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Review

Helper Innate Lymphoid Cells as Cell Therapy for Cancer

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Abstract: Although the first cancer immunotherapy was given in the clinic more than a century ago, this line of treatment has remained more of a distant goal than a practical therapy due to limited understanding of the tumor microenvironment and the mechanisms at play within it, which lead to failures of numerous clinical trials. However, in the last two decades, the immune checkpoint inhibitors and chimeric antigen receptor-T cell therapies have revolutionized the treatment of cancer and provided proof-of-concept that immunotherapies are a viable option. So far, immunotherapies have majoritarily focused on utilizing T cells, however T cells are not autonomous but rather function as part of, and therefore are influenced by, a vast cast of other immune cells, including innate lymphoid cells (ILCs). Here, we summarize the role of ILCs, especially helper ILCs, in tumor development, progression and metastasis, as well as their potential to be used as immunotherapy for cancer. By reviewing the studies that used helper ILCs as adoptive cell therapy, we highlight the rationale behind considering these cells as novel adoptive cell therapy for cancer as well as identify open questions and areas for future research.

Keywords: innate lymphoid cells; cell therapy; cancer; immunotherapy; antitumor immune response; adoptive cell therapy

1. Introduction

Immunotherapy is a major breakthrough for the treatment of cancer. There are five major categories of immunotherapy: cancer vaccines, oncolytic virus therapies, cytokine therapies, immune checkpoint inhibitors, and adoptive cell therapy (ACT). Up until recently, ACT has focused on utilizing autologous T cells, isolated or genetically engineered, *ex vivo* expanded, and reinfused back into patients. However, the failure of these cells to reach solid tumors has led to expanding the type of cells to be used for ACT to non-T cells. NK cells, a member of the innate lymphoid cell (ILC) family, have been the obvious cell type of choice to be considered next, due to their known cytotoxic abilities against tumor cells. There are now many preclinical and clinical ongoing investigations involving infusions of mature NK, stem-cell derived NK, or CAR-NK cells (Chiossone *et al.*, 2018; Daher and Rezvani, 2021; Myers and Miller, 2021).

However, cytotoxic ability ought not to be the only feature dictating the cell type chosen for ACT. Other features such as homing to tissues, and the ability to reign in and/or activate other cell types that may tip the balance of the tumor microenvironment (TME) towards tumor-suppressing, ought to be considered as well.

In this regard, helper ILCs are an adequate choice. Indeed, it is now clear that helper ILCs are present within tumors (Jacquelot *et al.*, 2022). It is also known that helper ILCs express a myriad of chemokine receptors (Soriani *et al.*, 2018), integrins (Karta *et al.*, 2018) and selectins (Munneke *et al.*, 2014), which allow them to traffic within the body and migrate to inflammatory sites. At the steady state, helper ILCs are tissue-resident cells. ILC2 cells are found preferentially in the lungs, adipose tissue, small intestine lamina propria

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and skin while ILC1 and ILC3 cells are found preferentially in the gut, particularly the colon and ileum respectively, and adipose and lymphoid tissue (Kim, Hashimoto-Hill and Kim, 2016; Simoni *et al.*, 2017) . Transcriptional analysis of ILC subsets isolated from various non-diseased tissue localization revealed that it is subset identity, and not tissue localization, that determines functionality (Yudanin *et al.*, 2019). Therefore, helper ILCs at the steady state may have subset-specific programs that mediate their tissue distribution and functionality. In light of these findings, some ILC subsets may be better suited for combatting certain cancers depending on the cancer tissue type. However, cancer arises and progresses under inflammatory conditions, which can induce plasticity in ILCs. Consequently, preclinical studies on the role of ILCs in specific types of cancer can shed light as to which subset is the most appropriate choice for immunotherapy depending on cancer tissue type.

Here, after giving a brief definition of ILCs, we will first summarize the current knowledge on the role of helper ILCs in tumor development, progression and metastasis, as well as anticipate which cancer tissue type a specific subset may be best suited to combat. Secondly, we will review the studies that have utilized helper ILCs as adoptive cell therapy. Finally, we will outline the areas that require further research in order for helper ILCs to be considered as ACT for cancer immunotherapy.

