

Shared Transcriptional Control of Innate Lymphoid Cell and Dendritic Cell Development

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Abstract

Innate immunity and adaptive immunity consist of highly specialized immune lineages that depend on transcription factors for both function and development. In this review, we dissect the similarities between two innate lineages, innate lymphoid cells (ILCs) and dendritic cells (DCs), and an adaptive immune lineage, T cells. ILCs, DCs, and T cells make up four functional immune modules and interact in concert to produce a specified immune response. These three immune lineages also share transcriptional networks governing the development of each lineage, and we discuss the similarities between ILCs and DCs in this review.

Keywords

transcription factors; hematopoiesis; dendritic cells; innate lymphoid cells; T cells

INTRODUCTION

A potent immune response requires cross talk and collaboration between the innate and adaptive immune systems, both of which contain highly specialized immune lineages. Innate immune responses involve many different types of innate cells, such as neutrophils, monocytes, and (specifically discussed in this review) innate lymphoid cells (ILCs) and dendritic cells (DCs). Innate cells recognize pathogens through their germline-encoded receptors and first initiate a proinflammatory response that aims to contain and rapidly clear the infection. Importantly, the innate cells direct the specific type of adaptive immune response that is most effective at clearing the particular type of infection by secreting cytokines and chemokines to alert the adaptive immune response. The adaptive immune response can be divided into three types of immunity, which are specific to the type of pathogen that evokes the response. Type I immunity is in response to intracellular microbes, such as bacteria and viruses, while type II immunity protects against helminths and environmental substances. Type III immunity is involved in protection against extracellular bacteria and fungi. Each of these immune responses corresponds to a specific type of T cell,

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which expresses antigen-specific receptors, and to specific innate cells, ILCs and DCs, that together effectively respond to a pathogen.

ILCs are often considered to be innate T cells, as both cell types share functional and developmental similarities. Like T cells, ILCs can be divided into several distinct subsets that correspond to the three types of immunity that cells elicit. However, unlike T cells, which have antigen-specific receptors, undergo clonal selection, and expand when stimulated, ILCs do not have antigen-specific receptors or the ability to undergo clonal selection. ILCs instead rapidly respond to the pathogen and secrete cytokines to control the infection. The developmental similarities between T cells and ILCs have been discussed in detail in other reviews (Eberl et al. 2015, Robinette & Colonna 2016) and are discussed only briefly in this review.

DCs are characterized as professional antigen presenting cells and are responsible for priming T cells for potent T cell activation. DCs encode a number of receptors that allow for antigen uptake, antigen processing, and antigen presentation to MHC molecules on T cells. Initially thought of as one family, DCs are now recognized for their heterogeneity in both location and function, with distinct subsets specialized for specific response. Two sets of classical/conventional DCs (cDCs), cDC1 and cDC2, as well as plasmacytoid DCs (pDCs) and epidermal Langerhans cells have been identified (Cella et al. 1999, Schuler et al. 1985, Siegal et al. 1999, Steinman & Witmer 1978).

This review focuses on the similarities between T cells and their innate counterparts, ILCs and DCs, in promoting a specialized immune response. We present a model in which these three immune cell types are distinguished by the major immune effector module they promote, and we then discuss recent progress in understanding the development of ILC and DC subsets. Both cell lineages share an unrecognized transcriptional network similarity that deepens our understanding of innate cell lineage communication with adaptive immunity.

COMMON EFFECTOR MODULES BETWEEN T CELLS, ILCs, AND DCs

As discussed above, there are three broad types of immune responses, types I, II, and III, where each type of immunity corresponds to specific ILC and DC subsets to elicit innate immunity, which in turn leads to a coordinated effort to prime a T cell subset for the proper adaptive immune response. Type I immunity protects against intracellular pathogens and can be divided into two types of responses: (a) a cytotoxic response led by NK cells, pDCs, and CD8⁺ T cells and (b) an intracellular defense module held by ILC1s, cDC1s, and T_H1 cells. Type II immunity protects against helminths and environmental substances and is elicited by ILC2, a subset of cDC2, and T_H2 cells. Finally, type III immunity is involved in protection against extracellular bacteria and fungi and involves ILC3s, a subset of cDC2, and T_H17 cells. Figure 1 shows a schematic of the types of immunity of each immune module and the cell types involved. Another subset of T cells, termed regulatory T cells defined by the transcription factor *Foxp3*, are not discussed in this review, as inhibitory innate counterparts are not well known.

Type I Immunity Involves Cytotoxic and Intracellular Defense Modules

NK cells, ILC1s, pDCs, and cDC1s interact with CD8⁺ T cells and T_H1 cells to defend against viruses and intracellular pathogens.

NK cells, pDCs, and CD8⁺ T cells compose the cytotoxic module to protect against viruses.

NK cells and pDCs are among the first cells to initiate and mount a response to viral infection. NK cells express activating or inhibitory receptors that can recognize ligands on infected cells and can directly lyse the infected cells through granules containing either pore-forming enzymes termed perforins or serine proteases termed granzymes. NK cells also express receptors for the proinflammatory cytokines IL-12, IL-15, IL-18, and type I interferons (IFNs), all of which are produced by other lineages during viral infection and are important for NK cell activation. Importantly, NK cells produce large amounts of IFN- γ , which activates macrophages for phagocytosis and prevents viral spread.

pDCs sense viruses through surface receptors such as Toll-like receptors 7 and 9 (TLRs 7 and 9) and cytosolic sensors such as RIG-I and MDA5. The main effector function of pDCs is to secrete large amounts of type I interferon to rapidly clear infected cells. Several studies have selectively ablated pDCs in vivo to demonstrate their function in regulating the antiviral immune response. Conditionally deleting the transcription factor *Tcf4* (E2-2) using an *Itgax-cre* that allows for deletion in CD11c⁺ immune cells results in an impaired innate response to mouse hepatitis virus and an impaired adaptive response to lymphocytic choriomeningitis virus (LCMV) (Cervantes-Barragan et al. 2012). Specifically, pDCs are vital in sustaining a cytotoxic T lymphocyte (CTL) response against chronic viral infection (Cervantes-Barragan et al. 2012). Another study in which pDC-specific expression of diphtheria toxin receptor was achieved using a human BDCA2 promoter indicated that lacking pDCs at the early stage of response against murine cytomegalovirus (MCMV) infection leads to lowered type I IFN production and attenuated NK cell activation (Takagi et al. 2011). pDCs may recruit and activate NK cells through their cytokine production (Guillerey et al. 2012).

