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Research Article

The function of lymphoid cells in some health conditions, such as fibrosis, digestive problems, and cancer grow

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Abstract

Recently, a class of immune cells known as innate lymphoid cells (ILCs) has been identified. ILCs are capable of maintaining homeostasis and defending humans and other mammals against infections and illnesses. In light of this, studies on ILC are still being conducted to learn more about the biology of these cells and how they function in the human body. Since ILCs are a diverse subset of immune cells, it is critical that the medical community stays up to date on the most recent findings about the roles played by ILC families in a number of disease states, including the development of cancer, metabolic disorders, and inflammation. Our understanding of ILC populations' roles and their involvement in various ailments will help us diagnose diseases more accurately and provide better patient care.

Keywords : *innate lymphoid cells, innate immunity, natural immunity cells.*

Families of innate lymphoid cells

Recently, innate lymphoid cells (ILCs) were identified as a component of natural immunity that can contribute to infections and infectious disorders as well as help keep organisms in a state of homeostasis [1–24]. The digestive, respiratory, and urogenital systems, in addition to the skin, adipose tissue, blood, and several internal organs, can all include innate lymphoid cells [24–27]. The ILC families were described by Adamiak et al as follows: ILC22 cells, which share characteristics with NK and LTi cells, ILC17 cells, which produce interleukin-17 (IL-17), ILC2 cells, which are natural T helper 2 (nTH2) cells, nuocytes, innate helper type 2 (IH2) cells, and MPP type 2 cells (multifocal progenitor type 2).

The ability of ILCs to produce important transcription regulators and cytokines, as well as their origin, are two other well-known and frequently used classification criteria [29, 30]. This classification, which is also shown in Table I, separates the cells into three groups. Group 1 (ILC-1) is made up of cells that are sensitive to IL-12, IL-15, and IL-18. These cells have the ability to release TNF or IFN-α or activate the transcription factor T-bet [23, 31]. Thymic stromal lymphopoietin (TSLP)-sensitive cells, IL-25, IL-33, and other cytokinesis-sensitive cells comprise Group 2 (ILC-2). These cells have the ability to activate the trans-acting-cell-specific transcription factor GATA-3 and produce IL-5, IL-13, IL-4, and amphiregulin (Areg), a protein that is part of the epidermal growth factor family [23]. The cells that respond to IL-1α and IL-23 make up Group 3 (ILC-3). which release IL-17a, IL-22, granulocyte-macrophage colony-stimulating factor (GM-CSF), and IFN-α and activate the ROR-t transcription factor [31]. The data that is now available indicates that there aren't many ways to determine ILC cells, in part due to technological constraints. Examples of these methods include confocal microscopy, mass cytometry, and flow cytometry.

Crucially, exposure to cytokines can modify the expression of different markers on ILCs (e.g., CD127, CD94, CRTH2). For this reason, the gating strategy should be modified based on the tissue and/or inflammatory circumstances. It is important to highlight that the ILC-1 group, which is made up of NK and ILC1 cells, is primarily involved in immunisation against intracellular bacteria, viruses, and tumour cells [37–40]. This is evident when describing the ILC cells within these three categories. While ILC1 cells have limited cytotoxicity and are more closely related to

Th1 (T helper) cells, which can activate PMN and MN cells by enhancing their cytotoxicity, phagocytosis, and neutrophil extracellular trap (NET) formation, NK cells have cytotoxic capabilities similar to CD8+ T cells [41].

According to Wang et al. [46], there is a lymphocyte subset of NK-like B cells in the spleen and mesenteric lymph nodes. These cells differ from T and B cells in certain ways, and they have the ability to release IL-12 and IL-18 early in the infection process. Through the release of IL-12 and IL-18, these NK-like B cells were essential in the elimination of microbial infection [46]. In all of the tissues examined, Simoni et al. [33] were unable to find ILC1 cells; however, they did find intra-epithelial-ILC1-like cells, which are able to produce cytotoxic granules but do not express CD127. These cells, seen in both mucosal and non-mucosal diseased tissues, belong to a wider subset of NK cells.

It's possible that in their earlier research, the presence of T cells, DCs, ILC3 cells, HSC, and NK cells contaminated the sample, leading to an incorrect definition of ILC1 cells. These intra-epithelial-ILC1-like cells exhibited CD103, the transcription factor T-bet, and surface NK cell markers CD56, NKp46, CD94, 2B4, CD161, CD160, CD122, CD69, and CD49a, but not CD16 or CD127, in contrast to NK cells from the same region. Only the tonsils (5%) and colon tissue (25%) have these intraepithelial-ILC1-like cells in non-pathological tissues, according to Simoni et al. [33]. ILC-2 cells comprised 40% of the total ILC population in human skin, and their frequency in cord blood (2.7% cells) was higher than in adult blood (0.63% cells). According to their research, ILC-2 cells obtained from adult blood and stimulated with IL-33 have functional similarities with those seen in cord blood. ILC-2 and ILC-3 cells are attracted in diseased tissues, such as lung and colorectal tumours; nonetheless, NK and ILC1-like cells made up over 95% of the ILCs that infiltrated these inflamed tissues.

