INNATE LYMPHOID CELLS: ROLES IN TUMOUR GENESIS AND PROGRESSION

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ABSTRACT

Innate lymphoid cells (ILCs) represent the most recently identified members of the innate immune system. These cells play important roles in inflammation, tissue remodelling and metabolic disease. ILCs can be subdivided into three major groups according to their cytokine production. The role of ILCs in tumourgenesis and tumour progression is not completely clarified. In this review, we discuss whether and how ILCs are involved in tumour genesis, growth and metastasis.

Keywords: Innate lymphoid cells, tumour, progression, antitumor immunity

INNATE LYMPHOID CELLS

The innate immune response is important in combating various microbes during the early phases of infection. Innate lymphoid cells (ILCs) represent the most recently identified constituents of the innate immune system by playing a role in inflammation, tissue remodelling and metabolic disease (1). ILCs lack the known immune cell lineage markers. Unlike T and B lymphocytes, ILCs do not have antigen receptors and memory functions (2). ILCs are localized in intestinal and lung mucosae as well as the skin and are capable of rapidly switching on responses to pathogens, even upon first exposure (1). These cells can be subdivided into three major groups according to their cytokine production (Fig 1; 3-4). The ILC2 group represents the innate equivalent of Th2 cells. This group only includes ILC2 cells (e.g., nuocytes, natural helper cells, innate helper cells, and multipotent progenitor cells) that secrete IL-5 and IL-13 in response to IL-25, IL-33 and thymic stromal lymphopoietin (TSLP), and they mediate innate responses during helminth infections and allergies (1-2). The ILC1 group is composed of ILC1 cells and natural killer (NK) cells. They represent the innate equivalent of adaptive Th1 and cytotoxic T cells, respectively. While NK cells play well-known roles in antiviral and antitumour immunity, several additional ILC1s have recently been identified that produce IFN-γ. The ILC3 group includes ILC3 cells and lymphoid tissue inducer (LTi) cells (1, 5). These cells mainly secrete IL-17 and IL-22 in response to IL-23 and IL-1β, and they represent the innate equivalents of Th17 and Th22 cells, respectively. The development and differentiation as well as effector functions of the ILCs are dependent upon the transcription factor, GATA3 (1, 6).

The role of ILCs in inflammatory immune responses, tissue remodelling and metabolic disease are well documented (Fig 1; 1, 2, 7). Recent studies described the involvement of ILCs in tumour growth and progression (8-11). In this paper, we summarize the role of ILCs in tumour genesis and anti-tumour immunity modulation.

THE HISTORY OF INNATE LYMPHOID CELLS

Natural killer (NK) cells were the first discovered ILCs. Five years ago, a new type of innate lymphoid cells was described in fat-associated lymphoid clusters (FALCs). These cells did...
Figure 1. Innate lymphoid cell classifications. The classification of innate lymphoid cells (ILCs) is based on functional criteria. ILC1s are defined by their capability to produce interferon-γ (IFNγ). ILC2s produce type 2 cytokines, interleukin-5 (IL-5) and IL-13. ILC3s are capable of producing the type 17 cytokines IL-17 and IL-22. Different subsets of ILCs cells play various roles in disease immuno-pathogenesis and subsequent tissue destruction and systemic manifestations.
not express lineage (Lin) markers but expressed c-Kit, Sca-1 (also known as Ly6a) and ST2 (12). The authors named them natural helper cells (NHCs). NHCs were shown to proliferate in response to IL-2 and to produce large amounts of type 2 cytokines such as IL-5 and IL-13 in response to IL-33 stimulation and also to require IL-7 for survival (12). NHCs regulate B-cell antibody production and self-renewal of B1 cells. The authors concluded that the described FALC Lin- c-Kit+ Sca-1+ B-cell antibody production and self-renewal of B1 cells. The cytokines such as IL-5 and IL-13 in response to IL-33 stimulation and also to respond to lung epithelium-derived cytokines. Further, they can be divided into two distinct populations: NK cells and cytokine producing ILCs (17). Barthelemes et al. described the IL-33 responsive ILCs that reside in the lungs (18). These lung lymphoid cells were Lin- c-Kit- Sca-1- CD44+ CD25- Thy1.2- IL-7Rα- ICOS- and produced large quantities of IL-5 and IL-13 after exposure to the fungal allergen, Alternaria alternata (18). The authors suggested that allergic airway inflammation can develop independently of adaptive immunity, and lung Lin- CD44+ CD25- cells were sufficient to induce airway inflammation (18). An important pathogenic role of novel ILCs was confirmed by the identification and expansion of these cells in various allergy and parasitic inflammation models (18-21). ILCs are important producers of IL-9 during airway inflammation (14, 22). It has now been shown that Lin- ST2- cells are the main source of IL-9. IL-33 was shown to induce the accumulation of ILCs that produce IL-9 (22).

