. Although some liver-resident cytolytic innate lymphocytes might be differentiated along the NK cell lineage, recent evidence based on their developmental requirements points to their closer relationship to ILC1s than NK cells. Genetic studies have demonstrated that NK cells require the transcription factors *Nfil3*[36] and *Eomes*[37] for development and maintenance. The majority of liver-resident CD49a $^{+}$CD127^{low} innate lymphocytes develop independently of *Nfil3* and *Eomes*, suggesting their closer lineage relationship to ILC1s than NK cells[35, 37]. Additionally, CD49a^{+}CD127^{low} innate lymphocytes share a similar progenitor with all other ILCs[34]. Hence, based on their cytotoxic potential we propose that type 1 ILCs could be further divided in two subsets: helper ILC1s, which are IL-7R-expressing cytokine producers, and killer ILCs (ILCks), which express cytotoxic molecules but have little to no IL-7R expression (Figure 1A)[38]. Yet, further work is required in order to define whether cytotoxic tissue resident innate lymphocytes are all ILCks or can, as well, be differentiated from NK cell lineage, as the *bona fide* tissue resident NK cells (trNK).

Both NK cells and ILC subsets have been described in humans[39]. Yet, the differentiation of NK and ILC lineages in humans remains less well understood. A NK-committed precursor with no helper-ILC potential has been identified[40]. Recently, a human circulating ILCP with potential for CD56^{+} cytotoxic lymphocytes and helper ILC1, 2, and 3 has been described[41]. This multipotent progenitor was present in lymphoid and non-lymphoid tissues of *Rorc*-deficient patients and retain potential for IFN-γ producing ILC1s, IL-13 producing ILC2s, and for IL-22, but not for IL-17A producing ILC3s as well as cytotoxic innate lymphocytes [41]. Considering that mouse ILCP can give rise to ILCks, it raises the possibility that the CD56^{+} cytotoxic lymphocytes are their human equivalents.

Although innate lymphocytes have been grouped into three types, with defined effector activities, an increasing literature suggest they exhibit functional plasticity in the presence of appropriate environmental stimuli[42, 43]. *In vitro*, culture of human type 3 innate lymphocytes with IL-2 or IL-15 will induce their conversion to IFN-γ producing type I innate lymphocytes[44, 45]. In addition, it has been shown that IL-23 could drive the opposite effect, i.e. the differentiation of ILC1 to ILC3[44]. *In vivo*, it was shown that CCR6$^{–}$NKp46^{+} ILC3s can convert into IFN-γ-producing NK1.1^{+} ILC1s, associated with reduced expression of Rorγt and increased expression of T-bet[46]. IL-12 and IL-1β have been shown to promote the conversion of ILC2s into IFN-γ producing ILC1-like cells[47–

49]. Additionally, it is unknown if helper cytokine producing ILC1s can convert to ILCks that express cytotoxic molecules.

3. Tissue-resident cytotoxic innate lymphocyte responses in cancer

As mentioned earlier, cell transformation presents a unique challenge to the immune system. The first described member of innate lymphocytes with anti-cancer properties were the NK cells. NK cells were initially identified and named on the basis of their ability to kill tumor cells *in vitro*[50]. The first evidence of a protective role of NK1.1+ cells (which the authors defined as NK cells) came from chemically-induced sarcoma and transplantable tumor models[12, 51]. These initial findings were confirmed in mice that lack natural killer cell p46-related protein (NKp46) [52–54]. However, most of these studies were done before the heterogeneity of group 1 innate lymphocytes was recognized. The use of depleting antibodies against NK1.1 or *NKp46*$^{-/-}$ mice target and eliminate not only conventional NK cells but also ILCs, since both cell populations express NK1.1 and NKp46. Therefore, it is difficult to conclude which of the affected populations contributes to the reported phenotype[55].

Compared to conventional circulating NK cells, tissue-resident cytotoxic innate lymphocytes are in an ideal place to play a primary role in sensing malignant transformation and initiating antitumor immunity. A recent study in PyMT-driven breast cancer, demonstrated that early control of tumor progression is critically dependent on CD49a^{+}NK1.1^{+} tumor-resident innate lymphocytes[56]. In this model, conventional NK cells were dispensable for anti-tumor responses because *Nfil3*-deficient mice, in which NK cells are diminished, did not exhibit accelerated tumor growth[56]. These ILC1-like cells expressed granzyme B and exhibited perforin-dependent cytotoxicity against tumor cells *in vitro*. Nonetheless, it remains to be determined whether they are derived from ILCPs, which will qualify them as ILCks; are differentiated from progenitors along the NK cell lineage, which will classify them as trNK; or are a mixed population of diverse origin.

Studies in humans have shown that many types of solid tumors are infiltrated by innate lymphocytes. Although the authors of these studies collectively named the infiltrated innate lymphocytes as NK cells, these cells can be distinguished in two populations based on the makers CD56 and CD16[57–60]. The CD56^{bright}CD16^{-} subset was enriched in tissues and expressed several tissue-resident markers[59, 60]. Clinical evidences suggest a potential anti-tumor role for type 1 innate lymphocytes and CD56^{bright} lymphocytes in clear cell renal carcinoma and gastrointestinal tumors respectively[61, 62].

In contrast, the CD56^{dim}CD16^{+} population was more abundant in the blood. It has been reported that some CD56^{bright} NK cells have longer telomeres compared to CD56^{dim} cells and can acquire the expression of CD16 and killer Ig-like receptors, *in vitro* as well as *in vivo* after transfer into immunodeficient mice[63–66]. These data support the theory of a linear developmental pathway in human NK cells, according to which CD56^{bright} cells give rise to CD56^{dim} NK cells [67]. Yet, more detailed analysis of human NK cell development and differentiation is needed in order to establish if CD56^{bright} and CD56^{dim} NK cells are of separate lineages or if CD56^{bright} cells are the progenitors of CD56^{dim} cells.

Some reports in the literature suggest that ILCs might facilitate tumor growth. It has been proposed that TGF-β signaling induces the conversion of NK cells into ILC1s, decreasing the control of local tumor growth and increasing metastasis[68, 69]. However, lineage tracing and adoptive cell transfer experiments have demonstrated that NK cells develop from distinct progenitors from those of $CD127^+$ helper ILCs and ILCks, , making NK to ILC conversion unlikely[32, 34]. Perhaps, the ILC-type of cells observed in these experiments are better defined as tissue-resident NK cells. To what extent the ILC versus NK cell lineages contribute to the tumor-resident type 1 innate lymphocyte pool and whether they have different functions remain to be determined. In humans, ILC1s have been correlated with colorectal carcinoma due to the observations that, first, ILC1s are increased in numbers and contribute to the pathology of inflammatory bowel disease (IBD)[44, 70] and, second, the incidence of colorectal carcinoma is higher in patients with IBD[71]. Yet, a direct role for ILC1s in the pathogenesis of colorectal carcinoma has not been demonstrated.

