Cytokine and Growth Factor Reviews xxx (xxxx) xxx–xxx

Contents lists available at ScienceDirect

Cytokine and Growth Factor Reviews

journal homepage: www.elsevier.com/locate/cytogfr

Lineage specification in innate lymphocytes

Arundhoti Das[a], Christelle Harly[a], Qi Yang[b], Avinash Bhandoola[a,*]

[a] Laboratory of Genome Integrity, Center for Cancer Research, National Cancer Institute, National Institutes of Health, Bethesda, MD, 20892, USA
[b] Department of Immunology and Microbial Disease, Albany Medical College, Albany, NY, 12208, USA

ARTICLE INFO

Keywords:
Innate lymphoid cells
ILC distribution
Central progenitors
Development
Homing
Peripheral ILC generation

ABSTRACT

Innate lymphoid cells (ILCs) are immune cells that lack specific antigen receptors but possess similar effector functions as T cells. Concordantly, ILCs express many transcription factors known to be important for T cell effector function. ILCs develop from lymphoid progenitors in fetal liver and adult bone marrow. However, the identification of ILC progenitor (ILCP) and other precursors in peripheral tissues raises the question of whether ILC development might occur at extramedullary sites. We discuss central and local generation in maintaining ILC abundance at peripheral sites.

1. Introduction

Innate lymphoid cells (ILCs) are considered innate counterparts of effector T cells. ILCs have been classified into three main subsets or types. Type 1 ILCs comprise conventional natural killer (NK) cells and ILC1; type 2 ILCs consist of ILC2; and Type 3 ILCs comprise ILC3 and Lymphoid Tissue inducer cells (LTi) [1]. The classification of ILCs is based on their expression of defining transcription factors and their functional characteristics, including their distinct cytokine production ability [1]. Additionally, recent evidence suggests the existence of ILC subsets functionally intermediate between the main ILC groups [2–8]. Whether these new subsets represent plasticity or are distinct lineages of ILC is presently unknown.

ILC immune effector functions are strikingly similar to T cells [9]. Like $CD8^+$ T cells, NK cells are cytotoxic to tumor cells and virus-infected cells. The signature cytokines secreted by Th1, Th2 and Th17 cells are produced by ILC1, ILC2 and ILC3 respectively [10]. ILCs and T cells share transcriptional networks that are perhaps responsible for the similarities of their immune functions [11,12]. Despite striking similarities between T cell and ILC effector functions, ILCs lack some unique features that distinguish them from T cells. They lack recombination activating gene (RAG)-dependent rearrangement of antigen specific receptors, and so would be predicted to lack immune memory. However, some reports suggest that long-lived ILC2s as well as NK cells do possess memory type characteristics [13,14]. Similar to innate-like T cells, ILCs are naturally distributed in various lymphoid and non-lymphoid tissues [15].

ILC development was initially studied at primary hematopoietic sites, which are the bone marrow in adult mice or liver in fetal mice [16]. However, many recent studies report the presence of ILC progenitors in peripheral tissues and organs in mouse and human, suggesting the existence of peripheral ILC development [17]. It is unclear to what extent the development and functional programming of ILC subsets occurs centrally versus at peripheral sites. ILC development at peripheral sites could allow generation of specific classes of ILCs tailored to local environments.

We review here recent advances in understanding the progressive steps of central ILC development in adult mice, and discuss some of the evidence for peripheral ILC development. We propose that migration of ILC progenitors in addition to ILC may economically allow tissues to elicit development and expansion of specific ILC types appropriate for each tissue.

