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REVIEW

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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 tumour microenvironment and the mechanisms at play within it, which led to failures of numerous clinical trials. However, in the last two decades, the immune checkpoint inhibitors (ICIs) 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 tumour 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 (ACT), we highlight the rationale behind considering these cells as novel ACT for cancer as well as identify open questions and areas for future research.

KEYWORDS
adoptive cell therapy, antitumour immune response, cancer, cell therapy, immunotherapy, innate lymphoid cells

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, ICIs 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 tumours has led to expanding the type of cells to be used for ACT to non-T cells. Natural killer (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 tumour cells. There are now many preclinical and clinical ongoing investigations involving infusions of mature NK, stem-cell derived NK or chimeric-antigen receptor (CAR)–NK cells [1–3].

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 tumour microenvironment (TME) towards tumour-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 tumours [4]. It is also known that helper ILCs express a myriad of chemokine receptors [5], integrins [6] and selectins [7], which allows 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 and skin, while ILC1 and ILC3 cells are found preferentially in the gut, particularly the colon and ileum, respectively, and adipose and lymphoid tissue [8, 9]. 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 [10]. Therefore, helper ILCs at the steady state may have subset-specific programmes 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 [11]. 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 tumour 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 ACT. Finally, we will outline the areas that require further research in order for helper ILCs to be considered as an ACT for cancer immunotherapy.

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 NK, ILC1, ILC2, ILC3 and lymphoid tissue-inducer (LTi) cells, based on differing developmental pathways [12]. 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 [13]. 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 [14–16]. 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 remodelling, maintenance of metabolic homeostasis, to participation in tumourigenesis [17, 18].

NK cells have been extensively studied in the context of cancer [19, 20], and current studies are focused on new therapeutic approaches for targeting NK cells, including using them as an ACT in the treatment of cancer [21]. Since the use of NK cells as cancer immunotherapy has been reviewed elsewhere [4], we will focus on helper ILCs for the remainder of this review.

The role of helper ILCs in cancer

ILC1 cells and cancer

ILC1 cells and NK cells share many similarities that have been extensively reviewed [4, 22]. NK cells have well-known antitumour properties, their own discovery over 40 years ago describing them as a lymphoid subset with an innate ability to lyse tumour cells [23–25]. Due to their similarity with NK cells, ILC1 cells tend to be viewed as antitumoural as well. However, as with the other helper ILC 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 [26], whereas they have limited capacity to contain tumour cells in fibrosarcoma and are unable to control the metastasis of melanoma cells [27]. ILC1 cells have been shown to have potent antitumour activity and to be a marker for favourable prognosis in breast, chromophobe renal cell carcinoma (chRCC) and head and neck cancers [28–30]; however, they were associated with unfavourable prognosis in colorectal cancer when not expressing SLAMF1 [31]. Recently, ILC1 cells from both mice and humans were shown to induce leukaemia stem cell apoptosis in vitro [32]. In this study, the authors showed that adoptive transfer of ILC1 cells in a mouse model of acute myeloid leukaemia (AML) could suppress leukaemogenesis via IFN-γ production through JAK–STAT or PI3K-AKT signalling and cell–cell contact with leukaemic stem cells [32]. 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 into ILC1 cells under the action of the cytokines TGF-β and IL-15 [27, 30]. Interestingly, this conversion had opposing consequences on tumour

growth and metastasis. TGF-β, which is often found in solid cancers and is known to limit tumour immunosurveillance [33], can induce the conversion of NK cells into intermediate ILC1 cells with high cytotoxic T-lymphocyte-associated antigen 4 expression, high production of TNF-α and GM-CSF, but low production of IFN-γ [27]. Consequently, these intermediate ILC1 cells contributed to the establishment of a protumoural 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 signalling [34]. On the contrary, IL-15 can drive the conversion of NK cells to intraepithelial ILC1 cells, which show high production of IFN-γ and antitumour activity in head and neck cancer [30]. Consistent with the latter finding, Kansler et al. recently showed that intraepithelial ILC1 cells expressing granzyme-A were enriched in chRCC human tumours, and that their abundance correlated with better survival [29]. 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 [35]. This conversion was shown to promote tumour progression in pulmonary squamous cell carcinoma [36].