The ILC-3 cell population that makes up the third group in the family is highly diverse and includes double negative (DN) NKp46–/CCR6– cells, LTi cells that express CCR6+, and cells that express NKp46+. Every cell in this category contributes to the growth and repair of lymphoid tissue as well as immune resistance against bacterial and fungal diseases. The ILC-3 group's flow cytometry investigations include the expression of the Lin-CD127+c-kit+CRTH2-NKp46+/NKp44+ markers. According to Hazen-berg Spits [32], at least eight fluorescence channels are necessary for a precise definition of the ILC-2 and ILC-3 populations in humans using multi-color flow cytometry. Consequently, a more thorough characterisation of these cells is hampered by the technological constraints of flow cytometry equipment, such as spectrum overlap. TNF, IL-22, GM-CSF, IFNα, and IL-17A can all be produced by activated ILC-3 cells [68–72, 78–80]. Simoni et al. [33] discovered using mass cytometry that ILC-3 cells can also produce IL-8 in response to IL-18 stimulation alone or in conjunction with IL-23. They saw IFN secretion in the presence of IL-18 and IL-23, but they did not detect the synthesis of IL-22 in response to IL-18 stimulation. The findings validate that ILC-3 cells had the ability to produce cytokines in vitro with flexibility. The CCR6+ cell population, which expresses NKp44 in humans and NKp46 in mice, is also present in ILC-3. This cell population comprises CD4+ and CD4-T cells.

Human cord blood contains more NKp44–-ILC3 cells (3.09% cells) than adult blood (1.05% cells) [33]. NKp44+-ILC-3 cells are mostly found in mucosal tissues, such as tonsil (18%), adenoid (49%), and colon (23%). These cells are also found in blood marrow (2%), spleen (3%), skin (18%), lung (2%), tonsil (30%), and adenoid (17%) [33].

Native lymphoid cells and the development of cancer A major factor in the development and metastasis of cancer is the interaction of immune system (IS) cells, such as ILCs, and tumor-developing cells with the cells that comprise the tumour microenvironment. Tumour cells and IS cells can link through cytokines, adhesion molecules generated by the tumor's growing cells as well as by the host cells; alternatively, metalloproteinases and so-called microbubbles may aid in the spread of the malignancy. The first reaction to the establishment of a tumour is the mobilisation of IS cells, which triggers cytotoxic mechanisms by producing cytokines, including antitumor ones, that cause cancer cells to undergo apoptosis and ultimately die. Cancer cells assume control of all microenvironment cells and start to create pro-tumor growth factors when they multiply and outcompete immune system cells [81–83]. T cells, including Th1, Th2, Treg, and Th17, B lymphocytes, NK cells, natural killer T (NKT) cells, DCs, macrophages (M1 and M2), myeloid-derived suppressor cells (MDSC), and the families of immune-like cells (ILCs), groups 1, 2, and 3, can be identified among the cells that form the tumor-forming microenvironment. Tissue healing during pregnancy as well as the advancement of the disease's early stages may be aided by innate lymphoid cells, a source of cytokines.

As a result, ILC families are crucial for both tissue continuity restoration and immunological activation. This unique property of ILC cells raises the possibility that they play a role in the formation and growth of tumours and may have an impact on

the surrounding microenvironment of growing tumour cells. A number of components must work together to trigger an immune response in a tissue that has been damaged but is not infected, including DCs, macrophages, epithelial cells with active inflammasomes, and dam-age-associated molecular pattern (DAMP). Intracellular proteinaceous complexes known as inflammatorysomes have the dual roles of stimulating the family of ILC cells and initiating a proinflammatory cascade that results in the creation of pro-caspase-1. Increased ILC cell activity can potentially promote the growth of tumours.

ILC-1 cells secrete IL-2, IL-12, IL-18, and IL-21 and exhibit cytotoxic activity that can inhibit the growth of tumours [89]. On the other hand, while tumours are developing, NK cells that are part of the ILC-1 group may exhibit an increase in the expression of receptors like CD158 that can inhibit antitumor receptors while decreasing the expression of receptors like CD16, CD69, and CD161 that are important for antitumor activity [89]. This illness causes an imbalance in homeostasis and immunosuppression, which in turn causes a reduction in the blood's supply of natural killer cells and ultimately accelerates the growth of cancer.