2. ILC subsets and their sites of prevalence

ILC subsets are widely distributed throughout the body [18]. ILCs have been isolated from primary lymphoid organs such as bone marrow and thymus, as well as from secondary lymphoid organs, peripheral blood and non-lymphoid tissues such as lung, small intestine, skin, liver, uterus, colon, and fat [19,20]. ILC1s are found in liver, intestinal lamina propria as well as the intraepithelial (IE) compartment [21]. ILC1s produce large amounts of IFN-γ and protect against intracellular pathogens like *Clostridium difficile* and *Toxoplasma gondii* [22,23]. NK cells are found in the bone marrow, liver, lymph nodes and spleen [24];

Abbreviations: ILC, innate lymphoid cell; LTi, lymphoid tissue inducer; NK, natural killer; ALP, all lymphoid progenitor; LMPP, lymphoid-primed multipotent progenitor; CLP, common lymphoid progenitors; CHILP, common helper innate lymphoid cell progenitor; ILCP, ILC progenitor; EILP, early innate lymphoid progenitor; α-LP, alpha-lymphoid progenitor; NKP, NK progenitor

* Corresponding author.
E-mail address: avinash.bhandoola@nih.gov (A. Bhandoola).

https://doi.org/10.1016/j.cytogfr.2018.01.005
Received 15 December 2017; Accepted 11 January 2018
1359-6101/