4. How do tissue-resident cytotoxic innate lymphocytes sense cell transformation?

In contrast to normal tissue development and remodeling, malignancy is associated with uncontrolled cell proliferation, loss of cell polarization, irregular angiogenesis, extracellular matrix re-organization and cell death. All these stimuli can directly or indirectly shape the fate of immune cells. Because parabiosis experiments suggested that, at least at steady state, tissue-resident cytotoxic innate lymphocytes are maintained through self-renewal with minimal contribution from bone marrow derived precursors[72], ILCs are in an ideal position to detect any ‘stress’ signals and respond accordingly. In the next chapter we will discuss and propose how ILCs could sense cell transformation.

4.1 IL-15 as alarmin

IL-15 is a cytokine important for differentiation, maintenance, and function of lymphocytes (e.g. T and NK cells)[73]. The IL-15 receptor (IL-15R) consists of a unique IL-15R α-chain (IL-15Rα), a β-chain (IL-2/IL-15Rβ), and a common cytokine receptor γ-chain (γc)[73]. IL-15 functions through transpresentation of an IL-15/IL-15Rα complex to recipient cells expressing IL-2/15Rβ and γc[74]. IL-15 deficiency impairs cytotoxic innate lymphocytes in the liver, salivary glands, and the small intestine lamina propria[34, 75, 76]. Since IL-15 has pleiotropic roles, it is still unknown if IL-15 is required for the development of innate lymphocytes, their maintenance or both. Although mice deficient for γc lack mature innate lymphocytes, innate lymphocyte progenitors are minimally affected[77], suggesting that γc signaling is required for the maintenance of the mature populations. Additionally, since IL-15 is expressed by many cells types[78], it is challenging to conclude which cell types control the development of specific lymphocytes. Animal studies have shown that myeloid-derived IL-15 supports the development and maintenance of circulating NK[79] and CD8 T cells[80]. Yet, further work is required to demonstrate if myeloid derived IL-15 as well regulates the development of tissue-resident cytotoxic innate lymphocytes.

It has been proposed that IL-15 is a stress induced “alarmin” that is express by distressed cells and license cytotoxic tissue resident mphocytes to become killers and destroy these

damaged cells[81]. In PyMT-driven breast cancer model, absence of IL-15 leads to loss of tissue-resident cytolytic innate lymphocytes and accelerated tumor growth[56]. Overexpression of IL-15 resulted in expansion of cytolytic innate lymphocytes and tumor protection[56]. Hence, it is plausible that IL-15 transpresentation could activate and license mammary gland ILC1ls to kill transformed cells (Figure 1B). Yet, since IL-15 can be expressed by many cells (e.g. epithelial cells, fibroblasts, endothelial cells)[81], the source of IL-15 in this model is unknown. Of note, IL-15 can also be produced by tumor cells[82]. A human study in patients with colorectal carcinoma concluded that IL-15 produced in the tumor microenvironment enhanced T cell responses and promoted survival[82]. In contrast, decreased IL-15 expression affected the local proliferation of T lymphocytes and correlated with a higher risk of tumor recurrence and poor patient survival[82]. Further work is needed in order to convincedly demonstrate if IL-15 produced by tumor cells or other cells acts as an alarmin for cytotoxic tissue resident innate lymphocytes.

4.2 IL-12-mediated tumor suppression

IL-12 is a heterodimer, consisting of a heavy (p40) and a light (p35) chain subunit, which are covalently linked by disulfide bonds[83]. The sensing of IL-12 is mediated through the heterodimeric IL-12 receptor (IL-12R) composed of IL-12Rβ1 and IL-12Rβ2[84]. IL-12 links innate and adaptive immune responses. It is mainly produced by myeloid cells[85] and subsequently it mediates the activation, proliferation and polarization of lymphocytes[84]. Mice lacking the IL-12 specific subunit p35 are more susceptible to carcinogen-induced tumors[86–88], while mice that lack IL-12Rβ2 develop spontaneous tumors[89]. These observations suggest that IL-12 has an important role in anti-tumor immunity.

In order to delineate the mechanisms by which IL-12 induces antitumor immune responses, numerous reports have engineered tumor cells to produce IL-12[90–93]. In an IL-12 producing B16 melanoma model, it was shown that antitumor immunity is mediated by NKp46$^+$ RORγt$^+$ cells[90], while rejection of breast cancer TSA cells was dependent on IFN-γ secreting CD8$^+$ cytotoxic T cells[93]. These results show that tumor cell type and tumor location determine the IL-12-mediated tumor-specific immune responses. Yet, the physiological relevance of these models is debatable since IL-12 is mainly produced by myeloid cells[85]. In addition, it needs to be determined if IL-12 can also activate tissue-resident cytotoxic innate lymphocytes to inhibit tumor growth.

4.3 Type I interferon in anti-tumor immunity

Type I interferons (IFNs) were initially identified as antiviral substances[94]. They are a family of monomeric cytokines consisting of 14 IFNα subtypes, IFNβ, IFNε, IFNκ, and IFNω. While IFNα and IFNβ have been extensively studied during the past decades, the functions of IFNε, IFNκ, and IFNω remain poorly understood[95]. IFNα and IFNβ signal through the interferon α/β receptor (IFNAR) and the JAK-STAT pathway to drive the expression of IFN-regulated genes. Beyond their role in anti-viral immunity, a growing number reports provided evidence that type I IFNs exhibit antitumor functions, in part, by lymphocyte activation[96].

Among innate lymphocytes, NK1.1$^+$ cells have been proposed to be the effector cell for type I IFNs-mediated tumor rejection. Using IFNAR-deficient mice it was shown that there is impairment of NK cell development in mice with germline deletion of IFNAR[97]. Swann et al further demonstrated that IFNAR-deficient NK cells exhibit impaired activation, reduced cytotoxity and fail to protect mice against carcinogen-induced fibrosarcomas[98]. Yet, a more recent report utilized conditional deletion of IFNAR on NKp46$^+$ cells and showed that although type I IFNs signaling on NKp46$^+$ cells is essential for cytotoxicity *in vitro*, it is not required for efficient tumor surveillance in *vivo*[99], suggesting that *in vivo* other mechanisms could compensate for type I IFNs signaling. Nowadays, with the recognized complexity of innate lymphocyte family additional work is needed to better characterize the role of type I IFN on tissue-resident cytotoxic innate lymphocyte-dependent cancer immunosurveillance.

4.4 Activating and inhibitory NK cell receptors

Tissue-resident cytotoxic innate lymphocytes express many activating and inhibitory NK cell receptors[100]. Therefore, it can be hypothesized that cytotoxic innate lymphocytes can sense and kill non-healthy, stressed or transformed cells in the tissue. Activating receptors, bind ligands induced by cellular stress, infection, or tumor transformation[101]. Activating signals are transmitted through immunoreceptor tyrosine-based activating motifs (ITAMs) located in the cytoplasmic tail of the receptor or through ITAMs in adaptor molecules, which associate with activating receptors at the cell surface[102]. Inhibitory receptors bind cell surface MHC antigen class I molecules expressed by healthy cells and signal through immunoreceptor tyrosine-based inhibitory motifs (ITIMS)[103].