In light of these findings, it may be suitable to use ILC1 cells as an ACT for liver metastasis, breast, head and neck cancers, AML and chRCC (Table 1); however, the cytokine profile of the TME should be addressed in order to anticipate a possible conversion of the transferred cells that could hinder therapeutic potential. A graphical summary of the pro and antitumoural roles of ILC1 cells per cancer type can be found in Figure 1.

TABLE 1 Helper innate lymphoid cells (ILCs) as tumour-suppressing agents per ILC subset and cancer type

Helper ILC subset	Cancer type	References
ILC1		
	Liver metastasis	[26]
	Breast cancer	[28,29]
	Head and neck cancer	[30]
	Acute myeloid leukaemia	[32]
	Chromophobe renal cell carcinoma	[29]
ILC2		
	Lymphoma	[37]
	Colorectal cancer	[38]
	Lung metastasis	[39]
	Pancreatic ductal adenocarcinoma	[40]
ILC3		
	Melanoma	[41]
	Colorectal cancer	[42]
	Non-small cell lung cancer	[43]

ILC2 cells and cancer

ILC2 cell numbers are increased in several human cancers, including breast [44], gastric [45], bladder [46], prostate and acute promyelocytic leukaemia (APL) [47]. 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 tumour progression and the promotion of tumour metastases [48, 49]. IL-13 expression by ILC2 cells has been shown to induce the selective recruitment of M-MDSCs that express the IL-13 receptor alpha1 [46]. Blocking IL-13 resulted in reduced M-MDSCs and prolonged survival in a humanized mouse model of APL [47]. In light of these findings, it was postulated that ILC2 cells act as tumour-promoting cells by recruiting M-MDSCs.

Other studies focusing on the cytokine IL-33 also favoured the model of ILC2 cells as tumour-promoting. IL-33 is an important activator of ILC2 cells; however, it is also known to act on numerous other innate and adaptive immune cells, rendering it a pleiotropic cytokine with both anti and protumourigenic reported activities [50, 51]. Consequently, the effects of IL-33 are highly dependent on the cancer type, expression levels and TME composition and may act in synergy or, on the opposite, independently with ILC2 cells, depending on the tumoural context. High levels of IL-33 were found in mouse and human breast cancers [52]. Using the 4T1 mouse mammary cancer model, Xiao et al. found that IL-33 was associated with an increase in M-MDSC [52]. Another study using the same mouse model corroborated that finding and reported that IL-33 also accelerated tumour growth and metastasis development by sustaining the ILC2/M-MDSC/regulatory-T-cell (Treg) immunosuppressive axis as well as by promoting neovascularization [53]. Another study using the B16 murine melanoma model found that ILC2 cells expanded by IL-33 promoted tumour growth by inhibiting the activation and cytotoxicity of NK cells [54]. In a spontaneous mouse model of colon cancer, Saadalla et al. described increased numbers of ILC2 cells in colon adenomas as compared to adjacent healthy tissue, although the impact of these ILC2 cells on