On the other hand, DCs in the tumour microenvironment have a positive feedback effect on NK cells. This is because DCs with expertise in antigen presentation and immune response activation can help NK cells produce more cytokines and increase their cytotoxicity against tumour cells. Additionally, by enhancing DCs' capacity to generate pro-inflammatory cytokines and stimulate T-helper (Th1) and T-cytotoxic (Tc) lymphocytes against tumour cells, NK cells "assist" in the activation of DCs [31]. New information about the possible contribution of innate-CD8+ T cells, also known as NK-like CD8+ cells, to the physicopathological advancement of cancer is offered by Barbarin et al. They note both the potential role of innate-CD8+ in solid tumours and chronic myeloid leukaemia, a myelo-proliferative condition regulated by the immune system.

T cells' vulnerability to tumour immune subversion and their role in controlling cancer illness. "Immune checkpoints" regulate innate-CD8+ T cells during tumour progression [90]. Additionally, it has been demonstrated that DC-activated NK cells may produce IL-12p70, a cytokine that can trigger a Th1 and Tc cell response and is resistant to inhibitory drugs, up to 100 times more efficiently [31]. Clinical investigations showing the great efficacy of combination therapy with NK and DCs in cutaneous melanoma have also confirmed these findings [31]. Moreover, it has been demonstrated that the NK cells' produced TNF-α and IFN-ε can stimulate Tc and NK cells [91] and prevent the proliferation of tumour cells and angiogenesis.

It should be highlighted, nonetheless, that IFN- may also have negative effects, as IFN-produced by ILC-1 cells early in the immune response might induce tumour growth [95]. IFN- has been shown to have a negative impact on human melanoma cell culture in vitro, leading to an aggressive phenotype and tumour formation [96]. The differences in NK cell distribution in cancer tissues are described by Carrega et al. The presence of NK cells was compared between neoplastic and comparable healthy tissues from a variety of human organs, including the kidney, lung, colon, stomach, breast, and adrenal gland. Only in the group with lung and breast cancer were statistically significant differences found. The frequency of NK cells is larger in human colorectal tumours (73% of cells) than in non-pathological colon tissues (34% of cells), according to data published by Simoni et al. However, there were no appreciable differences in the frequency of intra-epithelial-ILC1-like cells. In lung cancer diseases, it was observed that whereas there were more intra-epithelial-ILC1-like cells in human lung tumours (8% cells) than in non-pathological lung tissues (1% cells), the number of NK cells in human lung tumours was lower (80% cells) than in non-pathological lung tissues (95% cells).

ILC-2 cells play a protective function against tumours by secreting IL-13 and amphiregulin, which have the ability to suppress type 1 responses associated with Th1 lymphocytes. A significant quantity of IL-5, which is required for the selective growth of eosinophils, can also be released by ILC-2 cells [78]. A better prognosis for patients is indicated by the presence of eosinophilic granulocytes in the developing tumour location, which includes the colon, oesophagus, nasal cavity, larynx, pulmonary adenocarcinoma, bladder, and prostate [97–99]. Furthermore, IL-5 generated by mouse ILC-2 cells impeded lung cancer spread and decreased tumour growth due to eosinophilia [98]. Furthermore, IL-5 generated by mouse ILC-2 cells slowed the growth of the tumour and prevented lung cancer from spreading.

Additionally, it has been shown that IL-13, which is generated by IL-2 cells, is necessary for MDSC cell activation and can inhibit anti-tumor action by changing the growth factor-α (TGF-ε) that MDSC cells produce, which regulates the proliferation and differentiation of the majority of cell types. M2 macrophages can be stimulated by TGF-α and IL-13 to produce proangiogenic factors, which in turn promote the growth and metastasis of cancer cells. These factors include VEGF, matrix metallopeptidase

(MMP-9), and the growth factors epidermal growth factor (EGF) and fibroblast growth factor 2 (FGF-2) [100–102]. Therefore, it may be said that ILC-2 cells have a dual role in tumour formation. By generating type 2 cytokines, these cells can act in a way that promotes tumour growth. among them is IL-13, which encourages metastasis by stimulating the environment surrounding the developing tumour. ILC-2 cells are found in human colon tumours (1% cells) and non-pathological colon tissues (3% cells), as well as in human lung tumours (3% cells) and non-pathological lung tissues (2% cells), according to Simoni et al. [33].