2. Innate Lymphoid Cells

ILCs represent the newest member of the innate immune system, discovered just a little over 10 years ago. Initially divided into three groups, a consensus has now been reached to divide them into five groups, namely, natural killer (NK), ILC1, ILC2, ILC3 and lymphoid tissue-inducer cells (LTi), based on differing developmental pathways (Vivier *et al.*, 2018). ILCs are largely tissue resident cells and are especially enriched at mucosal and barrier surfaces, however some ILCs such as NK and inflammatory ILC2 cells can circulate in the bloodstream (Gasteiger *et al.*, 2015). Lacking specific antigen receptors, ILCs are actuated by stress signals, microbial compounds and cytokines. Their strategic location at mucosal barrier surfaces renders them the first immune cells to respond to pathogenic, host or environmental stimuli.

ILCs can be seen as the innate counterparts of T lymphocytes, with NK cells representing cytotoxic ILCs and mirroring CD8+ cytotoxic T lymphocytes, and ILC1, ILC2 and ILC3 cells representing the helper ILCs and mirroring CD4+ T helper 1, 2 and 17, respectively (Spits *et al.*, 2013; Artis and Spits, 2015; Eberl *et al.*, 2015). Helper ILCs act mainly by secreting various cytokines, which in turn activate other immune cells. As such, they can be considered master orchestrators of immune responses. Indeed, they have been found to take part in very diverse immune functions, from resistance to pathogens, regulation of inflammation, tissue remodeling, maintenance of metabolic homeostasis, to participation in tumorigenesis (Everaere *et al.*, 2018; Wang *et al.*, 2018).

NK cells have been extensively studied in the context of cancer (Morvan and Lanier, 2016; López-Soto *et al.*, 2017), and current studies are focused on new therapeutic approaches for targeting NK cells, including using them as adoptive cell therapy in the treatment of cancer (Rezvani *et al.*, 2017). Since the use of NK cells as cancer immunotherapy has been reviewed elsewhere (Jacquelot *et al.*, 2022), we will focus on helper ILCs for the remainder of this mini-review.

3. The role of helper ILCs in cancer

3.1. ILC1 cells and cancer

ILC1 cells and NK cells share many similarities that have been extensively reviewed (Nabekura and Shibuya, 2021; Jacquelot *et al.*, 2022). NK cells have well-known anti-tumor properties, their own discovery over forty years ago describing them as a lymphoid subset with innate ability to lyse tumor cells (Herberman, Nunn and Lavrin, 1975; Kiessling, Klein and Wigzell, 1975; Lanier *et al.*, 1986). Due to their similarity with NK cells, ILC1 cells tend to be viewed as anti-tumoral as well. However, as with the other helper ILC

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subsets, and more generally with many immune cell subsets, their function is critically context-dependent, thus cancer type and microenvironment-dependent. It has been shown that ILC1 cells are essential for the control of liver metastasis (Ducimetière *et al.*, 2021), whereas they have limited capacity to contain tumor cells in fibrosarcoma and were unable to control the metastasis of melanoma cells (Gao *et al.*, 2017). ILC1 cells have been shown to have potent antitumor activity and to be a marker for favorable prognosis in breast, and head and neck cancers (Dadi *et al.*, 2016; Moreno-Nieves *et al.*, 2021; Kansler *et al.*, 2022), however they were associated with unfavorable prognosis in colorectal cancer (Qi *et al.*, 2021). Recently, ILC1 cells from both mice and humans were shown to induce leukemia stem cell apoptosis *in vitro* (Li *et al.*, 2022). In this study, the authors showed that adoptive transfer of ILC1 cells in a mouse model of acute myeloid leukemia (AML) could suppress leukemogenesis via IFN-γ production through JAK-STAT or PI3K-AKT signaling and cell-cell contact with leukemic stem cells (Li *et al.*, 2022). They conclude that ILC1 cells may be suitable as a novel AML immunotherapy.