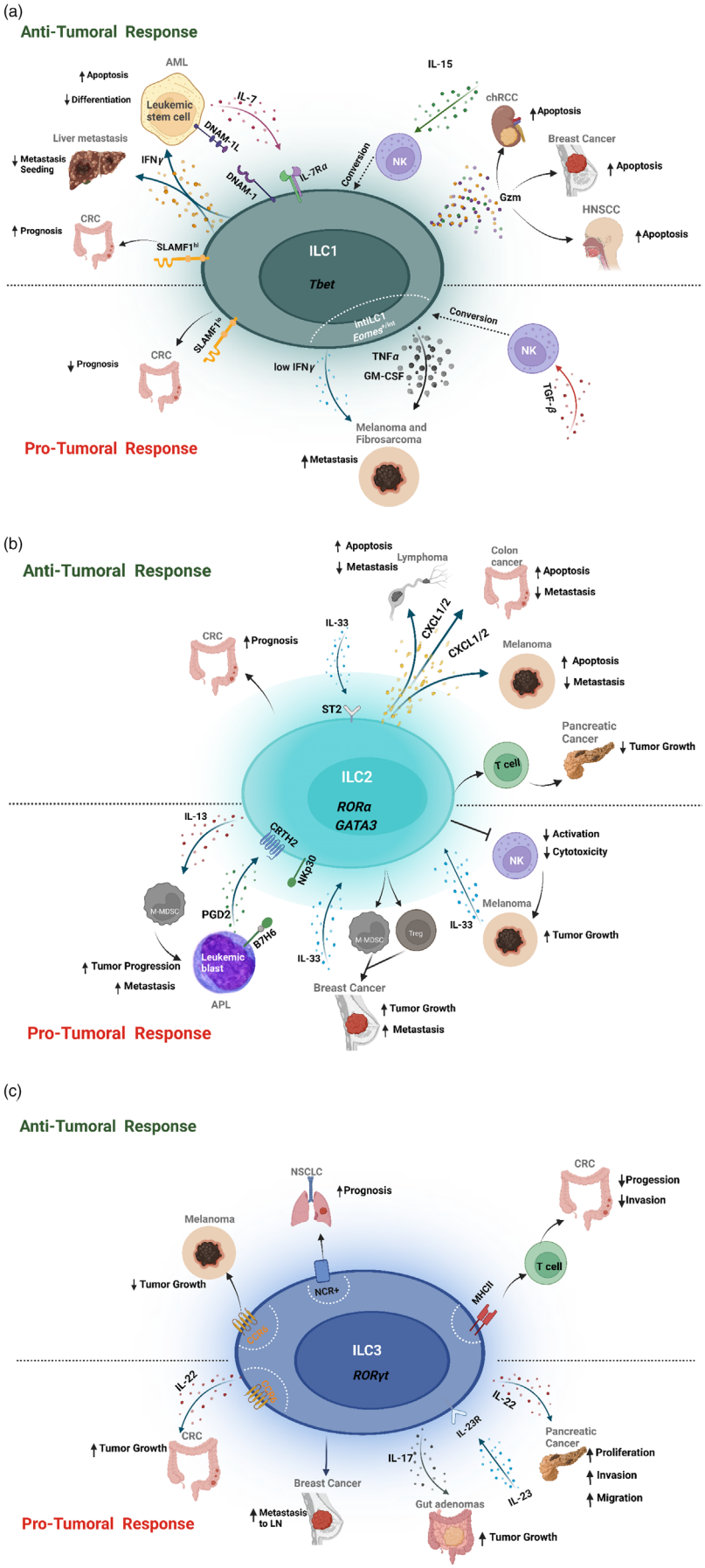

FIGURE 1 Legend on next page.

cancer progression was not addressed [55]. Consistent with ILC2 accumulation in colon cancer, IL-33 expression was shown to be elevated in mouse intestinal polyps [56], and was also detected in human colon cancer epithelial cells [57, 58]. However, the role of IL-33 in colon cancer is still controversial [51], indicating that further research is needed.

Adding to the view that ILC2 cells may be protumoural in certain contexts is the fact that ILC2 cells produce amphiregulin, which has been shown to play a role in tumourigenesis and metastasis [59], and to enhance Treg function and thus immunosuppression [60].