Additionally, ILCs play an important role in tissue remodelling. It was shown that, during influenza virus-induced airway inflammation, ILCs produce the epidermal growth factor-related cytokine, amphiregulin, which further regulates epithelial cell repair (23).

Common traits for all types of the described innate lymphoid cells are that they are systemically dispersed and expanded in response to IL-25 and IL-33, in various allergy and parasitic inflammation models (18-21). ILCs are important producers of IL-9 during airway inflammation (14, 22). It has now been shown that Lin- ST2- cells are the main source of IL-9. IL-33 was shown to induce the accumulation of ILCs that produce IL-9 (22).

Table 1. Innate lymphoid cells in tumour genesis and progression

<table>
<thead>
<tr>
<th>ILCs</th>
<th>Function</th>
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<tr>
<td>ILC2s</td>
<td>Eosinophil accumulation and antitumour immunity via IL-5 (11)</td>
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<td></td>
<td>MDSCs and Treg accumulation and immunosuppression via IL-13 (8)</td>
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<tr>
<td>ILC3s (IL-17+)</td>
<td>Carcinogenesis via IL-13 (51,52)</td>
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<tr>
<td></td>
<td>Facilitate tumourigenesis, angiogenesis and metastasis (55)</td>
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<tr>
<td>ILC3s (IL-22+)</td>
<td>Stimulate pro- and anti-tumour mechanisms (59)</td>
</tr>
<tr>
<td>ILC1s (NK)</td>
<td>Antitumour cytotoxicity and facilitate potent antitumour immunity (62-66)</td>
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kines and represented a population that is distinct from NK cells (2, 26, 27). The development of NK cells is dependent upon T-bet expression, and they occur independently of GATA3, while the development of ILC1s is dependent upon both GATA3 and T-bet expression (4). ILC1 cells express high T-bet levels and low RORγt levels (27). These CD117+ GATA3, while the development of ILC1s is dependent upon kines and represented a population that is distinct from NK cells, nuocytes and innate type 2 helper cells, and the majority of which were lineage negative and expressed Sca-1, Thy1.2, CD25, CD27, CD44, CD69, IL-7Ra and ST2, which is a subunit of IL-33R (11). Further, they showed responsiveness of ILCs to IL-25 and IL-33, indicating that these IL-5-producing cells belong to the ILC2 class of cells. After induction of a lung metastatic melanoma model, the authors found that exogenous IL-25 and IL-33 mediated infiltration of eosinophils into the lung via IL-5. Specifically, IL-25 and IL-33 induced accumulation of the innate IL-5-producing ILC2s, which in turn recruited eosinophils into the lung. Antitumour immunity is mediated by the innate and adaptive immune system (38, 39, 40, 41, 42). Polarization of antitumour immune response influences tumour growth in a dual manner. Polarization towards the type 1 response preferentially activates cellular immunity (by producing IFN-γ and IL-2), while the type 2 immune response suppresses cellular immunity by eliciting humoral immunity (via IL-4, IL-5 IL-10, and IL-13 production) (40, 43-45). The type 1-mediated antitumour immune response is followed by potent stimulation of T-cell cytotoxic activity (39, 40, 41, 46). On the contrary, type 2 polarization results in the production of growth factors and cytokines that support tumour growth and metastasis (43). Although type 2 cytokines downregulate antitumour immunity, they can promote the recruitment of tumouricidal eosinophils and macrophages into the tumour microenvironment (40, 41, 43, 44). In the present study, Ikutani et al. concluded that ILC2s facilitate the accumulation of tumouricidal eosinophils in the lung and may play an important role in tumour surveillance (11). However, eosinophils possess both pro- and anti-tumour activities that are dependent on the tumour microenvironment and type (47, 48). The role of ILC2s in tumour growth needs to be further clarified.