CD8⁺ T cells are essential for antiviral immunity, as they can both directly lyse cells through perforin and granzyme and provide memory to the immune system for protection against reinfection. In corroboration with earlier studies, Brewitz et al. (2017) showed that pDCs promote CD8⁺ T cell help in response to viral infection and moreover that pDCs are recruited to CD8⁺ T cell priming sites through the chemokines CCL3 and CCL4. Type I IFN produced by pDCs bolstered cDC1 maturation and cross-presentation efficacy (Brewitz et al. 2017).

Development of both NK cells and CD8⁺ T cells depends on the transcription factors T-bet (encoded by *Tbx21*) and Eomesodermin (Eomes, encoded by *Eomes*) (Gordon et al. 2012, Intlekofer et al. 2005). Both transcription factors belong to the T-box transcription factor family (Papaioannou 2014). Like other members in the family, these transcription factors share a highly similar T-box domain, suggesting that they bind to the same DNA motifs (Zhang et al. 2018). However, they possess divergent N and C termini, suggesting that they interact with distinct partners for activity (Pearce et al. 2003). In NK and CD8⁺ T cell

function, T-bet and Eomes play different roles but can only partially compensate for each other (Kaech & Cui 2012, Pearce et al. 2003). In T cell development, T-bet appears to act before Eomes (Cruz-Guilloty et al. 2009). While T-bet modulates the expression of IFN- γ and IL-12R β 2, Eomes nonredundantly drives perforin and granzyme B production (Pearce et al. 2003, Townsend et al. 2004). Additionally, studies have suggested that T-bet and Eomes mutually regulate each other to maintain a balance between NK cells and ILC1 populations (Daussy et al. 2014, Pikovskaya et al. 2016). The regulation of both transcription factors remains largely unclear, and studies have indicated that exogenous factors, such as TGF- β , may modulate Eomes and T-bet expression (Cortez et al. 2016).

ILC1s, cDC1s, and TH1 cells belong to the intracellular defense module.

ILC1s and cDC1s provide inflammatory signals to activate T_H1 cells and promote an immune response against intracellular pathogens, such as *Toxoplasma gondii*. ILC1s are found in nearly all tissues and secrete large amounts of IFN- γ (Sojka et al. 2014). While both NK cells and ILC1s produce IFN- γ , ILC1s produce IFN- γ more quickly than do NK cells in response to several viruses, such as MCMV, SeV, and PR8 influenza virus, in part due to cross talk with cDC1 (Artis & Spits 2015, Serafini et al. 2015, Weizman et al. 2017). cDC1s are the main and nonredundant producers of IL-12, a cytokine responsible for activating ILC1s, for driving IFN- γ production, and for instigating a T_H1 response (Bliss et al. 1999, 2000; Gazzinelli et al. 1994; Hou et al. 2011; Liu et al. 2006; Mashayekhi et al. 2011; Pepper et al. 2008; Reis e Sousa et al. 1997).

cDC1s are required for protection against intracellular pathogens and for rejection of tumors. Studies demonstrating the importance of this cDC subset have been done with *Batf3*^{-/-} mice, which specifically lack cDC1 (Hildner et al. 2008). Studies in which these mice were infected with *T. gondii* showed that cDC1 produce IL-12 and furthermore that IL-12 can restore cDC1 in infected *Batf3*^{-/-} mice (Mashayekhi et al. 2011, Tussiwand et al. 2012). Mice lacking all Batf family members (*Batf*^{-/-} *Batf2*^{-/-} *Batf3*^{-/-}) could not restore the cDC1 population after administration of IL-12, suggesting that Batf family members may be able to compensate for the lack of Batf3 in cases of infection (Mashayekhi et al. 2011, Tussiwand et al. 2012). cDC1s also promote production of IFN- γ by activating invariant NK T (iNKT) cells, as iNKT cells can produce IFN- γ after interacting with cDC1 pulsed with α -galactosylceramide (α -GalCer), a glycolipid antigen presented on CD1d molecules that are highly expressed on activated cDC1s (Arora et al. 2014; Fujii et al. 2002, 2004; Kawano et al. 1997). cDC1s are also uniquely capable of cross-presentation, which is crucial for antitumor immunity (Diamond et al. 2011, Fuertes et al. 2011, Hildner et al. 2008). Recent work has indicated a necessary role for the protein Wdfy4 in cross-presentation, but the precise mechanism by which this protein or other proteins play in the antigen presentation process remains unclear (Theisen et al. 2018).

T-bet is also important for the development of ILC1 and T_H1 cells (Daussy et al. 2014, Robinette et al. 2015). These cells are characterized by their shared function in producing IFN- γ and TNF- α and by their reliance on IL-12, IL-15, and IL-18 for activation. IL-12 signaling through STAT4 activation results in T_H1 differentiation in vivo but is dispensable for ILC1 polarization (Hsieh et al. 1993, O'Sullivan et al. 2016). In T cell development, T-

bet directly represses T_H2 specification, but it is unclear whether an analogy can be drawn in the ILC population where T-bet represses ILC2 polarization (Hwang et al. 2005, Zhu et al. 2012). T_H1s and ILC1s primarily participate in the immune response against viral infection and intracellular pathogens but are also associated with certain inflammatory bowel diseases and type I diabetes (Eberl et al. 2015). T-bet drives IFN- γ production by directly binding to the regulatory elements of the *IFNG* gene and inducing the expression of Runx3, another transcription factor that drives IFN- γ production. Recent studies indicate that Eomes is induced upon T_H1 cell activation and that it is expressed at steady state in certain ILC1 subsets (Bernink et al. 2015, Knox et al. 2014, Lupar et al. 2015). These data suggest that Eomes may play a role in intracellular defense module under certain circumstances, such as infection.