Adding to the complexity of determining the role of ILC1 cells in cancer, NK cells were shown to have high plasticity and to convert to ILC1 cells under the action of the cytokines TGF-β and IL-15 (Gao *et al.*, 2017; Moreno-Nieves *et al.*, 2021). Interestingly, this conversion had opposing consequences on tumor growth and metastasis. TGF-β, which is often found in solid cancers and is known to limit tumor immunosurveillance (Miyazono *et al.*, 2018), can induce the conversion of NK cells into intermediate ILC1 cells with high cytotoxic T-lymphocyte–associated antigen 4 (CTLA-4) expression, high production of TNFα and GM-CSF, but low production of IFNγ (Gao *et al.*, 2017). Consequently, these intermediate ILC1 cells contributed to the establishment of a pro-tumoral microenvironment. SMAD4 expression was found to be essential to prevent NK cells from becoming ILC1 cells when exposed to TGF-β, as SMAD4 restrained non-canonical TGF-β signaling (Cortez *et al.*, 2017). On the contrary, IL-15 can drive the conversion of NK cells to intraepithelial ILC1 cells, which show high production of IFNγ and anti-tumor activity in head and neck cancer (Moreno-Nieves *et al.*, 2021). Consistent with the latter finding, Kansler and colleagues recently showed that intraepithelial ILC1 cells expressing Granzyme-A were enriched in chromophobe renal cell carcinoma (chRCC) human tumors, and that their abundance correlated with better survival (Kansler *et al.*, 2022). Expansion, Granzyme-A expression and cytotoxicity of these ILC1 cells were promoted by IL-15, indicating that these ILC1 cells may in fact be converted NK cells.

ILC1 cells were also shown to have high plasticity and to convert into ILC3 cells under the action of the cytokines IL-1β and IL-23 (Bernink *et al.*, 2015). This conversion was shown to promote tumor progression in pulmonary squamous cell carcinoma (Koh *et al.*, 2019).

In light of these findings, it may be suitable to use ILC1 cells as adoptive cell therapy for liver, breast, head and neck cancers, AML and chRCC (**Table 1**), however the cytokine profile of the tumor microenvironment should be addressed in order to anticipate a possible conversion of the transferred cells that could hinder therapeutic potential.

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Table 1. Helper ILCs as tumor-suppressing agents per ILC subset and cancer type.

Helper ILC subset	Cancer type	Reference
ILC1		
	Liver cancer	Ducimetiere et al., 2021
	Breast cancer	Dadi et al., 2016 Kansler *et al.*, 2022
	Head and Neck cancer	Moreno-Nieves et al., 2021
	Acute Myeloid Leukemia	Li *et al.*, 2022
	Chromophobe Renal Cell Carcinoma	Kansler *et al.*, 2022
ILC2		
	Lymphoma, melanoma, colon carcinoma	Kim et al., 2016
	Metastatic melanoma	Ikutani et al., 2012
	Pancreatic ductal adenocarcinoma	Moral et al., 2020
ILC3		
	Melanoma	Nussbaum et al., 2017
	Colorectal cancer	Goc et al., 2021
	Non-small cell lung cancer	Carrega et al., 2015

3.2. ILC2 cells and cancer

ILC2 cell numbers are increased in several human cancers including breast (Salimi *et al.*, 2018), gastric (Bie *et al.*, 2014), bladder (Chevalier *et al.*, 2017), prostate and acute promyelocytic leukemia (APL) (Trabanelli *et al.*, 2017). Concomitant with ILC2 expansion in these cancers, the numbers of monocytic myeloid derived suppressor cells (M-MDSC) were also increased. M-MDSC is an important immunosuppressive cell population that contribute to tumor progression and the promotion of tumor metastases (Gabrilovich, 2017;Piranlioglu *et al.*, 2019). IL-13 expression by ILC2 cells has been shown to induce the selective recruitment of M-MDSCs that express the IL-13 receptor alpha1 (Chevalier *et al.*, 2017). Blocking IL-13 resulted in reduced M-MDSCs and prolonged survival in a humanized mouse model of APL (Trabanelli *et al.*, 2017). In light of these findings, it was postulated that ILC2 cells act as tumor-promoting cells by recruiting M-MDSCs.

Other studies on the cytokine IL-33, an important activator of ILC2 cells, also favor the model of ILC2 cells as tumor-promoting. High levels of IL-33 were found in mouse and human breast cancers (Xiao *et al.*, 2016). Using the 4T1 mouse mammary cancer model, Xiao and colleagues found that IL-33 was associated with an increase in M-MDSC. Another study using the same mouse model corroborated that finding and reported that IL-33 also accelerated tumor growth and metastasis development, by sustaining the ILC2/M-MDSC/regulatory-T-cell (Treg) immunosuppressive axis as well as by promoting neovascularization (Jovanovic *et al.*, 2014). Another study using the B16 murine melanoma model found that ILC2 cells expanded by IL-33 promoted tumor growth by inhibiting the activation and cytotoxicity of NK cells (Long *et al.*, 2018).