Our initial work on this subject was based on a highly malignant and poorly immunogenic murine tumour model, which shares many characteristics with naturally occurring human breast cancer (8). In this study, we aimed to investigate the effects of exogenously administered IL-33 on tumour appearance and progression and on the mechanisms of anti-tumour immunity. We found that IL-33 enhanced mammary carcinoma growth and lung and liver metastasis by facilitating the expansion of immune suppressor cells within the tumours and by diminishing innate anti-tumour immunity (8). IL-33 administration expanded IL-13 producing innate lymphoid cells within the mammary tumour. These tumour infiltrating lymphoid cells were CD45+ Lin Sca-1- CD44+ CD25+ ST2+ and produced IL-5 and IL-13 in response to IL-33 and were IL-4, IL-10 and IFN-γ negative, indicating that they had an ILC2 phenotype (8). IL-33 increased the frequencies of IL-5 and IL-13 expressing ILCs and circulating levels of IL-13 in tumour-bearing hosts (8). ILC2s have been shown to facilitate Type 2 immune responses while preventing Type 1-mediated immunity (11, 12, 14, 17, 49); however, their roles in cancer progression are not well defined. We assumed that ILC2s directly affect myeloid-derived suppressor cell (MDSC) activity via IL-13. MDSCs are usually recruited to tumour sites from peripheral lymphoid organs where they promote the CD4+Foxp3+ Treg generation (IJC 33) and exert immunosuppressive effects via TGF-b production. It is well known that MDSCs require the presence of IL-13 for
their activity, e.g., arginase and nitric oxide synthase II expression (50). In line with our conclusion, we also demonstrated IL-33 mediated an increase of CD11b+ CD11c+ Gr-1+ MDSCs within mammary tumours (8). These MDSCs expressed IL-13a1 receptors and produced TGF-β (8). Our findings revealed a novel role for IL-33 in the mechanisms of breast cancer immune escape via the ILC2s/IL-13/MDSCs/TGF-β/Tregs axis (8).

In another study, intra-biliary injection of IL-33 into mice with active Akt and Hippo pathways facilitated cholangiocarcinoma development, indicating a role of IL-33 in cholangiocyte proliferation, biliary repair, and carcinogenesis via the ILC2s/IL-13 axis (51, 52).

The role of ILC3s in tumour growth and progression was also described (Table 1). RORγt+ ILC3s are a main source of IL-17 and IL-22 (second to Th17 cells in terms of production) (53). Studies have shown that RORγt+ ILC3s accumulate in the intestine of inflammatory bowel disease (IBD) patients and are a crucial IBD pathogenic factor (33, 53). In chronic gastrointestinal infection or acute stimulation with chemical carcinogens, IL-17-producing IL-23R+ ILC3s induce gut tumourigenesis through the IL-23/IL-17 signalling pathway, which promotes angiogenesis and tumour metastasis (54, 55). Some experiments suggested that IL-22 producing ILC3s promote inflammation in active intestinal diseases (33, 56-58). IL-22 may promote pro- and anti-tumour mechanisms depending on the tissue microenvironment and tumour characteristics. Thus, in pathogen-induced cancers, IL-22 inhibits tumour growth by promoting the elimination of viral or bacterial infections and termination of inflammation. In contrast, IL-22 may facilitates angiogenesis and promotes cancer growth (59). Studies have shown that IL-22 together with other factors contributes to tumour formation (60, 61).

It has been known for decades that NK cells provide protection against viruses and tumour cells. The role of NK cells in immune surveillance is well established (62-66). NK cell activity is variable during tumour progression and is related to clinical stages and disease outcome (65-70). During the cytotoxic killing of tumour cells, NK cells and CD8+ T cells rapidly release granules that contain perforin and granzymes into immunological synapses, thereby inducing target cell death (71). NK cell activity is the major mechanism of innate immunity against tumours (42). NK cells lyse tumour cells without prior sensitization and represent the first line of defence against tumours and cancer metastasis (42).

Recent studies have achieved significant progress towards defining subpopulations of ILCs. ILC1s, ILC2s and ILC3s are now emerging as important cell populations that regulate tissue homeostasis and inflammation. Several studies have described the effects of ILCs on the genesis, growth and progression of tumours and the modulation of antitumour immune responses. However, much of the current knowledge regarding ILCs is based on experimental models and still requires confirmation in humans. Extensive clinical investigations are still needed to clarify the intrinsic roles of ILCs in response to tumours.

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CONFLICT OF INTEREST

The authors declare no financial or commercial conflicts of interest.

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