It has been shown that the activating receptor NKG2D is not necessary for innate lymphocyte development[11], yet it promotes the rejection of tumors that express or even shed NKG2D ligands[11, 104]. NKG2D ligands (e.g. MHC class I chain–related proteins A and B, MICA and MICB) are poorly expressed by normal cells but are up-regulated in cancer cells[105]. The recently identified ILC1ls that mediate cancer immunosurveillance in PyMT-driven mammary tumors and TRAMP model of prostate cancer constitutively express NKG2D, similar to conventional NK cells. Their rapid response in precancerous lesions could be attributed to their ability to sense tumor-associated stress signals, including the NKG2D ligands (Figure 1B). In addition, the lack of NK cells in *Nfil3*$^{-/-}$ mice did not affect tumor growth, suggesting that the previously demonstrated tumor suppressor function of NKG2D in the TRAMP model[11] may be attributed to ILC1ls instead of NK cells. Yet, it remains to be determined whether NKG2D (or other activating NK receptors) expressed on ILC1ls and which of its ligands expressed on tumor cells mediate tumor cell recognition.

Among the activating receptors is a specialized group of receptors termed natural cytotoxicity receptors (NCRs), comprising NKp46, NKp44 and NKp30 receptors[106]. They are type I transmembrane proteins belonging to the immunoglobulin superfamily and are composed of one or two extracellular immunoglobulin-like domains, which are responsible for ligand binding. Although it had been initially shown that NCRs are important for the killing of transformed cells, the first ligands identified for the NCRs were viral proteins (e.g. recognition of haemagglutinins by NKp46 and NKp44[107, 108]). It has been reported that

all three NCRs could bind to different heparan sulphates moieties, present on healthy and transformed cells[109, 110]. Nevertheless, the report that there was no influence on the activation of NK cells regardless of whether heparan sulphate was expressed on the cell surface of a target cell or not[111], prompt the notion that heparan sulphate might act as coreceptors in complex with other ligands to modify the NK cell response[106]. Proliferating cell nuclear antigen (PCNA), which is overexpressed on tumor cells[112], was the first cellular molecule identified as ligand for NKp44[113]. Since NKp44-PCNA ligation inhibits NK-cell mediated tumor cell killing[113], tumor cells might exploit his mechanism to avoid killing by NK cells. More recently, platelet-derived growth factor (PDGF)-DD has been identified as a new ligand for NKp44[114]. Engagement of NKp44 triggered NK cell secretion of IFNγ and alpha TNFα that induced tumor cell growth arrest[114].

Siglecs is a lectin family of surface receptors that bind to sialoglycans and are predominantly expressed on cells of the hematopoietic system[115]. Distinct sialoglycan structures are recognized by individual Siglec receptors, depending on identity and linkage to subterminal carbohydrate moieties[116]. Siglec-7 and-9 are inhibitory receptors, containing their own cytoplasmic ITIM motif[116]. A number of primary tumors express glycan ligands for Siglec-7 and Siglec-9, and expression, or lack thereof, of these ligands correlates with cytotoxicity of NK cells towards susceptible versus resistant tumors[117]. These results suggest that cancers expressing high levels of Siglec-7 and −9 ligands may evade NK cell killing. In support of this notion, it was shown that increasing sialylated glycans on cancer cells inhibits human NK cell activation through the recruitment of Siglec-7[118]. Yet, whether blockade of Siglec-7 and −9 would promote cancer immunosurveillance by tissue-resident cytotoxic innate lymphocytes needs to be further investigated.

The inhibitory NK receptors expressed by NK cells are important to mediate functional maturation of NK cells, termed “licensing”[119]. Licensing involves the engagement of inhibitory receptors with major histocompatibility complex (MHC) class I molecules on the surface of the target cell, resulting in blockage of NK cell activation[120]. Yet, it is currently unknown if such a maturation process mediated by inhibitory NK receptors takes place in tissue resident cytotoxic innate lymphocytes.

4.5 Extracellular matrix cues

The extracellular matrix (ECM) is defined as the non-cellular component of tissue that provides both biochemical and essential structural support for its cellular constituents[121]. ECM is not a passive intercellular filling. It is an active component of the tissue, responsible for cell–cell communication, cell adhesion, and cell proliferation[122]. It has long been recognized that deregulated ECM dynamics play an important role in cancer initiation and progression. ECM stiffness enhances cell growth and survival and promotes migration[123], and ECM rigidity disrupts tissue morphogenesis by increasing cell tension[124]. Reduction of cell tension repressed the malignant behavior of mammary epithelial cells and normalized the behavior of breast cancer cells in culture[124].

Although ECM stiffness could regulate malignancy by enhancing integrin-dependent mechanotransduction to tumor cells, it could also regulate lymphocyte functions[125]. Mechanical cues from ECM are transduced to cells mainly via integrins, which initiate

biochemical signaling and stimulate cytoskeletal remodeling[126]. Tissue-resident type 1-like innate lymphoid cells in the mammary gland express the integrin α1β1 (also known as CD49a or VLA1)[56]. The best-known ligands for CD49a are the collagens[127]. CD49a could regulate ILC1ls by multiple ways. It could promote their tissue retention at steady state and their expansion in tumorigenesis as shown for T cells and monocytes in inflammation[128–131]. Secondly, CD49a could promote ILC1ls cytotoxicity by stabilizing adhesion to ECM proteins on target cells, as shown for β1 and β3 integrins in $CD8^+$ cytotoxic T lymphocytes[132]. Additionally, transformation-mediated ECM remodeling and stiffness could be transduced to ILC1ls as a 'stress' or 'danger' signal, which will lead to their activation (Figure 1B).

ECM could also shape lymphocyte function by proving a source of TGF-β[133]. Transforming growth factor-β (TGF-β) is a pleiotropic cytokine, which has three known mammalian family members (TGF-β1, -β2, and -β3) that regulate multiple physiological processes[134]. The pivotal function of TGF-β in the immune system is to maintain tolerance via the regulation of lymphocyte proliferation, differentiation, and survival[135]. TGF-β has been shown to promote tissue retention of $CD8^+$ memory T cells[136, 137], which have been associated with better prognosis in melanoma[138] and lung cancer[139]. TGF-β also induces CD103 expression[140], which is required for the retention of tissue-resident lymphocytes[141–143]. In addition to conventional T cells, recent evidences suggest that TGF-β regulates the differentiation of innate lymphocytes. In salivary gland, deletion of *Tgfbr2* in *NKp46* expressing cells (which includes ILCs and NK cells) resulted in significantly reduced numbers of innate lymphocytes, with concomitant loss of tissue residency markers (e.g. CD49a), and effector molecules (e.g. TRAIL)[144]. Whether or not ECM-TGF-β regulates the maintenance and differentiation of tissue-resident cytotoxic innate lymphocytes in transformed tissues remains an open question.

4.6 E-Cadherin-CD103 axis

Cell-cell adhesion and formation of epithelial barriers is a fundamental process in embryonic development and morphogenesis. Cadherins comprise a large family of transmembrane or membrane-associated glycoproteins that mediate specific cell-cell adhesion in a Ca^{2+}-dependent manner. Among cadherins, E-cadherin is considered the prototype of all cadherins[145]. E-cadherin is frequently deleted, mutated or epigenetically silenced in solid tumors, the majority of which are carcinomas derived from epithelial tissues[145]. Although E-cadherin is considered a tumor suppressor gene, deletion of E-cadherin alone is insufficient to cause tumorigenesis[146].