However, some studies support the opposing view. ILC2 cells were shown to bear antitumour properties through tumour cell-specific apoptosis via CXCR2 signalling in lymphoma, melanoma and colon cancer mouse models [37]. Consistent with these findings in colon cancer, a recent study also found ILC2 cells to be protective against colorectal cancer [38]. However, the results of Kim et al. [37] in melanoma are in contrast with those of Long et al. [54], who used the same B16F10 tumour cell line modified to express IL-33. Long et al. suggest that the discrepancy may be due to different ILC2 subsets identified in each study, as different markers were used. In addition, different IL-33 levels may be expressed by the cell lines used in each study since they were generated using differing methods. Nevertheless, the discrepancy suggests that additional studies for the role of ILC2 cells in melanoma are needed. In a mouse model of lung metastasis, ILC2 cells secreted IL-5, which in turn mediated the recruitment of eosinophils, resulting in increased tumour surveillance [39]. Moreover, ILC2 cells were found to be enriched in human pancreatic ductal adenocarcinomas and to exert antitumour activity in response to IL-33 activation and antiPD-1 immunotherapy [40].

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 [10, 61] and to play a role in lung infections and asthma [62–64]. 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 antitumour responses [43], while another study found their numbers to be significantly increased in PBMCs and tumours of NSCLC patients as compared to healthy donors [65]. 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 tumour growth and metastasis, it may be suitable to consider ACT of ILC2 cells for

FIGURE 1 Anti and protumoural roles of helper ILCs per cancer type. ILC1 (a), ILC2 (b) and ILC3 (c) cells can limit cancer and metastasis (top half of each figure) or promote them (bottom half of each figure). (a) In human studies of colorectal cancer (CRC), accumulation of SLAMF1-positive ILC1 cells is associated with increased prognosis, while high numbers of SLAMF1-negative cells with reduced prognosis. High IFN-γ production by ILC1 cells leads to reduced metastasis seeding of tumour cells in the liver, as well as increased apoptosis and decreased differentiation of leukaemic stem cells in acute myeloid leukaemia (AML). The latter is induced by IL-7 signalling and cell–cell contact via DNAM-1. In chromophobe renal cell carcinoma (chRCC), breast cancer and head and neck squamous cell carcinoma (HNSCC), IL-15-mediated conversion of natural killer (NK) cells to granzyme (Gzm)-producing ILC1 cells leads to increased apoptosis of tumour cells. TGF-β-mediated conversion of NK cells results in intermediate ILC1 cells (intILC1) that express Eomes (Eomes$^{+/int}$). These intILC1 cells produce low IFN-γ and high TNF-α and GM-CSF, leading to increased metastasis of melanoma and fibrosarcoma. (b) ILC2 cells are associated with better prognosis in CRC patients. In mice, IL-33 expression by lymphoma, colon cancer and melanoma cells leads to ILC2-mediated reduced metastasis and increased apoptosis of tumour cells via the release of CXCR2 ligands. In pancreatic cancer, IL-33-activated ILC2 cells lead to CD8 T cell priming and subsequent reduced tumour growth. Tumour-derived prostaglandin D2 (PGD2) and tumour cell-ILC2 direct contact via B7H6-NKp30 engagement lead to IL-13 secretion by ILC2 cells and recruitment of monocytic myeloid-derived suppressor cells (M-MDSC) that increase tumour progression and metastasis in acute promyelocytic leukaemia (APL). IL-33 produced by breast cancer cells and melanoma cells leads to ILC2-mediated recruitment of M-MDSC and regulatory T cells (Tregs) and decreased activation and cytotoxicity of NK cells, respectively, and subsequent increased tumour growth and metastasis. (c) CCR6+ ILC3-derived IL-22 increases the progression of CRC. ILC3 cells promote breast cancer metastasis to lymph nodes (LNs). IL-23R signalling in ILC3 cells leads to IL-17 and IL-22 secretion and subsequent increased numbers of gut adenomas, and increased proliferation, invasion and migration of pancreatic cancer cells, respectively. MHCII+ ILC3 cells directly interact with T cells to reduce the progression and invasion of CRC. NCR+ ILC3 cells are associated with better prognosis in non-small cell lung cancer (NSCLC) patients. CCR6+ ILC3 cells suppress tumour growth in a mouse model of melanoma. The white dashed lines within the IL1 and ILC3 cell drawings represent subsets. The black arrows pointing up represent the word increased, while those pointing down represent the word decreased.

lymphoma, colorectal carcinoma, pancreatic ductal adenocarcinomas and lung metastasis (Table 1), while further research should be conducted on their role in primary lung cancer and melanoma since opposing results were found in these specific cancers (Figure 1).

