Available online at www.sciencedirect.com

ScienceDirect

Current Opinion in Immunology

Role of group 3 innate lymphoid cells in antibody production

Giuliana Magri[1] and Andrea Cerutti[1,2,3]

Innate lymphoid cells (ILCs) constitute a heterogeneous family of effector lymphocytes of the innate immune system that mediate lymphoid organogenesis, tissue repair, immunity and inflammation. The initial view that ILCs exert their protective functions solely during the innate phase of an immune response has been recently challenged by evidence indicating that ILCs shape adaptive immunity by establishing both contact-dependent and contact-independent interactions with multiple hematopoietic and non-hematopoietic cells, including B cells. Some of these interactions enhance antibody responses both systemically and at mucosal sites of entry.

Addresses
[1] Institut Hospital del Mar d'Investigacions Mèdiques, Barcelona Biomedical Research Park, Barcelona, Spain
[2] Catalan Institute for Research and Advanced Studies (ICREA), Barcelona Biomedical Research Park, Barcelona, Spain
[3] Immunology Institute, Department of Medicine, Division of Clinical Immunology, Icahn School of Medicine at Mount Sinai, New York, NY, USA

Corresponding author: Cerutti, Andrea (acerutti@imim.es, andrea.cerutti@mssm.edu)

Current Opinion in Immunology 2015, **33**:36–42

This review comes from a themed issue on **Lymphocyte development and activation**

Edited by **Sidonia Fagarasan** and **Jeroen P Roose**

http://dx.doi.org/10.1016/j.coi.2015.01.008

Introduction

Innate lymphoid cells (ILCs) include developmentally related groups of helper-like cells of the innate immune system that functionally mirror well-defined subsets of $CD4^+$ T helper (T_H) cells [1,2]. Some of the effector molecules expressed by ILCs are known modulators of adaptive antibody responses emerging from T cell-dependent (TD) or T cell-independent (TI) pathways of B cell activation. This review discusses how group 3 ILC modulates homeostasis and antibody production in systemic and mucosal lymphoid tissues.

Phenotype and function of ILCs

Multiple subsets of ILCs emerge from a common lymphoid progenitor through a developmental pathway initiated by bone marrow or fetal liver stem cells. This pathway is dictated by signals from common cytokine receptor γ-chain and various transcription factors, including ID2, nuclear factor interleukin-3 regulated (NFIL3) and GATA3 [3–6]. Despite their phenotypic and functional heterogeneity, ILCs share multiple properties, including lymphoid morphology, absence of common lineage-specific molecules, and lack of somatically recombined antigen receptors [1,2].

Besides cytotoxic natural killer (NK) cells, ILCs include three groups of helper-like innate cells characterized by the expression of distinct sets of transcription factors and cytokines [3,7]. Similar to type 1 T_H (T_H1) cells, group 1 ILCs (ILC1) depend on the transcription factor T-bet and secrete interferon (IFN)-γ and tumor necrosis factor (TNF) in response to interleukin-12 (IL-12) [5,8,9]. In contrast, ILC2 require the transcription factors GATA3, ROR-α and TCF1 [10–12] and release IL-5 and IL-13 in response to IL-25, IL-33 and thymic stromal lymphopoietin (TSLP), thus resembling T_H2 cells [1,13,14]. Finally, ILC3 are highly dependent on the transcription factor RORγt and secrete IL-22 and IL-17A in response to IL-23 and IL-1β, therefore mimicking T_H22 and T_H17 cells [15–17]. Metabolites of dietary vitamin A, including retinoic acid (RA), further contribute to the development and homeostasis of ILC3 [18].

ILCs secrete effector cytokines during the innate phase of an immune response, prior to the initiation of adaptive immunity [1]. ILC1 provide protection against viruses, intracellular bacteria and tumors and play an important role in inflammation, whereas ILC2 enhance immunity against nematodes and contribute to allergic inflammation [2]. Finally, ILC3 include lymphoid tissue inducer (LTi) cells, which mediate lymphoid organogenesis, as well as natural cytotoxicity receptor $(NCR)^+$ ILC3 and NCR^- ILC3, which promote epithelial integrity and immune responses against extracellular bacteria [1,2,7]. These responses may entail the induction of protective antibodies by systemic and mucosal B cells of the adaptive immune system.

Role of ILC3 in lymphoid organ development

ILC3 form a heterogeneous family of developmentally related lymphoid populations that rely on the cytokine IL-7 and the transcription factor RORγt for their differentiation [15,19–21]. LTi cells are prototypic members of the ILC3 family [22]. These cells were first described some 20 years ago as fetal $CD4^+CD3^-$ lymphocytes

inhabiting the anlagen of mouse lymph nodes and embryonic Peyer's patches (PPs) [23]. Subsequent studies demonstrated that LTi cells are essential for the development of lymphoid organs during fetal life [24].