Beyond the role of E-cadherin in epithelial barrier function, recent findings have highlighted a role of E-cadherin in shaping immune cells. The integrin CD103 (αEβ7) expressed on many immune cells (including innate lymphocytes in salivary gland[144], and mammary gland[56]) binds to E-cadherin. Overall, a robust body of evidence indicates that CD103 is involved in tissue-specific retention and/or effector functions of immune cells[141–143]. In cytotoxic lymphocytes it was demonstrated that αEβ7 interaction with E-cadherin is required for cytolytic granule polarization and subsequent exocytosis[147]. Similarly, E-

cadherin homophilic interactions between Langerhans cells (LCs) and keratinocytes is required for the differentiation of LCs into Langerin$^+$ cells[148].

In the mammary gland tumor model tissue-resident cytotoxic ILC1ls express high levels of CD103[56]. It is possible that E-cadherin-CD103 axis maintains ILC1ls localization within the epithelial barrier and stabilizes epithelial cell-ILC1ls interactions allowing ILC1ls to perform their tumor immunosurveillance functions (Figure 1B).

Concluding Remarks

Over the last years our knowledge about lymphocyte evolution and lymphocyte-mediated immune responses has increased tremendously with the discovery of the incredibly diverse and heterogeneous group of innate lymphoid cells. Albeit controversial, increasing evidences suggest that tissue-resident cytotoxic innate lymphocytes can mediate antitumor immunity. Yet, more work is needed to shed light on their precise, their ontogeny and mechanisms of tumor sensing, before targeting these cells for cancer immunotherapy.

Funding

This work was supported by the National Institute of Allergy and Infectious Diseases (R01 CA198280–01 to ML), the Howard Hughes Medical Institute (Faculty Scholar Award to ML), Functional Genomics Initiative grant by MSKCC, and the Memorial Sloan Kettering Cancer Center Support Grant/Core Grant (P30 CA008748). EGS is a recipient of a Fellowship from the Alan and Sandra Gerry Metastasis and Tumor Ecosystems Center of MSKCC.

References

1. Hanahan D and Weinberg Robert A. (2011) Hallmarks of Cancer: The Next Generation. Cell 144 (5), 646–674. [PubMed: 21376230]
2. Burnet FM (1971) Immunological surveillance in neoplasia. Transplant Rev 7, 3–25. [PubMed: 5146537]
3. Grivennikov SI et al. (2010) Immunity, inflammation, and cancer. Cell 140 (6), 883–99. [PubMed: 20303878]
4. Shankaran V et al. (2001) IFNgamma and lymphocytes prevent primary tumour development and shape tumour immunogenicity. Nature 410 (6832), 1107–11. [PubMed: 11323675]
5. Koebel CM et al. (2007) Adaptive immunity maintains occult cancer in an equilibrium state. Nature 450 (7171), 903–7. [PubMed: 18026089]
6. Matsushita H et al. (2012) Cancer exome analysis reveals a T-cell-dependent mechanism of cancer immunoediting. Nature 482 (7385), 400–4. [PubMed: 22318521]
7. DuPage M et al. (2012) Expression of tumour-specific antigens underlies cancer immunoediting. Nature 482 (7385), 405–9. [PubMed: 22318517]
8. Topalian SL et al. (2012) Targeting the PD-1/B7-H1(PD-L1) pathway to activate anti-tumor immunity. Curr Opin Immunol 24 (2), 207–12. [PubMed: 22236695]
9. Willimsky G and Blankenstein T (2005) Sporadic immunogenic tumours avoid destruction by inducing T-cell tolerance. Nature 437 (7055), 141–6. [PubMed: 16136144]
10. Savage PA et al. (2008) Recognition of a ubiquitous self antigen by prostate cancer-infiltrating CD8+ T lymphocytes. Science 319 (5860), 215–20. [PubMed: 18187659]
11. Guerra N et al. (2008) NKG2D-deficient mice are defective in tumor surveillance in models of spontaneous malignancy. Immunity 28 (4), 571–80. [PubMed: 18394936]
12. Smyth MJ et al. (2000) Perforin-mediated cytotoxicity is critical for surveillance of spontaneous lymphoma. J Exp Med 192 (5), 755–60. [PubMed: 10974040]

13. Street SE et al. (2007) Host perforin reduces tumor number but does not increase survival in oncogene-driven mammary adenocarcinoma. Cancer Res 67 (11), 5454–60. [PubMed: 17545627]
14. Finnberg N et al. (2008) TRAIL-R deficiency in mice promotes susceptibility to chronic inflammation and tumorigenesis. J Clin Invest 118 (1), 111–23. [PubMed: 18079962]
15. Klose CSN and Artis D (2016) Innate lymphoid cells as regulators of immunity, inflammation and tissue homeostasis. Nature Immunology 17, 765. [PubMed: 27328006]
16. Kiessling R et al. (1975) “Natural” killer cells in the mouse. I. Cytotoxic cells with specificity for mouse Moloney leukemia cells. Specificity and distribution according to genotype. European Journal of Immunology 5 (2), 112–117. [PubMed: 1234049]
17. Kiessling R et al. (1975) “Natural” killer cells in the mouse. II. Cytotoxic cells with specificity for mouse Moloney leukemia cells. Characteristics of the killer cell. European Journal of Immunology 5 (2), 117–121. [PubMed: 1086218]
18. Herberman RB et al. (1975) Natural cytotoxic reactivity of mouse lymphoid cells against syngeneic and allogeneic tumors. I. Distribution of reactivity and specificity. International Journal of Cancer 16 (2), 216–229. [PubMed: 50294]
19. Spits H et al. (2016) NK cells and type 1 innate lymphoid cells: partners in host defense. Nature Immunology 17, 758. [PubMed: 27328005]
20. Weizman O-E et al. (2017) ILC1 Confer Early Host Protection at Initial Sites of Viral Infection. Cell 171 (4), 795–808.e12. [PubMed: 29056343]
21. Wong SH et al. (2012) Transcription factor RORα is critical for nuocyte development. Nature Immunology 13, 229. [PubMed: 22267218]
22. Hoyler T et al. (2012) The Transcription Factor GATA-3 Controls Cell Fate and Maintenance of Type 2 Innate Lymphoid Cells. Immunity 37 (4), 634–648. [PubMed: 23063333]
23. von Moltke J et al. (2015) Tuft-cell-derived IL-25 regulates an intestinal ILC2–epithelial response circuit. Nature 529, 221. [PubMed: 26675736]
24. Lund S et al. (2013) Type 2 Innate Lymphoid Cells in Allergic Disease. Current Immunology Reviews 9 (4), 214–221. [PubMed: 24876829]
25. Martinez-Gonzalez I et al. (2015) Lung ILC2s link innate and adaptive responses in allergic inflammation. Trends in Immunology 36 (3), 189–195. [PubMed: 25704560]
26. Cording S et al. (2014) Development and regulation of RORγt+ innate lymphoid cells. FEBS Letters 588 (22), 4176–4181. [PubMed: 24681095]
27. Sanos SL et al. (2008) RORγt and commensal microflora are required for the differentiation of mucosal interleukin 22–producing NKp46+ cells. Nature Immunology 10, 83. [PubMed: 19029903]
28. Sawa S et al. (2011) RORγt+ innate lymphoid cells regulate intestinal homeostasis by integrating negative signals from the symbiotic microbiota. Nature Immunology 12, 320. [PubMed: 21336274]
29. Zheng Y et al. (2008) Interleukin-22 mediates early host defense against attaching and effacing bacterial pathogens. Nature Medicine 14, 282.
30. Xiong H et al. (2016) Innate Lymphocyte/Ly6Chi Monocyte Crosstalk Promotes Klebsiella Pneumoniae Clearance. Cell 165 (3), 679–689. [PubMed: 27040495]
31. Yang Q et al. (2015) TCF-1 upregulation identifies early innate lymphoid progenitors in the bone marrow. Nature Immunology 16, 1044. [PubMed: 26280998]
32. Constantinides MG et al. (2014) A committed precursor to innate lymphoid cells. Nature 508, 397. [PubMed: 24509713]
33. Yu Y et al. (2016) Single-cell RNA-seq identifies a PD-1hi ILC progenitor and defines its development pathway. Nature 539, 102. [PubMed: 27749818]
34. Klose Christoph S.N. et al. (2014) Differentiation of Type 1 ILCs from a Common Progenitor to All Helper-like Innate Lymphoid Cell Lineages. Cell 157 (2), 340–356. [PubMed: 24725403]
35. Sojka DK et al. (2014) Tissue-resident natural killer (NK) cells are cell lineages distinct from thymic and conventional splenic NK cells. eLife 3, e01659. [PubMed: 24714492]
36. Di Santo JP (2009) A defining factor for natural killer cell development. Nature Immunology 10, 1051. [PubMed: 19767724]