Type II Immunity Protects Against Helminths and Environmental Substances

ILC2s and a subset of cDC2 defined by the transcription factor *Klf4*, along with T_H2 cells, are important in maintaining barrier immunity.

ILC2s, *Klf4*-dependent cDC2s, and TH2 cells contribute to maintaining barrier immunity.

The third immune module is characterized by immunity to helminth infection and maintenance of barrier function. ILC2s and *Klf4*-dependent cDC2 are important innate cells for this type of immunity, and T_H2 cells provide the adaptive help. This type of immunity is modulated by the cytokines IL-5, IL-9, and IL-13. ILC2s are the major innate sources of IL-5 and IL-13 (von Moltke & Locksley 2014). These cytokines bolster the production of IL-4, which is required for T_H2 differentiation. This group of cells is further characterized by their expression of the transcription factor GATA3. GATA3 is essential for the development for both lineages and drives the production of IL-5 and IL-13 by binding directly to the promoter region of these genes, and conditional deletion of GATA3 results in the reduction of IL-5 and IL-13 production (Hoyler et al. 2012; Mjosberg et al. 2012a; Yagi et al. 2011, 2014; Zheng & Flavell 1997; Zhu et al. 2004, 2006). Upon induction, GATA3 needs to overcome a repressive threshold maintained by FOG-1 expression to stabilize the polarization of both lineages via autoactivation (Ouyang et al. 2000, Zhou et al. 2001). Such polarization can also be achieved via cytokine production. In particular, ILC2s in mouse small intestine produce IL-13 to actively drive differentiation of and IL-25 production by Tuft cells. IL-25 in turn further drives IL-13 production by ILC2s and maintains lineage stability (von Moltke et al. 2016).

While the cDC1 population appears to be homogeneous, the cDC2 population seems to be heterogeneous. Conditional deletion of Kruppel-like factor 4 (*Klf4*) results in the loss of CD24⁺ CD172⁺ cDC2s in the lung and lymph node, as well as a decrease in a progenitor population in the bone marrow (Tussiwand et al. 2015). Moreover, *Klf4*-deficient mice showed impaired protection against *Schistosoma mansoni* infection but not *herpes simplex virus*, *T. gondii*, or *Citrobacter rodentium* infections, indicating a specific defect in type II but not CTL, type I, or type III responses (Tussiwand et al. 2015). *Klf4* is a transcription activator or repressor and modulates the development of multiple lineages in epithelial tissues such as skin, lung, and intestine (Alder et al. 2008, Dang et al. 2000, Feinberg et al. 2007, Ghaleb et al. 2005, Katz et al. 2002, Kurotaki et al. 2013, McConnell & Yang 2010,

Segre et al. 1999, Yamanaka 2008, Yoshida & Hayashi 2014, Zheng et al. 2009). However, the specific function and target of KLF4 in cDC2 remain unclear. Several studies argue that cDC2s may modulate T_H2 responses to house dust mite (HDM) antigen (Hammad et al. 2010, Williams et al. 2013). Upon HDM challenge, cDC2s are rapidly recruited to lung airways and migrate to the lymph node to induce type II immunity (Mesnil et al. 2012). Also, IL-13 produced by ILC2s induce CCL17 production by lung and dermal cDC2s to attract memory T_H2 cells in response to allergen (Halim et al. 2016).

Type III Immunity Protects Against Extracellular Bacteria and Fungi

ILC3s and a subset of cDC2s dependent on *Notch2* are required for immunity against extracellular pathogens and fungi.

ILC3s, *Notch2*-dependent cDC2s, and TH17 cells protect against extracellular pathogens and fungi.

ILC3s and *Notch2*-dependent cDC2s compose the innate lineages for the fourth immune module. These cells are associated with defense against extracellular pathogens and fungi and can contribute to tissue homeostasis. Deregulation of these cells often results in autoimmune diseases such as multiple sclerosis, psoriasis, and Crohn's disease. STAT3 is required for proper response to IL-23 in ILC3s (Guo et al. 2014, Rankin et al. 2016), whereas it is wholly required for IL-23 signaling and subsequent in vivo T_H17 polarization.

Conditional deletion of *Notch2* in CD11c⁺ cells revealed that cDC2 nonredundantly produce IL-23 in response to the extracellular bacteria *C. rodentium*, a mouse model for enteropathogenic *Escherichia coli* (Satpathy et al. 2013). *Notch2* is a member of Notch family transcription factors that has four members in mammals, Notch 1–4. Members of this family of transcription factors function through ligand-mediated activation. Upon binding of ligands such as Delta-like family proteins, sequential proteolytic cleavages release the Notch intracellular domain (NICD). NICD then enters the nucleus and drives the expression of target genes in cooperation with several cofactors, including RBPJ and Mam. Differential CX3CR1 and ESAM expression reveals two subsets within the cDC2 population, and *Notch2* deficiency results in the specific loss of the CX3CR1^{lo} ESAM^{hi} subset in the spleen (Lewis et al. 2011, Mesnil et al. 2012). Mice with conditional deletion of *Notch2* in cDCs using *Itgax*-cre have shown a decrease in T_H17 numbers in the MLN (Lewis et al. 2011), and loss of *Irf4* results in impaired T_H17 differentiation induced by small intestine CD103⁺CD11b⁺ cDC2s (Persson et al. 2013, Schlitzer et al. 2013). The same phenomenon occurs with the specific deletion of small intestine lamina propria CD103⁺CD11b⁺ cDC2s using a human Langerin-DTA transgenic mouse model that also leads to a decrease in T_H17 cell numbers (Welty et al. 2013). Although ESAM^{hi} cDC2s are required for resistance to *C. rodentium*, mice lacking expression of *Irf4* or *CCR7* and thereby having DCs with impaired migration capacity do not exhibit significant susceptibility to *C. rodentium*, suggesting that IL-23 production by lamina propria resident cDC2s is sufficient for the effective control of this pathogen (Bajana et al. 2012, Satpathy et al. 2013). As mentioned above, IL-23 is required for ILC3 secretion of IL-22, and therefore cDC2s modulate intestine type III immunity by targeting both T_H17 and ILC3s.