Lymphoid tissue organogenesis involves a specialized subset of stromal cells (SCs) that express elevated levels of LTβ receptor (LTβR) [22]. These SCs are referred to as lymphoid tissue organizer (LTo) cells and become strongly activated in response to engagement of LTβR by transmembrane lymphotoxin $\alpha_1\beta_2$ ($LT\alpha_1\beta_2$) from LTi cells [22]. Signals from LTβR stimulate LTo cell upregulation of vascular cell adhesion molecule (VCAM), intercellular adhesion molecule (ICAM), mucosal addressin cell adhesion molecule (MAdCAM) and receptor activator of NF-κB ligand (RANKL) as well as LTo cell release of chemokines such as CXCL13, CCL19, CCL20 [22]. Such activation-related events promote the recruitment and spatial organization of B and T cells. Recently, a population of $CD4^-CD127^+RORC^+$ ILCs with LTi-like function was identified in developing lymph nodes and mesentery from humans during the first trimester of gestation [25].

Immediately after birth, LTi cells form primitive lymphoid clusters, termed cryptopatches, in the lamina propria (LP) of both small and large intestinal segments [26]. These LTi cells retain lymphoid tissue-inducing activity and indeed promote the induction of more organized lymphoid structures, called isolated lymphoid follicles (ILFs), in response to postnatal colonization by intestinal bacteria [27,28].

ILC3 with LTi-like function have also been identified in adult secondary lymphoid organs different from ILFs, including peripheral lymph nodes, spleen and PPs from the small intestine [29••,30••]. These ILC3 facilitate the segregation of B and T cell areas and the generation of optimal immune responses by interacting with SCs, including marginal reticular cells (MRCs) [31]. Similar ILC3-SC interactions foster the reparation of the lymphoid microenvironment after infection with lymphocytic choriomeningitis virus [32]. Finally, ILC3 cooperate with B cells to induce the development of follicular dendritic cells (FDCs) from ubiquitous perivascular precursors [33]. These SCs specialize in providing a structural scaffold to lymphoid follicles and in trapping antigen during immune responses [33].

Role of ILC3 in homeostasis and immunity

Besides promoting the development, maintenance and repair of peripheral lymphoid tissues, ILC3 maintain gut homeostasis in two ways: by preserving the integrity of intestinal epithelial cells (IECs) and by segregating commensal bacteria in the intestinal lumen [15,17,34–36]. These effects largely rely on ILC3 secretion of powerful IEC-stimulating cytokines, namely IL-*22* [17,35,36]. Indeed, depletion of ILC3 causes systemic inflammation by inducing mucosal translocation and peripheral dissemination of intestinal bacteria predominantly belonging to the *Alcaligenes* genus [36]. Similarly, loss of IL-*22* from ILC3 triggers intestinal inflammation by causing outgrowth of segmented filamentous bacteria (SFB), a mouse-specific group of commensals that stimulate the expansion of pro-inflammatory T_H17 cells [37].

Mucosal ILC3 release IL-*22* upon exposure to IL-23 from dendritic cells (DCs) and macrophages [15,38]. This response contributes to the segregation of commensal bacteria in the intestinal lumen by inducing IEC release of β-defensins, RegIIIβ, RegIIIγ and other antimicrobial proteins through a transcriptional program dictated by signal transducer and activator of transcription 3 (STAT3) [15,38,39]. IL-*22* further reinforces the gut barrier by stimulating IEC production of MUC1, a transmembrane mucin that forms a protective glycocalix on the gut epithelium [40]. Together with LT, IL-*22* also stimulates extensive fucosylation of the glycoproteins that form the glycocalyx, a key requirement for host–microbiota symbiosis [41,42].

Besides promoting gut homeostasis, IL-*22* from ILC3 provides a first line of defence against enteric pathogens. Indeed, loss of IL-*22* exacerbates the invasion of the large intestine by *Citrobacter rodentium*, a murine pathogen used as model for human attaching and effacing infections [17,39]. Also in this case, the protective effect of IL-*22* is largely dependent on IEC release of antimicrobial peptides, suggesting that ILC3 use similar signaling programs to control intestinal commensals and pathogens.

Role of ILC3 in systemic antibody responses

Growing evidence indicates that, besides mediating innate immunity, ILC3 regulate adaptive immune responses (Figure 1), including antibody production by B cells [1,29••,43••,44••]. After recognizing antigen through transmembrane immunoglobulin M (IgM) and IgD antibodies generally referred to as B cell receptor (BCR), mature naïve B cells usually follow a TD pathway to generate humoral immunity [45]. This pathway involves cognate interactions of B cells with effector $CD4^+$ T follicular helper (T_{FH}) cells positioned at the outer edge of the lymphoid follicle, also known as T-B border [45]. At this stage, B cells receive robust antigenic signals and multiple T_{FH} cells co-stimulatory signals, including signals from the TNF family member CD40 ligand (CD40L) and the cytokines IL-4 and IL-21 [46,47]. Antigen-activated B cells emerging from this initial cognate interaction progress along two distinct maturation pathways to generate a primary antibody response [48].

In the extrafollicular pathway, B cells differentiate into short-lived plasmablasts that secrete IgM with low affinity for antigen [48]. In the follicular pathway, B cells migrate