37. Pikovskaya O et al. (2016) Cutting Edge: Eomesodermin Is Sufficient To Direct Type 1 Innate Lymphocyte Development into the Conventional NK Lineage. The Journal of Immunology 196 (4), 1449. [PubMed: 26792802]
38. Chou C and Li MO (2018) Re(de)fining Innate Lymphocyte Lineages in the Face of Cancer. Cancer Immunology Research 6 (4), 372. [PubMed: 29610422]
39. Montaldo E et al. (2016) Human innate lymphoid cells. Immunology Letters 179, 2–8. [PubMed: 26844414]
40. Renoux Virginie M. et al. (2015) Identification of a Human Natural Killer Cell Lineage-Restricted Progenitor in Fetal and Adult Tissues. Immunity 43 (2), 394–407. [PubMed: 26287684]
41. Lim AI et al. (2017) Systemic Human ILC Precursors Provide a Substrate for Tissue ILC Differentiation. Cell 168 (6), 1086–1100.e10. [PubMed: 28283063]
42. Colonna M (2018) Innate Lymphoid Cells: Diversity, Plasticity, and Unique Functions in Immunity. Immunity 48 (6), 1104–1117. [PubMed: 29924976]
43. Gronke K et al. (2016) Innate lymphoid cells, precursors and plasticity. Immunology Letters 179, 9–18. [PubMed: 27394700]
44. Bernink Jochem H. et al. (2015) Interleukin-12 and −23 Control Plasticity of CD127+ Group 1 and Group 3 Innate Lymphoid Cells in the Intestinal Lamina Propria. Immunity 43 (1), 146–160. [PubMed: 26187413]
45. Cella M et al. (2010) Expansion of human NK-22 cells with IL-7, IL-2, and IL-1β reveals intrinsic functional plasticity. Proceedings of the National Academy of Sciences 107 (24), 10961.
46. Vonarbourg C et al. (2010) Regulated expression of nuclear receptor RORγt confers distinct functional fates to NK cell receptor-expressing RORγt(+) innate lymphocytes. Immunity 33 (5), 736–751. [PubMed: 21093318]
47. Lim AI et al. (2016) IL-12 drives functional plasticity of human group 2 innate lymphoid cells. The Journal of Experimental Medicine 213 (4), 569. [PubMed: 26976630]
48. Ohne Y et al. (2016) IL-1 is a critical regulator of group 2 innate lymphoid cell function and plasticity. Nature Immunology 17, 646. [PubMed: 27111142]
49. Silver JS et al. (2016) Inflammatory triggers associated with exacerbations of COPD orchestrate plasticity of group 2 innate lymphoid cells in the lungs. Nature immunology 17 (6), 626–635. [PubMed: 27111143]
50. Trinchieri G (1989) Biology of Natural Killer Cells In Advances in Immunology (Dixon FJ ed), pp. 187–376, Academic Press.
51. Smyth MJ et al. (2001) NK cells and NKT cells collaborate in host protection from methylcholanthrene-induced fibrosarcoma. International Immunology 13 (4), 459–463. [PubMed: 11282985]
52. Glasner A et al. (2012) Recognition and Prevention of Tumor Metastasis by the NK Receptor NKp46/NCR1. The Journal of Immunology 188 (6), 2509. [PubMed: 22308311]
53. Halfteck GG et al. (2009) Enhanced In Vivo Growth of Lymphoma Tumors in the Absence of the NK-Activating Receptor NKp46/NCR1. The Journal of Immunology 182 (4), 2221. [PubMed: 19201876]
54. Glasner A et al. (2018) NKp46 Receptor-Mediated Interferon-γ Production by Natural Killer Cells Increases Fibronectin 1 to Alter Tumor Architecture and Control Metastasis. Immunity 48 (1), 107–119.e4. [PubMed: 29329948]
55. Jiao Y et al. (2016) Type 1 Innate Lymphoid Cell Biology: Lessons Learnt from Natural Killer Cells. Frontiers in Immunology 7, 426. [PubMed: 27785129]
56. Dadi S et al. (2016) Cancer Immunosurveillance by Tissue-Resident Innate Lymphoid Cells and Innate-like T Cells. Cell 164 (3), 365–77. [PubMed: 26806130]
57. Levi I et al. (2015) Characterization of tumor infiltrating natural killer cell subset. Oncotarget 6 (15), 13835–13843. [PubMed: 26079948]
58. Carrega P and Ferlazzo G (2017) Natural Killers Are Made Not Born: How to Exploit NK Cells in Lung Malignancies. Frontiers in Immunology 8, 277. [PubMed: 28348567]
59. Cristiani CM et al. (2016) Human NK Cell Subsets in Pregnancy and Disease: Toward a New Biological Complexity. Frontiers in Immunology 7, 656. [PubMed: 28082990]