Because ILC-3 cells can secrete IL-17, IL-22, or IL-23, which can induce chronic inflammation and raise the risk of colon cancer [104], it has been determined that these cells play a part in the formation of cancer. It's possible that the IL-22 that ILC-3 cells release is what causes colorectal cancer to spread [11, 12]. In addition, IL-23 stimulates ILC-3 cells to promote the growth of tumours in the stomach, ovary, lung, and intestines.

High IL-23 expression and IL-17 release are unfavourable prognostic variables in cancer because IL-17 promotes the growth of new blood vessels that supply the tumour by activating proangiogenic factor (VEGF) [107]. Furthermore, by activating STAT2 pathways, the IL-22 generated by ILC-3 cells promotes the growth of intestinal cancer cells and may result in persistent and recurring inflammatory conditions that may serve as a cancer risk factor [109]. There have been reports indicating ILC-3 cells have natural cytotoxic receptors (NCR) that are characteristic of natural killer (NK) cells, such as NKp46, NKp30, and NKp44. As a result, these cells can identify tumour cells or virus-infected cells [110–112]. Research has demonstrated that ILC-3 cells, through NKp44 receptor and cytokine Only a subset of ILC-3 cells in the immediate proximity of the tumour was found to have an active NKp44 receptor in lung cancer patients, but this receptor was dormant in healthy lung tissue [113]. After receiving hematopoietic stem cell transplantation (HSCT) for 12 weeks, patients with acute myeloid leukaemia (AML) have already shown signs of reconstructing their ILC-3 cell populations [114]. Patients undergoing allogeneic stem cell transplantation may suffer from tissue damage and graft-versus-host disease (GvHD), which can result in potentially fatal clinical signs include intestinal mucosal and skin inflammation. Additionally, it has been shown that the ILC-3 cell-synthesised IL-22 is a critical modulator of tissue susceptibility to GvHD and shields intestinal stem cells from harm. In order to verify this, researchers looked at AML patients, and they found a link between the lack of GvHD clinical symptoms and the existence of a sizable circulating population of NKp44+ ILC-3 cells [114]. In contrast to non-pathological colon tissues (15% cells) and NKp44+ILC3 cells (1% and 23%, respectively), the frequency of NKp44–-ILC3 cells in human colorectal tumours (3% cells) is lower, according to Simoni et al. [33]. NKp44-ILC3 cells are more prevalent in human lung tumours (8% cells) than in non-pathological lung tissues (2% cells) in lung cancer diseases; however, there were no appreciable differences in the number of NKp44+ILC3 cells, which account for over 14% of all ILCs in barrier tissues like tonsils.

Huber et al. [115] state that ILC-3 cells that produce IL-22 may also have a protective effect on chronic colitis patients by reducing tissue damage. Consequently, IL-17 produced by ILC-3 can inhibit tumour cell proliferation by activating T cell-dependent pathways, as reported by Kryczek et al. [116]. This restricts the process of colon cancer metastasis and colon carcinogenesis in mice. According to Carrega et al. [117], these data suggest that a deeper comprehension of ILC cell biology, including the development of cancer, may lead to the development of new therapeutic pathways based on the activation and/or blocking of receptors and intracellular ILC cell signalling, thereby halting the spread of cancer.

Innate lymphoid cells and metabolic disorders

It has been demonstrated that ILC families 1, 2, and 3 are abundant in both adult and foetal livers [38], play a significant role in the maintenance of metabolic homeostasis [2, 5–9], and are implicated in the development of adipose tissue [118]. In certain liver disorders, different ILC subpopulations may show different roles. The tissue microenvironment and the level of inflammation may have an impact on these seemingly contradictory results. Liu et al. provided a summary of the protective or harmful roles of ILCs in liver disorders [119]. The immunological regulation of viral hepatitis, mechanical liver injury, and fibrosis is mediated by the hepatic ILCs. Adipocytes in obese individuals generate higher amounts of IL-12, which can promote ILC-1 formation and proliferation in adipose tissue. Additionally, all pro-inflammatory cytokines generated by ILC-1 disrupt the immune system [120]. Additionally, ILC-1 cells have the ability to produce IFN-α and work together to polarise macrophages and encourage insulin resistance in obese people [120]. The body's homeostasis is dependent on both IFN- and TNF-, which are produced by ILC-1 and impact macrophages in adipose tissue [121]. This tissue is abundant in NK cells, eosinophils, alternatively activated macrophages (AAMs), and ILC-2 cells [8,

122, 123]. ILC-2 cells control the conversion of brown fat into white fat tissue and are in charge of controlling the quantity of adipose tissue. Furthermore, ILC-2 cells produce IL-25 and IL-33, which raise the quantity of AAM cells and eosinophilia in the fat tissue [7, 8], which is also the site of IL-5 synthesis [124, 125]. Crucially, a deficiency in IL-5 can cause obesity and interfere with the metabolism of glucose [122]. It should be noted that eosinophils, AAM cells, and catecholamine assist adipocyte precursor cells originating from bone marrow in differentiating into brown adipose tissue cells in response to cold stress [6]. Furthermore, ILC-2 cells can be activated by cold stress through the mobilisation of eosinophils to produce IL-5 [6]. Furthermore, ILC-2 can directly induce the emergence of brown fat by producing the protein methionine/enkephalin, which in turn increases the expression of thermogenin, a protein found in brown mitochondria.