The master regulator for this module is transcription factor ROR γ t, and a defect in this factor results in the complete absence of both lineages in vivo (Ivanov et al. 2016, Sawa et al. 2010). They also share a reliance on the transcription factor AHR, a receptor that binds various ligands with high risk of exposure in daily life, including dietary metabolites and pollutants (Cella & Colonna 2015). AHR is also essential for IL-22 production by this module (Basu et al. 2012, Kiss et al. 2011, Qiu et al. 2012).

ILC, DC, AND T CELL PLASTICITY IN IMMUNE MODELS

Although all three cell types reviewed here can be divided into subsets, each contributing to a specific type of immunity, recent work has shown that considerable plasticity can exist between the subsets. This imparts an important role for the local microenvironment in shaping an immune response. Plasticity has also been observed in both mouse and human.

The ability of some T cell subsets to convert to other subsets has been extensively studied (DuPage & Bluestone 2016, Murphy & Stockinger 2010). IL-2 and IL-4, the instructive signals for T_H1 and T_H2 polarization, respectively, drive lineage conversion. Recently polarized T_H1 cells can start to produce IL-4, cease IFN- γ production, and convert to T_H2-like cells upon IL-4 treatment in vitro or helminth infection in vivo (Panzer et al. 2012, Szabo et al. 1995). T_H2 cells are relatively more stable than T_H1s, partially because of GATA3 autoactivation and the mutual exclusion between GATA3 and T-bet (Ouyang et al. 2000). However, under circumstances in which IL-12R β expression is restored in T_H2 polarized cells by type I IFNs, IL-12 treatment can result in conversion to the T_H1 phenotype (Hegazy et al. 2010). Plasticity has also been demonstrated in the T_H17 lineage, which may be the most plastic member of the T helper family (Stockinger & Omenetti 2017). Another study demonstrated that IL-12 treatment induces T_H17 to downregulate ROR γ t and IL-17 expression and start to express T-bet and IFN- γ and retains a T_H1-like gene expression profile (Lee et al. 2009a,b). In humans, a population of cells expressing both ROR γ t and T-bet that could produce both type I and type III cytokines was identified in patients with Crohn disease (Annunziato et al. 2007).

ILC plasticity largely mirrors T cell plasticity, with most ILC plasticity in ILC3s (Cherrier et al. 2018, Murphy & Stockinger 2010). In vitro treatment of ILC3 with IL-2 or IL-5 can transform ILC3s into IFN- γ -producing ILC1-like cells (Bernink et al. 2015, Cella et al. 2010). In mice, an increase in T-bet expression and Notch signaling together with a decrease in ROR γ t expression converts CCR6⁻ NKp46⁺ ILC3s into NK1.1⁺ ILC1s that can produce IFN- γ (Vonarbourg et al. 2010). This conversion was later shown to be T-bet dependent (Klose et al. 2013, Rankin et al. 2013). ILC2s also show some degree of plasticity. ILC2s can produce IL-17 and be converted into ILC3s by injection of IL-25 or exposure to Notch ligand (Huang et al. 2015, Zhang et al. 2017). These converted ILC2s also induce ROR γ t expression (Zhang et al. 2017). Multiple groups have also shown that ILC2s secrete IFN- γ in response to IL-12 and IL-1B and convert to ILC1s (Lim et al. 2016, Ohne et al. 2016, Silver et al. 2016).

Many of the studies of DC plasticity have focused on functional plasticity without investigating changes in transcriptional profile (Pulendran et al. 2008). In this sense, plasticity refers to altered ability to stimulate T cell response. For example, DCs cultured

with IFN- γ can induce T_H1 responses (Ochsenbein et al. 2001), while thymic stromal lymphopoietin (TSLP) can strongly activate and modulate DCs to stimulate T_H2 responses in an OX40-L-dependent manner (Ito et al. 2005). However, these studies failed to determine whether the differential ability to induce a T cell response is simply because the same subset of DCs is responding to different extracellular signaling or whether there is actually subset conversion driven by differential expression of lineage-defining transcription factors such as *Irf8*, *Batf3*, and *Klf4* induced by environmental cues.

TRANSCRIPTIONAL BASIS OF EARLY ILC AND DC DEVELOPMENT

We now focus on the transcriptional networks governing ILC and DC development. Models of ILC and DC development can be divided into three distinct stages, as discussed for ILCs in a recent review by Serafini et al. (2015). Briefly, stage 1 is the specification of common precursors from a multipotent progenitor that has not excluded other cell fates. Stage 2 is the commitment of the precursors to their mature counterparts. Both stages 1 and 2 normally occur in the bone marrow. Stage 3 involves the maintenance and regulation of the mature cell subsets in tissues. Figure 2 shows both ILC development and DC development.