60. Michel T et al. (2016) Human CD56bright NK Cells: An Update. J Immunol 196 (7), 2923–31. [PubMed: 26994304]
61. Eckl J et al. (2012) Transcript signature predicts tissue NK cell content and defines renal cell carcinoma subgroups independent of TNM staging. Journal of Molecular Medicine 90 (1), 55–66. [PubMed: 21870102]
62. Rusakiewicz S et al. (2017) NKp30 isoforms and NKp30 ligands are predictive biomarkers of response to imatinib mesylate in metastatic GIST patients. OncoImmunology 6 (1), e1137418. [PubMed: 28197361]
63. Huntington ND et al. (2009) IL-15 trans-presentation promotes human NK cell development and differentiation in vivo. The Journal of Experimental Medicine 206 (1), 25. [PubMed: 19103877]
64. Juelke K et al. (2010) CD62L expression identifies a unique subset of polyfunctional CD56^{dim} NK cells. Blood 116 (8), 1299. [PubMed: 20505160]
65. Romagnani C et al. (2007) CD56^{bright}CD16[−] Killer Ig-Like Receptor[−] NK Cells Display Longer Telomeres and Acquire Features of CD56^{dim} NK Cells upon Activation. The Journal of Immunology 178 (8), 4947. [PubMed: 17404276]
66. Chan A et al. (2007) CD56^{bright} Human NK Cells Differentiate into CD56^{dim} Cells: Role of Contact with Peripheral Fibroblasts. The Journal of Immunology 179 (1), 89. [PubMed: 17579025]
67. Luetke-Eversloh M et al. (2013) Signatures of Human NK Cell Development and Terminal Differentiation. Frontiers in Immunology 4, 499. [PubMed: 24416035]
68. Cortez VS et al. (2017) SMAD4 impedes the conversion of NK cells into ILC1-like cells by curtailing non-canonical TGF-β signaling. Nature immunology 18 (9), 995–1003. [PubMed: 28759002]
69. Gao Y et al. (2017) Tumor immunoevasion by the conversion of effector NK cells into type 1 innate lymphoid cells. Nature Immunology 18, 1004. [PubMed: 28759001]
70. Fuchs A et al. (2013) Intraepithelial Type 1 Innate Lymphoid Cells Are a Unique Subset of IL-12- and IL-15-Responsive IFN-γ-Producing Cells. Immunity 38 (4), 769–781. [PubMed: 23453631]
71. Karvellas CJ et al. (2007) Increased Risk of Colorectal Cancer in Ulcerative Colitis Patients Diagnosed after 40 Years of Age. Canadian Journal of Gastroenterology 21 (7).
72. Gasteiger G et al. (2015) Tissue residency of innate lymphoid cells in lymphoid and nonlymphoid organs. Science 350 (6263), 981. [PubMed: 26472762]
73. Ma A et al. (2006) Diverse functions of IL-2, IL-15, and IL-7 in lymphoid homeostasis. Annu Rev Immunol 24 (1), 657–79. [PubMed: 16551262]
74. Ma LJ et al. (2009) Trans Presentation of IL-15 by Intestinal Epithelial Cells Drives Development of CD8αα IELs. The Journal of Immunology 183 (2), 1044. [PubMed: 19553528]
75. Cortez VS et al. (2014) Cutting Edge: Salivary Gland NK Cells Develop Independently of Nfil3 in Steady-State. The Journal of Immunology 192 (10), 4487. [PubMed: 24740507]
76. Satoh-Takayama N et al. (2010) IL-7 and IL-15 independently program the differentiation of intestinal CD3[−]NKp46⁺ cell subsets from Id2-dependent precursors. The Journal of Experimental Medicine 207 (2), 273. [PubMed: 20142427]
77. Harly C et al. (2018) Development and differentiation of early innate lymphoid progenitors. The Journal of Experimental Medicine 215 (1), 249. [PubMed: 29183988]
78. Cui G et al. (2014) Characterization of the IL-15 niche in primary and secondary lymphoid organs in vivo. Proceedings of the National Academy of Sciences of the United States of America 111 (5), 1915–1920. [PubMed: 24449915]
79. Castillo EF et al. (2009) Dendritic Cells Support the In Vivo Development and Maintenance of NK Cells via IL-15 Trans-Presentation. The Journal of Immunology 183 (8), 4948. [PubMed: 19786554]
80. Mortier E et al. (2009) Macrophage- and Dendritic-Cell-Derived Interleukin-15 Receptor Alpha Supports Homeostasis of Distinct CD8+ T Cell Subsets. Immunity 31 (5), 811–822. [PubMed: 19913445]
81. Jabri B and Abadie V (2015) IL-15 functions as a danger signal to regulate tissue-resident T cells and tissue destruction. Nature Reviews Immunology 15, 771.

82. Mlecnik B et al. (2014) Functional Network Pipeline Reveals Genetic Determinants Associated with in Situ Lymphocyte Proliferation and Survival of Cancer Patients. Science Translational Medicine 6 (228), 228ra37.

83. Gubler U et al. (1991) Coexpression of two distinct genes is required to generate secreted bioactive cytotoxic lymphocyte maturation factor. Proceedings of the National Academy of Sciences 88 (10), 4143.

84. Tugues S et al. (2015) New insights into IL-12-mediated tumor suppression. Cell death and differentiation 22 (2), 237–246. [PubMed: 25190142]

85. Heufler C et al. (1996) Interleukin-12 is produced by dendritic cells and mediates T helper 1 development as well as interferon-γ production by T helper 1 cells. European Journal of Immunology 26 (3), 659–668. [PubMed: 8605935]

86. Meeran SM et al. (2006) Interleukin-12-deficient mice are at greater risk of UV radiation–induced skin tumors and malignant transformation of papillomas to carcinomas. Molecular Cancer Therapeutics 5 (4), 825. [PubMed: 16648552]

87. Liu J et al. (2004) Role of IFN Regulatory Factor-1 and IL-12 in Immunological Resistance to Pathogenesis of N-Methyl-N-Nitrosourea-Induced T Lymphoma. The Journal of Immunology 173 (2), 1184. [PubMed: 15240709]

88. Smyth MJ et al. (2000) The Anti-Tumor Activity of IL-12: Mechanisms of Innate Immunity That Are Model and Dose Dependent. The Journal of Immunology 165 (5), 2665. [PubMed: 10946296]

89. Airoldi I et al. (2005) Lack of Il12rb2 signaling predisposes to spontaneous autoimmunity and malignancy. Blood 106 (12), 3846. [PubMed: 16081683]

90. Eisenring M et al. (2010) IL-12 initiates tumor rejection via lymphoid tissue–inducer cells bearing the natural cytotoxicity receptor NKp46. Nature Immunology 11, 1030. [PubMed: 20935648]

91. Martinotti A et al. (1995) CD4 T cells inhibit in vivo the CD8-mediated immune response against murine colon carcinoma cells transduced with interleukin-12 genes. European Journal of Immunology 25 (1), 137–146. [PubMed: 7843224]

92. Zilocchi C et al. (1998) Interferon γ–independent Rejection of Interleukin 12–transduced Carcinoma Cells Requires CD4⁺ T Cells and Granulocyte/Macrophage Colony–stimulating Factor. The Journal of Experimental Medicine 188 (1), 133. [PubMed: 9653090]

93. Cavallo F et al. (1997) Antitumor Efficacy of Adenocarcinoma Cells Engineered to Produce Interleukin 12 (IL-12) or Other Cytokines Compared With Exogenous IL-12. JNCI: Journal of the National Cancer Institute 89 (14), 1049–1058. [PubMed: 9230887]

94. Isaacs A et al. (1957) Virus interference. I. The interferon. Proceedings of the Royal Society of London. Series B - Biological Sciences 147 (927), 258–267.

95. Ivashkiv LB and Donlin LT (2014) Regulation of type I interferon responses. Nature reviews. Immunology 14 (1), 36–49.