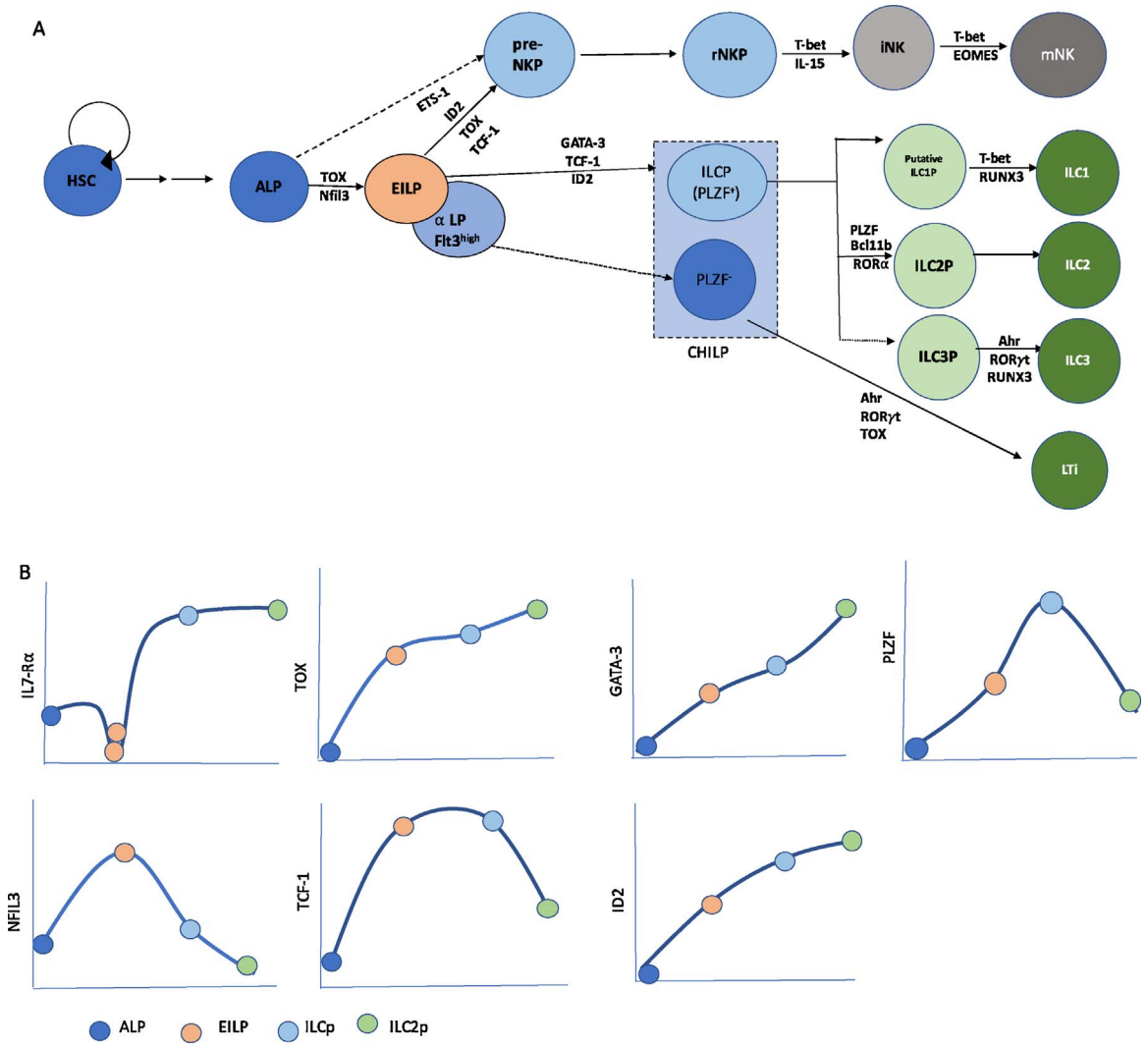

Fig. 1. (A) Developmental stages in ILC lineage, along with the requirements for key transcription factors at each developmental transition. (B) The level of IL7-Rα and key transcription factors during the progressive stages of ILC development.

and can kill target cells through the release of perforins and granzymes [25]. Tissue-resident natural killer cells in liver have been shown to display distinct markers and transcription factors as compared to thymic and conventional splenic NK cells [26]. ILC2s are dominant in lung especially in the collagen-rich regions but not in alveolar areas, where they induce eosinophilia through production of IL-5 and airway hyper-sensitivity through production of IL-13 [27]. ILC2s are found in significant proportion in small intestinal lamina propria where they mediate anti-helminth responses. ILC2s exist abundantly in skin and white adipose tissues [28]. Recently, gut ILC2s have been also shown to co-localize with cholinergic neurons and are responsive to the neuropeptide neuromedin U [29]. ILC3s are found in abundance in small intestinal lamina propria, intestinal cryptic areas and Payer's patches (PPs) where they secrete IL-17 and IL-22 thereby providing immunity against intestinal pathogens and help maintain the integrity of the intestinal barrier [30]. ILC3s also reside within marginal zone areas of spleen, and orchestrate innate-like antibody production through secreting B-cell helper factors APRIL, BAFF, and signaling via CD40L [31]. Lymphoid tissue inducer cells play a significant role in fetal organogenesis of lymph nodes and Peyer's patches [32].

Analysis of ILCs in humans and mice across different tissues revealed tissue-dependent heterogeneity in phenotype and number [33,34]. The phenotype and function of ILCs can be modified by cues from the environment [29,35]. For example, splenic retinoic acid-related orphan receptor gamma t $(ROR\gamma t)^+$ ILC3s have distinct characteristics compared to ILC3s from small intestinal lamina propria. Splenic $ROR\gamma t^+$ ILCs can suppress tumor growth, whereas intestinal $ROR\gamma t^+$ ILCs fail to do so. Additionally, adoptive transfer experiments suggest that the transferred ILCs phenotypically and functionally adapt to the particular tissue where they settle, suggesting an important role of tissue environment in shaping functional specialization of ILCs [35]. Indeed, tissue specific factors and microbiota contribute greatly to the heterogeneity in the intestinal ILC subsets. Single cell transcriptomics analysis has identified multiple transcriptional states within the known gut ILC subsets under homeostatic conditions. Antibiotic treatment showed profound changes in ILC1 and ILC2-specific gene expression and chromatin landscapes [36]. Nutrient deficiency has also been shown to affect ILC subsets. Vitamin A deficiency leads to significant reduction in ILC3 numbers and increase in ILC2 numbers in the small intestine, imparting protection against intestinal helminths. This suggests ILCs act as a sensor for dietary stress and respond to the altered immunity at barrier surfaces [37]. Also, local tissue signals have been shown to play a crucial role in driving terminal differentiation of ILC2 and their T cell counterpart Th2 cells. Effector Th2 cells exhibit distinct chromatin accessibility from that of ILC2s at the *Il4* and *Arg1* loci but they acquire similar terminal effector functions when they are exposed to signals like IL-25, IL-33 and thymic stromal lymphopoietin (TSLP) [38].