ILC Development

All subsets of ILCs are found in nearly all organs and tissues in the body, but ILC progenitors develop in the fetal liver and bone marrow. In the fetal liver, ILC progenitors that are phenotypically similar to LTis arrive on day E12.5–13.5 and subsequently express lymphotoxins to support lymphoid structure development. ILC progenitors in the bone marrow, which are a subset of the common lymphoid progenitor (CLP) that do not express the surface marker Ly6D, arise from the all-lymphoid progenitor (ALP) and from the IL-7Ra⁺ lymphoid-primed multipotent progenitor (LMPP) (Cherrier & Eberl 2012, Ghaedi et al. 2016, Inlay et al. 2009, Ishizuka et al. 2016, Klose et al. 2014, Moro et al. 2010, Possot et al. 2011, Yang et al. 2011). Another faction of the CLP, designated by positive expression of the integrin $\alpha_4\beta_7$, is thought to include the first uncommitted ILC progenitor, but further studies are needed to identify this progenitor (Seillet et al. 2016). Briefly, stage 1 is the specification of common ILC precursors from the CLP, which include the α LP, the CHILP (the common progenitor to the helper-like ILC lineages), and the ILCP (the common precursor to ILCs). These progenitors have largely excluded B and T cell potentials, making them distinct from the CLP, but may not represent fully committed ILC precursors. Within the α LP progenitor, only the CXCR6⁺ subset excludes T cell potential, but it does give rise to conventional NK (cNK) and non-NK ILC1, ILC2, and ILC3 cell types. However, the CXCR6⁻ subset can develop into T cells as well (Yu et al. 2014). This α LP may be the most uncommitted ILC progenitor found thus far, but further studies are required to dissect this population. The next progenitor, the CHILP, was discovered in 2014. The CHILP gives rise only to non-NK ILC1s, ILC2s, and ILC3s. ILC2, ILC3, and non-NK ILC1 cells (Klose et al. 2014). [←**AU: Are these non-NK also?***yes,] The last progenitor—the ILCP—was also discovered in 2014 and expresses high levels of the transcription factor PLZF (Constantinides et al. 2014). This progenitor is committed to all three ILC lineages but excludes LTi and NK cell potentials (Constantinides et al. 2014). Early innate lymphoid progenitors (EILPs) were identified in 2015 using a reporter mouse specific for the

transcription factor TCF-1, which is expressed by all ILC progenitors (Yang et al. 2015). Recently, EILPs were established as intermediate progenitors between ALPs and ILCPs because certain transcription factors, such as PLZF and GATA-3, were expressed at intermediate levels between ALPs and ILCPs (Harly et al. 2018). Importantly, EILPs are a functionally distinct cell type relative to ALPs and ILCPs because they are specified but not committed to the ILC lineage (Harly et al. 2018). Progenitors identified in stage 1 represent cells specified to the ILC lineage but, because they can give rise to other cell lineages under in vivo or in vitro conditions, do not represent committed progenitors.

Commitment to specific ILC subsets occurs in stage 2 of ILC development. In this stage, identification of progenitors specific to NK cells, ILC1, ILC2, and ILC3 [**←**AU: are these non-NK?***] is aided by knowledge of T helper subsets, as ILCs and T helper cells are similar in both development and function. Recent studies have attempted to find a committed progenitor to the ILC1 lineage that is distinct from a proposed progenitor of cNK cells. Both lineages express T-bet and Eomes. T-bet is important for the development of ILC1 and cNK cells, as *T-bet*^{-/-} mice do not have liver or intestinal ILC1 (Daussy et al. 2014, Gordon et al. 2012, Klose et al. 2014, Townsend et al. 2004). ILCs express T-bet, but only cNK cells express Eomes (Pikovskaya et al. 2016). Additionally, while a committed progenitor of the non-NK cell ILC1 is yet to be defined, fate mapping studies of PLZF suggest that PLZF governs the divergence between ILC1 and NK cells (Constantinides et al. 2015).

A precursor committed to the ILC2 lineage, termed ILC2p, has been identified by high expression of GATA3 (Hoyler et al. 2012). While GATA3 is also expressed in the CHILP, continuous expression of GATA3 is required for ILC2 maturation and function, as described in GATA3 reporter mice (Hoyler et al. 2012). GATA3^{-/-} mice lack ILC1, ILC2, and a subset of ILC3, so while GATA3 might not be a commitment factor for ILC2, it is critical for the maintenance of this ILC subset (Yagi et al. 2014). Other transcription factors necessary for ILC2 development are TCF-1 (encoded by *Tcf7*) and ROR α . *Tcf7*^{-/-} mice lack ILC2 in the lung and lack immature ILC2 in the bone marrow (Mielke et al. 2013, Yang et al. 2013). These mice also have reduced numbers of ROR γ ⁺ ILCs, suggesting that TCF-1 is required for the full development of more than one ILC subset. However, TCF-1 is absolutely required for ILC2 development in a cell-intrinsic manner (Mielke et al. 2013, Yang et al. 2013). Likewise, ROR α is a transcription factor required for ILC2 development in a cell-intrinsic manner (Halim et al. 2012, Wong et al. 2012). The latter two transcription factors may depend on Notch signaling, similar to their dependence in the T cell lineage, but that has not been explored completely.

ILC3 development depends on the transcription factor ROR γ t, which is analogous to the requirement of this transcription factor in T_H17 development. ROR γ t is necessary for LTi cells and for NKp46⁺ ILC3s (Cherrier & Eberl 2012, Eberl et al. 2004, Vonarbourg et al. 2010). The transcription factor TOX is also necessary for full development of LTi cells and for complete differentiation into NK cells (Aliahmad et al. 2010). AHR deficiency also affects the same populations as ROR γ t and TOX deficiency (Halim et al. 2012; Kiss et al. 2011; Lee et al. 2012a,b; Qiu et al. 2012).

Stage 3 of ILC development is about ILC maintenance and regulation in peripheral tissues. We do not go into much detail in this review, but studies have suggested that cytokines and some transcription factors are required for control of ILC populations and can contribute to ILC plasticity, as described above.

DC Development

In this review, we draw a comparison between ILC and DC development and believe that, like ILC development, DC development can also be divided into three distinct stages. Furthermore, both ILC development and DC development rely on some of the same transcription factors, and we explore where those similarities occur and what role the transcription factor plays in either lineage.