96. Müller L et al. (2017) Type I Interferons and Natural Killer Cell Regulation in Cancer. Frontiers in immunology 8, 304–304. [PubMed: 28408907]

97. Guan J et al. (2014) Role of Type I Interferon Receptor Signaling on NK Cell Development and Functions. PLOS ONE 9 (10), e111302. [PubMed: 25333658]

98. Swann JB et al. (2007) Type I IFN Contributes to NK Cell Homeostasis, Activation, and Antitumor Function. The Journal of Immunology 178 (12), 7540. [PubMed: 17548588]

99. Mizutani T et al. (2012) Conditional IFNAR1 ablation reveals distinct requirements of Type I IFN signaling for NK cell maturation and tumor surveillance. Oncoimmunology 1 (7), 1027–1037. [PubMed: 23170251]

100. Fan X and Rudensky Alexander Y. (2016) Hallmarks of Tissue-Resident Lymphocytes. Cell 164 (6), 1198–1211. [PubMed: 26967286]

101. Cerwenka A and Lanier LL (2001) Ligands for natural killer cell receptors: redundancy or specificity. Immunological Reviews 181 (1), 158–169. [PubMed: 11513137]

102. Cerwenka A and Lanier LL (2001) Natural killer cells, viruses and cancer. Nature Reviews Immunology 1, 41.

103. Long EO (2008) Negative signaling by inhibitory receptors: the NK cell paradigm. Immunological Reviews 224 (1), 70–84. [PubMed: 18759921]

104. Deng W et al. (2015) A shed NKG2D ligand that promotes natural killer cell activation and tumor rejection. Science 348 (6230), 136. [PubMed: 25745066]
105. Raulet DH et al. (2013) Regulation of Ligands for the NKG2D Activating Receptor. Annual Review of Immunology 31 (1), 413–441.
106. Kruse PH et al. (2014) Natural cytotoxicity receptors and their ligands. Immunology & Cell Biology 92 (3), 221–229. [PubMed: 24366519]
107. Mandelboim O et al. (2001) Recognition of haemagglutinins on virus-infected cells by NKp46 activates lysis by human NK cells. Nature 409, 1055. [PubMed: 11234016]
108. Jarahian M et al. (2009) Activation of Natural Killer Cells by Newcastle Disease Virus Hemagglutinin-Neuraminidase. Journal of Virology 83 (16), 8108. [PubMed: 19515783]
109. Hecht M-L et al. (2009) Natural Cytotoxicity Receptors NKp30, NKp44 and NKp46 Bind to Different Heparan Sulfate/Heparin Sequences. Journal of Proteome Research 8 (2), 712–720. [PubMed: 19196184]
110. Bloushtain N et al. (2004) Membrane-Associated Heparan Sulfate Proteoglycans Are Involved in the Recognition of Cellular Targets by NKp30 and NKp46. The Journal of Immunology 173 (4), 2392. [PubMed: 15294952]
111. Warren HS et al. (2005) Evidence That the Cellular Ligand for the Human NK Cell Activation Receptor NKp30 Is Not a Heparan Sulfate Glycosaminoglycan. The Journal of Immunology 175 (1), 207. [PubMed: 15972650]
112. Stoimenov I and Helleday T (2009) PCNA on the crossroad of cancer. Biochemical Society Transactions 37 (3), 605. [PubMed: 19442257]
113. Rosental B et al. (2011) Proliferating Cell Nuclear Antigen Is a Novel Inhibitory Ligand for the Natural Cytotoxicity Receptor NKp44. The Journal of Immunology 187 (11), 5693. [PubMed: 22021614]
114. Barrow AD et al. (2018) Natural Killer Cells Control Tumor Growth by Sensing a Growth Factor. Cell 172 (3), 534–548.e19. [PubMed: 29275861]
115. Crocker PR et al. (2007) Siglecs and their roles in the immune system. Nature Reviews Immunology 7, 255.
116. von Gunten S and Bochner BS (2008) Basic and clinical immunology of Siglecs. Annals of the New York Academy of Sciences 1143, 61–82. [PubMed: 19076345]
117. Jandus C et al. (2014) Interactions between Siglec-7/9 receptors and ligands influence NK cell-dependent tumor immunosurveillance. The Journal of clinical investigation 124 (4), 1810–1820. [PubMed: 24569453]
118. Hudak JE et al. (2014) Glycocalyx engineering reveals a Siglec-based mechanism for NK cell immunoevasion. Nature chemical biology 10 (1), 69–75. [PubMed: 24292068]
119. Yokoyama WM and Kim S (2006) Licensing of natural killer cells by self-major histocompatibility complex class I. Immunological Reviews 214 (1), 143–154. [PubMed: 17100882]
120. Kim S et al. (2005) Licensing of natural killer cells by host major histocompatibility complex class I molecules. Nature 436, 709. [PubMed: 16079848]
121. Walker C et al. (2018) Role of Extracellular Matrix in Development and Cancer Progression. International Journal of Molecular Sciences 19 (10).
122. Frantz C et al. (2010) The extracellular matrix at a glance. Journal of Cell Science 123 (24), 4195. [PubMed: 21123617]
123. Lo C-M et al. (2000) Cell Movement Is Guided by the Rigidity of the Substrate. Biophysical Journal 79 (1), 144–152. [PubMed: 10866943]
124. Paszek MJ et al. (2005) Tensional homeostasis and the malignant phenotype. Cancer Cell 8 (3), 241–254. [PubMed: 16169468]
125. Gardner H (2014) Integrin α1β1. In I Domain Integrins (Gullberg D ed), pp. 21–39, Springer Netherlands.
126. Miranti CK and Brugge JS (2002) Sensing the environment: a historical perspective on integrin signal transduction. Nature Cell Biology 4, E83. [PubMed: 11944041]

127. Eble JA et al. (1993) The alpha 1 beta 1 integrin recognition site of the basement membrane collagen molecule [alpha 1(IV)]2 alpha 2(IV). The EMBO Journal 12 (12), 4795–4802. [PubMed: 8223488]

128. de Fougerolles AR et al. (2000) Regulation of inflammation by collagen-binding integrins alpha1beta1 and alpha2beta1 in models of hypersensitivity and arthritis. The Journal of clinical investigation 105 (6), 721–729. [PubMed: 10727440]

129. Fiorucci S et al. (2002) Importance of Innate Immunity and Collagen Binding Integrin α1β1 in TNBS-Induced Colitis. Immunity 17 (6), 769–780. [PubMed: 12479823]

130. Ben-Horin S and Bank I (2004) The role of very late antigen-1 in immune-mediated inflammation. Clinical Immunology 113 (2), 119–129. [PubMed: 15451466]

131. Meharra EJ et al. (2000) Reduced Gut Intraepithelial Lymphocytes in VLA1 Null Mice. Cellular Immunology 201 (1), 1–5. [PubMed: 10805967]

132. Doucey M-A et al. (2003) The β1 and β3 Integrins Promote T Cell Receptor-mediated Cytotoxic T Lymphocyte Activation. Journal of Biological Chemistry 278 (29), 26983–26991. [PubMed: 12690105]

133. Horiguchi M et al. (2012) Matrix control of transforming growth factor-β function. The Journal of Biochemistry 152 (4), 321–329. [PubMed: 22923731]

134. Oh SA and Li MO (2013) TGF-β: Guardian of T Cell Function. The Journal of Immunology 191 (8), 3973. [PubMed: 24098055]

135. Li MO et al. (2006) TRANSFORMING GROWTH FACTOR-β REGULATION OF IMMUNE RESPONSES. Annual Review of Immunology 24 (1), 99–146.