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 antitumour 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 [66]. Another subset of ILC cells termed regulatory ILCs (ILCregs) was recently reported [67]. They resemble ILC3 cells because they secrete IL-22 and express NKp46, but they do not express RORγt. These ILCregs were found to inhibit tumour-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 tumour progression and is secreted mainly by CCR6+ ILC3 cells [68], as well as human and mouse breast cancer where ILC3 cell numbers are increased in tumour tissue and promote metastasis to lymph nodes by altering the chemokine profile of the TME [69]. Moreover, systemic administration of IL-23, an activator of ILC3 cells, was found to induce gut adenomas in an ILC3-dependent manner [70], and IL-23-activated ILC3 cells promoted the proliferation and migration of pancreatic cancer cells in an IL-22-dependent manner [71].

On the other hand, ILC3 cells were recently found to harbour 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 [42]. Both NCR+ ILC3 cells and CCR6+ ILC3 cells were shown to be involved in tertiary lymphoid structure formation, known to be an indication of a favourable outcome for many cancers [72]. The NCR+ ILC3 cells were shown to recognize tumour cells directly and their accumulation within tumours of patients with NSCLC was correlated with better prognosis [43]. In a mouse melanoma model, CCR6+ ILC3s could suppress tumour growth [41].

Taking these findings into account, ILC3 cells may be used as ACT for melanoma, colorectal cancer and NSCLC (Table 1); however, the correct phenotype of the transferred ILC3 cells should be ensured as it was shown different subsets of ILC3 cells can have opposing effects on tumour progression (Figure 1).

ACT WITH HELPER 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.

Some preclinical studies using helper ILCs as ACT have been done, although the vast majority have focused on diseases other than cancer. Liu et al. have demonstrated that the reduction of ILC2 numbers leads to a delay in corneal wound healing, while the adoptive transfer of ILC2 cells partly restores the healing process of the damaged cornea [73]. In another study, the supplementation of ILC2 cells through adoptive transfer attenuated arthritis [74]. 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 [75]. Recently, adoptive transfer of ILC1 cells in a mouse model of AML suppressed leukaemogenesis [32]. These studies, and many others where in vivo or ex vivo generation/expansion of ILC cells is performed [54, 63, 76–78], 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 [79–81].

Clinical studies of helper ILCs as ACT for cancer have never been done. ACT requires the isolation of the cell population of interest from human samples and its expansion ex vivo. Since helper ILCs are largely tissue-resident cells except ILC2 cells, which can also be found in the peripheral blood [9, 12], the question arises on how to obtain mature helper ILCs for ACT in cancer patients. ILCs are considered to have embryonic as well as bone marrow origins, and ILC precursors can be found in the foetal liver, cord blood and adult blood [82, 83]. Thus, obtention of mature ILCs can be achieved by mobilizing ILC precursors from cord or adult blood and inducing their differentiation into the desired subset in vitro. In fact, human ILCs have successfully been obtained from umbilical cord blood-derived CD34+ haematopoietic stem cells [84, 85]. Similarly, all mature ILC subsets have been generated by in vitro differentiation of human circulating peripheral blood ILC precursors [86]. Drawbacks of the aforementioned studies include costly,

laborious and lengthy protocols that give rise to only small numbers of mature cells, therefore, requiring additional in vitro expansion protocols. Moreover, since ILC3 cells comprise at least two different subtypes [66], additional research is needed in order to determine the exact conditions giving rise to one or the other.

Mature ILC2 cells, which are the only ILC subset found in the adult peripheral blood [9], can be enriched and expanded from human peripheral blood mononuclear cells (PBMCs) as has previously been done [77, 87]. In fact, commercial kits are available from various vendors for the enrichment of peripheral blood ILC2 cells, which can make the task easier.