Stage 1 begins with the specification of DC precursors from progenitor cells that are multipotent for myeloid potential [termed the common myeloid progenitor (CMP)] to cells that are multipotent for macrophage and DC potentials [termed the macrophage/DC progenitor (MDP)] to progenitors that retain only DC potential [termed the common dendritic cell progenitor (CDP)]. DCs comprise three subsets—pDCs, cDC1, and cDC2—and the CDP gives rise to all three subsets. Stage 2 is defined by the commitment of the specified progenitor to specific DC subsets. Recent work has defined progenitors that are committed to either the cDC1 or the cDC2 fate, and newer work has aimed to elucidate a progenitor that is committed to pDC fate. Stage 3 is the maintenance of DCs in peripheral tissues.

Stage 1 is the specification of multipotent progenitors that have lymphoid, granulocyte, and myeloid potentials to progenitors that retain only DC potential. Early progenitors that can give rise to DCs *in vivo* are the CMP and the LMPP (Naik et al. 2013, Onai et al. 2007, Schlenner et al. 2010, Traver et al. 2000). The next progenitor thought to arise from the CMP and still retain DC potential is the granulocyte/macrophage progenitor (GMP), but recent studies have shown that the GMP cannot develop into DCs (Yanez et al. 2017). The MDP arises from the CMP and produces only macrophages and DCs both *in vitro* and *in vivo* (Auffray et al. 2009a,b; Fogg et al. 2006; Yanez et al. 2017). The exact transcriptional mechanisms that cause the divergence and the exclusion of these progenitors from neutrophil fate are not known. However, the transcription factors PU.1 and IRF8, along with members of the CEBP family, are thought to influence the development of these cell lineages. The MDP is thought to give rise to the CDP, but how the MDP gives rise to the CDP and how macrophage potential is lost are unanswered questions. The LMPP can give rise to other lymphoid progenitors, such as the CLP, which has the potential to give rise to pDCs (Rodrigues et al. 2018, Sathe et al. 2014, Yang et al. 2005). pDCs have been thought to arise from lymphoid cells, as they can be traced with IL7R, and recent work has shown that the majority of pDCs come from the CLP rather than the CDP (Rodrigues et al. 2018).

Stage 2 of DC development is the commitment of the CDP to clonogenic progenitors that give rise to cDC1s, cDC2, or pDCs. Clonogenic progenitors for cDC1s and cDC2, namely pre-cDC1s and pre-cDC2s, were identified in 2015 (Grajales-Reyes et al. 2015, Schlitzer et al. 2015), and a progenitor of pDCs was elucidated in 2018 (Rodrigues et al. 2018). Many transcription factors have been identified as important factors for cDC1, cDC2, and pDC

development, and recent work has identified how transcription factors interact in the cDC1 lineage.

cDC1 development depends on expression of the transcription factors IRF8, Batf3, Nfil3 (nuclear factor interleukin 3 regulated, also known as E4bp4), and Id2 (inhibitor of differentiation 2) and on suppression of the transcription factor Zeb2 (Grajales-Reyes et al. 2015, Hildner et al. 2008, Schiavoni et al. 2002, Scott et al. 2016, Sichien et al. 2016, Tamura et al. 2005, Wu et al. 2016). IRF8 is a lineage-defining factor for cDC1, and *Irf8*^{-/-} lack CDPs, pre-cDC1, and cDC1. Progenitors deficient in IRF8 diverted toward the granulocyte lineage and produced more neutrophils, indicating a role for IRF8 in regulating myeloid/granulocyte potential (Schönheit et al. 2013). Batf3, a transcription factor belonging to the Batf family, has a leucine zipper domain that heterodimerizes with JUN and IRF factors (Vinson et al. 2002). Studies aiming to understand the relationship between IRF8 and Batf3 began in 2015, when the pre-cDC1 was identified as a lineage ⁻CD117^{int}CD135⁺MHC-II^{low-int}CD11c⁺SiglecH⁻ cell that was either CD24⁺ or *Zbtb46*^{gfp+} (Grajales-Reyes et al. 2015). *Zbtb46*, a transcription factor belonging to the Broad Complex, Tramtrack, Bric-a-Brac, and Zinc Finger family, is selectively expressed in cDCs and their progenitors but is not required for their development (Satpathy et al. 2012a,b). The pre-cDC1 is present in *Batf3*^{-/-} mice, but not in *Irf8*^{-/-} mice, indicating that specification of the pre-cDC1 could occur in the absence of Batf3. *Batf3*^{-/-} pre-cDC1s fail to maintain IRF8 expression, causing it to divert into the cDC2 lineage (Grajales-Reyes et al. 2015). High expression of IRF8 is necessary for the cDC1 lineage, and Batf3 is required to maintain IRF8 autoactivation following specification to the cDC1 fate (Grajales-Reyes et al. 2015). CHIP-seq analysis identified a +32-kb *Irf8* enhancer that contains several AP1-IRF composite elements and that binds IRF8 and BATF3 in cDC1s in vivo. Recently, CRISPR-mediated deletion of the +32-kb *Irf8* enhancer in mice (*Irf8 +32*^{-/-}) suggests that *Batf3* supports IRF8 autoactivation using this enhancer (V. Durai, P. Bagadia, J.M. Granja, A.T. Satpathy, D. Kulkarni, et al., submitted). Like *Batf3*^{-/-} mice, *Irf8 +32*^{-/-} mice lack mature cDC1 but maintain pre-cDC1 development in vivo. Development of this progenitor instead depends upon a +41-kb *Irf8* enhancer, which binds E proteins and is active in mature pDCs and cDC1 progenitors, but not in mature cDC1s. Deletion of this enhancer eliminated IRF8 expression in pDCs and completely eliminated development of the specified pre-cDC1. This enhancer activity requires E proteins to induce sufficient levels of IRF8 during specification of the pre-cDC1, but it is still unclear why mature cDC1s require BATF3 and the +32-kb *Irf8* enhancer to maintain IRF8 expression.