It has been demonstrated that ILC-3 cells react to specific chemicals, such as vitamin A and D, with regard to their role in metabolism [126–129]. It has been demonstrated that via binding the retinoic acid receptor at locus Il22, retinoic acid, a biolog-ically active metabolite of vitamin A, promotes the production of IL-22 in ILC-3 cells [126]. This demonstrates how vitamin A affects ILC-3 cell growth, distribution, and function inside the body. ILC-2 cell numbers and survival duration can both rise in response to vitamin A deprivation, possibly through elevated IL-7a receptor expression. Additionally, it has been demonstrated that a vitamin A shortage reduces the amount of ILC-3 in adult mice's intestines. This suggests that vitamin D might be able to suppress these cells [128]. Through lymphotoxin (LT) and IL-22, which relieve metabolic problems and regulate liver metabolism, ILC-3 also modulates metabolic homeostasis [9]. Research has demonstrated that exogenous IL-22 treatment of diet- or genetic mutation-induced obese mice (micedb/db) results in decreased serum levels of cholesterol and triglycerides, which in turn decreases blood glucose and increases insulin sensitivity [9]. Furthermore, even after consuming a high-fat meal, mice without lymphotoxin receptors exhibited a lower body weight in comparison to control mice with an active LT receptor. Reduced expression of IL-22 has been shown to lower the expression of the antimicrobial peptide RegIIIc, which may contribute to the expansion of

Innate lymphoid cells and inflammation

According to the findings of Simoni et al. [33], in all nine distinct healthy tissues and three diseased tissues they examined, NK or intraepithelial-ILC1-like cells constituted more than 95% of the ILCs recruited under inflammatory conditions. Oral and gastrointestinal mucosal and skin tissues had a greater frequency of helper-type ILCs compared to non-mucosal and lung tissues. This is consistent with these cells' role in human barrier surface immunity, which has already been partially established in mice [13]. It has been established in theory that ILC cells play a part in inflammatory and allergic reactions, such as asthma, atopic dermatitis, and chronic sinusitis. Genes associated with atopic disorders, such as those encoding TSLP, IL-4, IL-5, and IL-13, as well as IL-33 and its receptor, have been shown to be important for ILC-2 cell activation [134]. Asthma in Rag–/– mice is reportedly induced by papain, but not in Rag–/– Il2rg–/– double knockout mice or Rag–/– mice with a low ILC-2 cell count [135]. A new group of non-conventional IFN-producing cells was discovered by Resende et al. [136]. These cells were distinguished by Thy1.2 expression and the absence of lymphoid, myeloid, and NK lineage markers. Their findings show that in immunocompromised mice devoid of natural killer cells, a population of Thy1.2+ non-NK innate-like cells in the liver expresses IFN and can provide protection against Mycobacterium avium infection.

Conclusions

One type of immune cell that has multiple functions is the innate lymphoid cell. Their capacity to release immunoregulatory cytokines quickly enables them to support the early stages of the immune response following infection. Examining ILC cells' function more closely could help establish new protocols that could result in better medical care, particularly in the area of immunity. It is constantly being researched how important ILC cells are to mammals' immunity and homeostasis, including humans, in their role as "guardians." A study that was released by the organisation Immunological Genome Consortium [37] defined the ILC code and detailed the transcriptional expression profiles of the ILC family in a variety of organs. They also made a recommendation regarding the other potential roles that ILCs may play in health protection, such as serving as a source of cells and markers for diagnosis, the existence of which can be utilised for both fundamental and diagnostic research. There are few studies that analyse every known ILC subset for a single tissue simultaneously, and it is difficult to compare human and mouse immunology. The first group to thoroughly examine the phenotypic characteristics of human ILCs was Simoni et al. [33].

They simultaneously examined 29 parameters in several primary, healthy, and diseased human samples using mass cytometry (CyTOF). These findings offer a thorough, worldwide, and in-depth account of ILC populations and the variations within and across persons and tissues.

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