Adding to the view that ILC2 cells are generally pro-tumoral is the fact that ILC2 cells produce amphiregulin, which has been shown to play a role in tumorigenesis and metastasis (Busser *et al.*, 2011), and to enhance Treg function and thus immunosuppression (Zaiss *et al.*, 2015).

However, some studies support the opposing view. ILC2 cells were shown to bear anti-tumor properties through tumor cell-specific apoptosis via CXCR2 signaling in lymphoma, melanoma and colon cancer mouse models (Kim *et al.*, 2016). In a mouse model of lung metastatic melanoma, ILC2 cells secreted IL-5, which in turn mediated the recruitment of eosinophils that could suppress lung tumor metastasis (Ikutani *et al.*, 2012).

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Moreover, ILC2 cells were found to be enriched in human pancreatic ductal adenocarcinomas and to exert anti-tumor activity in response to IL-33 activation and anti-PD-1 immunotherapy (Moral *et al.*, 2020).

Lung cancer may be the obvious cancer to look at when considering the role of ILC2 cells in cancer progression since ILC2 cells are known to be residents of this organ (Drake and Kita, 2014; Yudanin *et al.*, 2019) and to play a role in lung infections and asthma (Monticelli *et al.*, 2011; Bartemes *et al.*, 2012; Halim *et al.*, 2012). Due to their exacerbating role in asthma, one may anticipate that ILC2 cells would promote lung cancer, however opposing results concerning their numbers in patients with non-small cell lung cancer (NSCLC) have been found. One study found their numbers to be reduced in patients with NSCLC as compared to healthy controls suggesting they may play a positive role in anti-tumor responses (Carrega *et al.*, 2015), while another study found their numbers to be significantly increased in PBMCs and tumors of NSCLC patients as compared to healthy donors (Shen *et al.*, 2021). In the latter study, PD-1 expression was found to be upregulated in ILC2 cells of NSCLC patients and PD-1^{high} ILC2 cells could polarize macrophages to an M2 phenotype *in vitro*, suggesting an immunosuppressive phenotype of ILC2 cells in NSCLC patients. In light of these discrepancies, additional studies are necessary in order to elucidate the role of ILC2 cells in lung cancer.

In light of current findings concerning the potential of ILC2 cells as suppressors of tumor growth and metastasis, it may be suitable to consider adoptive cell therapy of ILC2 cells for lymphoma, melanoma, colon carcinoma and pancreatic ductal adenocarcinomas (**Table 1**), while further research should be conducted on their role in lung cancer.

3.3. ILC3 cells and cancer

As with the other helper ILC subsets, the role of ILC3 cells in cancer is controversial and seems to be context-dependent. Cell heterogeneity in group 3 ILCs may also explain some of the variations observed in the anti-tumor immune response. Indeed, ILC3 cells are considered to be RORγt+ and to secrete IL-22, IL-17, IL-8 and TNF-α, but there seems to be different subsets of ILC3 cells as defined by expression of certain receptors on their surface, such as NCR+ ILC3 cells or CCR6+ ILC3 cells. Another subset of ILC cells termed regulatory ILCs (ILCregs) was recently reported (Crome *et al.*, 2017). They resemble ILC3 cells because they secrete IL-22 and express NKp46, however they do not express RORγt. These ILCregs were found to inhibit tumor-infiltrating lymphocytes in human high grade serous ovarian cancer resulting in reduced immunosurveillance and shorter relapse time.

Other reports of ILC3 cells as promoting cancer development include *Helicobacter hepaticus* driven colorectal cancer where IL-22 is found to be essential for tumor progression and is secreted mainly by CCR6+ ILC3 cells (Kirchberger *et al.*, 2013), as well as human and mouse breast cancer where ILC3 cell numbers are increased in tumor tissue and promote metastasis to lymph nodes by altering the chemokine profile of the TME (Irshad *et al.*, 2017). Moreover, systemic administration of IL-23, an activator of ILC3 cells, was found to induce gut adenomas in an ILC3-dependent manner (Chan *et al.*, 2014) and IL-23-activated ILC3 cells promoted the proliferation and migration of pancreatic cancers in an IL-22-dependent manner (Xuan *et al.*, 2020).