Recent work from our lab has organized the transcription factors Nfil3, Id2, and Zeb2 into a transcriptional network that promotes cDC1 fate (P. Bagadia, X. Huang, T. Liu, V. Durai, G. Grajales-Reyes, et al., submitted). Nfil3, a basic leucine zipper (bZIP) transcription repressor (Cowell et al. 1992, Zhang et al. 1995), is expressed in and is required for cDC1, but not for cDC2 or pDC, development (Kashiwada et al. 2011, Seillet et al. 2013). Id2 is a known inhibitor of E proteins and is expressed in cDC1 and cDC2, but not in pDCs, and is required only for cDC1 development (Hacker et al. 2003, Kusunoki et al. 2003). Current models propose that Id2 excludes the pDC fate in DC progenitors by blocking the activity of E proteins, particularly E2-2 (*Tcf4*), required for pDCs (Ghosh et al. 2010, Grajkowska et al. 2017, Watowich & Liu 2010). The transcription repressor Zeb2 is expressed in pDCs and

cDC2s, but not cDC1s. It suppresses cDC1 development and is required for pDC development, perhaps through inhibition of *Id2* transcription (Scott et al. 2016, Wu et al. 2016).

We found that the CDP originates in a *Zeb2*^{hi} and *Id2*^{lo} state in which IRF8 expression is maintained by the +41-kb *Irf8* enhancer. Single-cell RNA sequencing of the CDP identified a fraction of the CDP that is already specified to the cDC1 fate, in a stage earlier than the pre-cDC1. This fraction expresses transcription factors required for cDC1 development, such as *Id2*, *Batf3*, and *Zbtb46*, and excludes transcription factors required for pDC development, such as *Zeb2* and *Tcf4*. This fraction's development arises when *Nfil3* induces a transition into a *Zeb2*^{lo} and *Id2*^{hi} state. A circuit of mutual *Zeb2-Id2* repression stabilizes states before and after this transition. *Id2* expression in the specified pre-cDC1 inhibits E proteins, blocking activity of the +41-kb *Irf8* enhancer and thereby imposing a new requirement for *Batf3* for maintaining IRF8 expression via the +32-kb *Irf8* enhancer (P. Bagadia, X. Huang, T. Liu, V. Durai, G. Grajales-Reyes, et al., submitted).

The transcriptional mechanisms governing cDC2 and pDC development are less known, but progenitors for each lineage have been identified. The pre-cDC2 was identified in 2015 as a lineage⁻CD117^{low}CD135⁺CD115⁺MHC-II⁻CD11c⁺*Zbtb46*^{gfp}⁺ cell in the bone marrow (BM) (Grajales-Reyes et al. 2015). Although the pre-cDC2 expresses IRF8, mature cDC2 expresses only IRF4. However, *Irf4*^{-/-} mice do not lack cDC2, although the cDC2 that develops exhibits defective migration (Bajana et al. 2012). As discussed above, two transcription factors, *Klf4* and *Notch2*, have selectively ablated specific cDC2 populations, but how heterogeneity in the cDC2 lineage occurs and how the pre-cDC2 specifies to each cDC2 population remain unclear. Additionally, how the pre-cDC2 loses IRF8 to become IRF4 dependent is unknown.

pDC development depends on the transcription factors *Tcf4*, *Zeb2*, and *Bcl11a* (Cisse et al. 2008; Ghosh et al. 2010; Wu et al. 2013, 2016). pDCs also express high levels of IRF8 but are present in *Irf8*^{-/-} mice with altered phenotype and functionality (Sichien et al. 2016). The basis for lineage divergence between pDCs and cDCs from the CDP is not known, but analysis of the +41-kb *Irf8* enhancer suggests that a shared progenitor between pDCs and cDC1s may exist. Alternatively, pDCs may have arisen completely separately from the CLP, as suggested in a recent work that identified a pre-pDC (Rodrigues et al. 2018). This study characterized a pre-pDC as a lineage⁻CD16/32⁻B220⁻Ly6C⁻CD117^{int/lo}CD135⁺CD115⁻CD127⁺SiglecH⁺Ly6D⁺ cell (Rodrigues et al. 2018). Pre-pDCs express high levels of IRF8 and, once matured, express *Tcf4*.

Stage 3 of DC development concerns maintenance and regulation in peripheral tissues. Studies have suggested that cytokines and some transcription factors are required for control of DC populations and may regulate DC plasticity in tissues, as discussed above.

SIMILARITIES BETWEEN ILC AND DC DEVELOPMENT

ILC development and DC development depend on some of the same transcription factor families and often the same transcription factors. Here, we discuss the similarities between the development of these lineages by studying E proteins/Id proteins, Nfil3, and Zeb2.

E protein and Id protein family member interactions are often portrayed as transcriptional switches in the development or function of specific immune subsets. Both types of proteins belong to the basic-helix-loop-helix (bHLH) family of transcription factors and exert both transcription activation and transcription repression roles in the immune system. bHLH family members contain two protein domains that are highly conserved but functionally different. The N terminus of the proteins contains the basic region, which allows for binding to DNA at a specific sequence, known as an E box. The C terminus of the proteins contains the HLH domain, which allows for hetero- or homodimeric binding to other protein subunits. bHLH proteins also contain two activation domains, ADI and ADII, which map to regions that are distinct from the zipper (Aronheim et al. 1993). These activation domains were identified in the N-terminal half of E2A and are conserved in the E protein subfamily, and they can function independently of bHLH and employ different roles. ADI is active in many cell types (Aronheim et al. 1993) and can recruit the SAGA chromatin-remodeling complex (Massari et al. 1999). ADII is thought to direct transcription activation, as site-directed mutagenesis at this region decreased transactivation potential (Aronheim et al. 1993).

E proteins are a member of the class I bHLH family and canonically bind to the DNA sequence *CA_nnTG*. There are three known E proteins in mouse: E2A, HEB, and E2-2. The *E2a* gene encodes for two proteins, E12 and E47, by alternative splicing. E47 can homodimerize, while E12 can bind to other members of the bHLH family. *HEB* can also be alternatively spliced to produce HEBA_{lt} and HEBC_{an}.