136. Zhang N and Bevan MJ (2013) Transforming growth factor-β signaling controls the formation and maintenance of gut-resident memory T cells by regulating migration and retention. Immunity 39 (4), 687–696. [PubMed: 24076049]

137. Mackay LK et al. (2013) The developmental pathway for CD103+CD8+ tissue-resident memory T cells of skin. Nature Immunology 14, 1294. [PubMed: 24162776]

138. Malik BT et al. (2017) Resident memory T cells in the skin mediate durable immunity to melanoma. Science Immunology 2 (10).

139. Ganesan A-P et al. (2017) Tissue-resident memory features are linked to the magnitude of cytotoxic T cell responses in human lung cancer. Nature Immunology 18, 940. [PubMed: 28628092]

140. Robinson PW et al. (2001) Studies on transcriptional regulation of the mucosal T-cell integrin αEβ7 (CD103). Immunology 103 (2), 146–154. [PubMed: 11412301]

141. Pauls K et al. (2001) Role of Integrin αE(CD103)β7 for Tissue-Specific Epidermal Localization of CD8+ T Lymphocytes. Journal of Investigative Dermatology 117 (3), 569–575. [PubMed: 11564161]

142. Schon MP et al. (1999) Mucosal T lymphocyte numbers are selectively reduced in integrin alpha E (CD103)-deficient mice. J Immunol 162 (11), 6641–9. [PubMed: 10352281]

143. Schön MP et al. (2002) Dendritic Epidermal T Cells (DETC) are Diminished in Integrin αE(CD103)-Deficient Mice. Journal of Investigative Dermatology 119 (1), 190–193. [PubMed: 12164945]

144. Cortez VS et al. (2016) Transforming Growth Factor-β Signaling Guides the Differentiation of Innate Lymphoid Cells in Salivary Glands. Immunity 44 (5), 1127–1139. [PubMed: 27156386]

145. van Roy F and Berx G (2008) The cell-cell adhesion molecule E-cadherin. Cellular and Molecular Life Sciences 65 (23), 3756–3788. [PubMed: 18726070]

146. Schneider MR and Kolligs FT (2014) E-cadherin's role in development, tissue homeostasis and disease: Insights from mouse models. BioEssays 37 (3), 294–304. [PubMed: 25449798]

147. Floc et al. (2007) αEβ7 integrin interaction with E-cadherin promotes antitumor CTL activity by triggering lytic granule polarization and exocytosis. The Journal of Experimental Medicine 204 (3), 559. [PubMed: 17325197]

148. Mayumi N et al. (2012) E-cadherin interactions are required for Langerhans cell differentiation. European Journal of Immunology 43 (1), 270–280. [PubMed: 23135957]

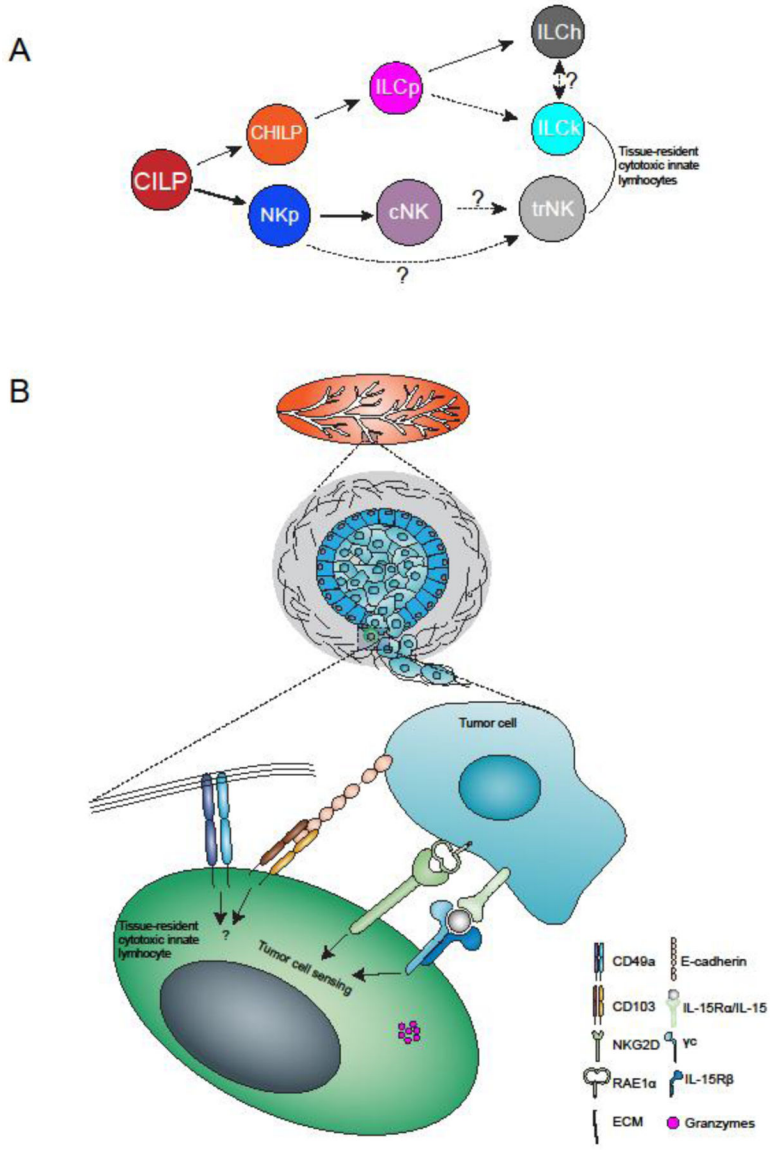

Figure 1. Lineage of Cytotoxic Innate Lymphocyte Differentiation

A. The common innate lymphoid progenitor (CILP) gives rise to the natural killer (NK) and innate lymphoid cell (ILC) lineages. Downstream of the CILP, the common helper innate lymphoid cell progenitor (CHILP) gives rise to all helper ILCs but has lost NK cell potential. In the liver, ILCk are derived from PLZF-expressing ILCp. However, it remains to be determined whether ILCk are differentiated via a distinct pathway downstream of ILCp or converted from helper ILC. The identity of a NK-committed progenitor downstream of the CILP remains unclear. Tissue-resident NK cells may be converted from conventional NK cells but may also be derived from an earlier progenitor.

B. Cytotoxic innate lymphocytes survey epithelial to detect cancer associated danger signals. They could sense malignancy via IL-15R and NKG2D-mediated signals, while the role of ECM cues and E-cadehrin-CD103 axis is less clear.

Table 1.

Innate Lymphocyte Progenitors and Their Phenotypic Profile

Progenitor	Markers	Reference(s)
CILP	Lin−CD127−α4β7 +Thy1−TCF−1+	31
CHILP	Lin−CD127+ α 4β7 +CD25−ld2+	34
ILCP	Lin−CD127+ α 4β7 +PLZF+PD−1+	32, 33

Abbreviations: CILP, common innate lymphoid progenitor; CHILP, common helper innate lymphoid progenitor; ILCP, innate lymphoid cell precursor