On the other hand, ILC3 cells were recently found to harbor a protective role in colorectal cancer through direct interaction with T cells via MHC Class II leading to type 1 immunity in both humans and mice (Goc *et al.*, 2021). Both NCR+ ILC3 cells and CCR6+ ILC3 cells were shown to be involved in tertiary lymphoid structures (TLS) formation, known to be an indication of a favorable outcome for many cancers (Hwang *et al.*, 2012; Mei *et al.*, 2014; Geng *et al.*, 2015; Mao *et al.*, 2016; Barnes and Amir, 2017). NCR+ ILC3 cells were shown to recognize tumor cells directly and their accumulation within tumors of patients with NSCLC was correlated with better prognosis (Carrega *et al.*, 2015). In a mouse melanoma model, CCR6+ ILC3s could suppress tumor growth (Nussbaum *et al.*, 2017).

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Taking these findings into account, ILC3 cells may be used as adoptive cell therapy for melanoma, colorectal cancer and NSCLC (**Table 1**).

4. Adoptive cell therapy and ILCs

ACT is now recognized as a powerful treatment for cancer. Its efficacy has been demonstrated in patients with liquid cancers and metastatic melanoma. So far, the focus of ACT has been on the use of autologous T cells. However, shortcomings in many solid cancers have led to a search for other immune cell types that may provide better outcomes. In light of what is now known about the role of ILCs in cancer as well as their homing abilities to tissues and solid tumors, using them as ACT for cancer deserves to be explored.

Some preclinical studies using helper ILCs as ACT have been done, although the vast majority has focused on diseases other than cancer. Liu et al. have demonstrated that the reduction of ILC2 numbers lead to a delay in corneal wound healing, while the adoptive transfer of ILC2 cells partly restored the healing process of the damaged cornea (Liu *et al.*, 2017) . In another study, the supplementation of ILC2 cells through adoptive transfer attenuated arthritis (Omata *et al.*, 2018). Adoptive transfer of RORγt+ ILC3 cells that express IFN-γ, termed ex-ILC3s, was shown to inhibit and regulate chlamydial colonization in the mouse colon (He *et al.*, 2021). Recently, adoptive transfer of ILC1 cells in a mouse model of AML suppressed leukemogenesis (Li *et al.*, 2022). These studies and many others where *in vivo* or *ex vivo* generation/expansion of ILC cells is performed (Halim *et al.*, 2012; Mirchandani *et al.*, 2014; Taylor *et al.*, 2017; Long *et al.*, 2018; Patel *et al.*, 2019) are proof-of-concept that studies of helper ILCs as ACT for cancer treatment can be done in mice. In fact, detailed protocols for the purification, expansion, and adoptive transfer of ILCs in mice already exist (Guo *et al.*, 2016; Frech *et al.*, 2020; de Lucía Finkel *et al.*, 2021).

Clinical studies of ILCs as ACT have never been done. Some groups have successfully obtained human ILCs from umbilical cord blood-derived CD34+ hematopoietic stem cells (Cella, Otero and Colonna, 2010; Tang *et al.*, 2011; Xing et al.,2017; Tufa *et al.*, 2020). Other groups have also provided protocols for obtention of mature ILCs from peripheral blood of human donors and *ex vivo* expansion (Xing et al., 2017; Patel *et al.*, 2019). These studies provide proof-of-concept that obtaining human ILCs for adoptive transfer purposes is feasible, however it is not clear how many cells can be obtained with these methods. Since large number of cells are typically required for ACT in cancer studies, optimization and detailed protocols that will provide sufficient numbers for ACT in cancer patients are needed.

5. Perspectives

The failures of adoptive T-cell therapy in solid tumors have prompted a surge in the field of cancer ACT to expand the cell type to non-T cells. ILCs are increasingly being recognized as major orchestrators of immune responses. Their role in cancer is also starting to be elucidated and it is now clear that these cells are present in tumors, are able to home and/or expand within tumors and, in some instances, can elicit anti-tumoral responses. The plethora of pre-clinical studies on the role of the ILC subsets in various cancers can guide clinicians in the choice of the subset best suited to combat a specific type of cancer. Pre-clinical studies have also provided proof-of-concept that ILCs can be used successfully as ACT, although such studies in the context of cancer are lacking. Obtention of mature human ILCs either after differentiation of umbilical-cord blood derived hematopoietic stem cells or after *ex vivo* expansion of mature ILCs isolated from peripheral blood has been successfully achieved, however protocols giving exact cell numbers are lacking. Altogether, due to their anti-tumoral properties, their homing abilities to tissues and to tumors, and the availability of protocols for *ex vivo* generation and /or expansion, testing ILCs or engineered-ILCs as ACT against cancer is a promising option that deserves to be explored.

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