Autologous or allogeneic ACT may be performed. Autologous ACT with helper ILCs has the advantage of not generating a host-versus-graft reaction; however, it requires that ILCs in the cancer patient are not dysregulated, and this has been shown to be the case for certain cancer types [42, 75]. Allogeneic ACT using healthy donor PBMCs bears the advantage of producing off-the-shelf universal cellular therapies; however, cells need to be engineered in order to prevent a host-versus-graft reaction [88, 89].

The efficacy of ACT with helper ILCs may be hindered by the cytokine milieu of the TME, which may promote conversion into a different subset, since ILCs were reported to bear high plasticity [11]. Assessing the cytokine milieu of the TME when possible may anticipate a conversion and therefore guide the choice of the best suited ILC subset. Alternatively, engineering ILCs or providing additional relevant cytokine receptor-blocking antibodies may be considered in order to prevent their in vivo conversion.

A recent study showed that PD-1 blockade could unleash intra-tumoural ILC2 cells to boost antitumour immunity [40]. This raises the interesting idea that combining helper ILC ACT with checkpoint inhibition immunotherapy may yield synergistic effects. This area requires further research.

PERSPECTIVES

The failures of adoptive T-cell therapy in solid tumours have prompted a surge in the field of cancer ACT to expand the cell type to non-T cells. So far, the focus lies largely on NK cells, with many ongoing clinical trials evaluating the efficacy of allogeneic NK or engineered CAR–NK infusions, often in combination with checkpoint inhibitors. Recently, another type of immune cell, the mucosal-associated invariant (MAIT) T cell, has been engineered and tested as a novel cancer immunotherapy regimen [90]. Both NK- and MAIT- ACTs rely on the infused cells' direct cytotoxicity against tumour cells.

Another approach to cancer immunotherapy is to boost the immune response already present within the TME. As such, there are the now widely used ICIs and cytokine therapies. Both of these therapies bear major limitations: ICIs are effective only in a fraction of patients, many of the responders eventually relapse, and there is growing recognition of long-term immune-related adverse events [91]; cytokine therapy's limitations include the difficulty of systemically administered cytokines to reach the tumour site, rapid clearance of the cytokines by the body and toxicity from high dosage [92].

Helper ILCs may be excellent alternatives for circumventing the aforementioned limitations. Indeed, helper 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 tumours, are able to home and/or expand within tumours and, in some instances, can elicit antitumoural responses via the production of high amounts of cytokines [93]. As such, ACT with helper ILCs in cancer patients would provide a cell-based source of the cytokine, ensuring persistence and local delivery of the cytokine. Preclinical studies have shown proof-of-concept that such an approach is promising in treating cancer and other inflammatory disorders [32, 74]. However, additional preclinical studies evaluating this new approach for different cancer types are critically needed. The choice of the helper ILC subset best suited to combat a specific type of cancer can be guided by the plethora of studies on the role of each ILC subset in various cancers, which are summarized in Figure 1 and Table 1. Additional studies are also needed to evaluate combinatorial therapies with ICI since ILCs are known to express immune checkpoints [93], and some studies suggest a synergistic effect of ICI on ILC and T cells [40], while others suggest that a restoration of the ILC compartment is needed for ICI efficacy [42].

The studies of ACT with helper ILCs made so far give no report on adverse events. Recent evidence shows that ILC2 cells make close contact with and can be modulated by mucosal neurons [94], which raises the possibility of neurotoxicities. Moreover, ILCs are known to home not only to tumours, but to healthy tissues as well, and they may induce inflammation there. This area therefore represents an open question that needs to be addressed.

Altogether, due to their antitumoural properties, their homing abilities to tumours, 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.

AUTHOR CONTRIBUTIONS

Fay C. Magnusson wrote the general outline of the article. Ilham Bahhar wrote the first draft, which was consequently reviewed, edited and expanded by Fay C. Magnusson. Fay C. Magnusson prepared the table and Ilham Bahhar contributed to it. Fay C. Magnusson guided the elaboration of the figure and Ilham Bahhar prepared it. Both authors contributed to the elaboration of the final version of the manuscript.

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CONFLICT OF INTEREST

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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