Id proteins are a member of the class V bHLH family and lack the basic DNA binding domain present in other bHLH family members. There are four known Id proteins in mouse: Id1, Id2, Id3, and Id4. Their primary function is to inhibit the activity of E proteins by sequestering E proteins and acting as dominant-negative inhibitors of E protein function. The HLH domain of Id proteins can heterodimerize with the bHLH domain of E proteins, thus causing nonfunctional heterodimers.

Id and E proteins are required in the initial stages of ILC development. Id2 is required in the ILC lineage to extinguish T cell potential and is required for all ILC subsets. The discovery of the CHILP as a lineage⁻IL-7R⁺CD135⁻α₄β₇⁺CD25⁻Id2^{high} progenitor cell elucidated the fate-determining role of Id and E proteins in the ILC/T cell lineage split. Id2 is required for total ILC development (Verykokakis et al. 2014, Yokota et al. 1999) but is necessary only for proper CD4/CD8 T cell function. Id2 is also required specifically for the differentiation of ILC2s and type 2 ILCs and for the induction of α₄β₇ (Hwang & McKenzie 2013). Overexpression of Id2, in contrast, prevents the development of T and B cells, as well as of pDCs, and promotes NK cell and ILC differentiation (Mjosberg et al. 2012b). Sequestration of E47, a protein subunit of E2a, by Id2 promotes mature NK and LT_i cell development

(Mjosberg et al. 2012b), but loss of both E2a and Id2 in doubly deficient mice can restore mature NK cells in the bone marrow and LT α development (Boos et al. 2007). These particular results suggested that Id2 does have a function in mature NK cell development but has other requirements in the bone marrow and thymus.

In DCs, Id2 is absolutely required for cDC1 development and is, as discussed above, required for early cDC1 specification. Work done in our lab has elucidated a newfound role for E proteins in the cDC1 lineage. E proteins are required for the activity of the +41-kb *Irf8* enhancer, but *Id2* expression in the cDC1-specified fraction of the CDP blocks activity at this enhancer and allows for a cDC1 fate through the activation of the +32-kb *Irf8* enhancer. In summary, for both ILC and DC lineages, E proteins and Id proteins act as switches to specify one subtype over the other.

Nfil3 is a bZIP transcriptional regulator and regulates many diverse biological processes (Keniry et al. 2013). The N-terminal portion of the bZIP domain contains a basic motif, which directly binds to DNA. The C-terminal portion of the bZIP domain contains the leucine zipper region, which is responsible for homodimerization. The Nfil3 protein also contains a unique transcription repression domain that is transferable since its fusion with the GAL4 DNA binding domain leads to transcription repression in reporter assays.

In the hematopoietic system, Nfil3 is essential for NK cell development. Nfil3 was the first transcription factor shown to be selectively and critically required for NK cell development, as *Nfil3*^{-/-} mice lack those populations but do not lack B cells, T cells, or NKT cells (Gascoyne et al. 2009, Kamizono et al. 2009). The defect in NK cells is intrinsic in nature, which leads to failure to eliminate major histocompatibility complex class I-deficient target cells and to produce IFN- γ . However, further studies suggest that the NK cell population is far more complex and may have several different origins. Firth et al. (2013) showed that the MCMV/recombinant virus expressing the viral m157 glycoprotein could induce a Ly49H⁺ NK cell population in *Nfil3*^{-/-} mice. The virus-induced Ly49H⁺ NK cells are fully functional with respect to IFN- γ production and cytotoxicity and could produce long-lived memory NK cells comparable to NK cells from wild-type mice. Even at steady state, the development of several tissue-resident NK cells, particularly in mucosal sites, such as salivary gland NK cells (Cortez et al. 2014, Erick et al. 2016), kidney tissue-resident NK cells (Victorino et al. 2015), and uterine NK cells (Redhead et al. 2016), is Nfil3 independent. Nfil3 is required for the formation of Eomes-expressing NK cells, whereas Eomes⁻ NK cells develop independently of Nfil3 (Crotta et al. 2014, Seillet et al. 2014b).

Nfil3 acts early in NK cell specification, as ablation of Nfil3 in immature NK cells in bone marrow or mature peripheral NK cells through the use of Ub- or Nkp46-cre lines in combination with *Nfil3* floxed mice does not influence NK lineage maintenance or homeostasis (Firth et al. 2013). A later study examined the different stages of NK cell progenitors in *Nfil3*^{-/-} mice and showed that Nfil3 is required at the NK lineage commitment point when NK progenitors develop from CLPs (Male et al. 2014). Both studies conclude that Nfil3 acts early in NK cell specification.

How Nfil3 regulates NK cell development is an open question. Male et al. (2014) showed that *Eomes*, *T-bet*, and *Id2* can rescue NK production from *Nfil3*^{-/-} progenitors because Nfil3 binds directly to the regulatory regions of both *Eomes* and *Id2*, promoting their transcription. Nandakumar et al. (2013) further demonstrated that the histone H2A deubiquitinase MYSM1 interacts with Nfil3 and recruits Nfil3 to the *Id2* locus. They observed that MYSM1 is involved in maintaining active chromatin at the *Id2* locus to promote NK cell development (Nandakumar et al. 2013). In addition, Brady and colleagues showed that *Notch1* is another novel Nfil3 target gene (Kostrzewski et al. 2018). While abrogation of Notch signaling impedes NK cell production, Notch peptide ligands could rescue NK cell development from *Nfil3*^{-/-} progenitors (Kostrzewski et al. 2018).

In addition to having a role in NK cell development, Nfil3 is also essential for the development of nearly all ILC subtypes. All ILC subsets exhibit high Nfil3 expression, and thus Nfil3 deficiency leads to compromised development of all ILC subsets in a cell-intrinsic manner (Geiger et al. 2014; Seillet et al. 2014a,b). The only known ILC subtype that does not require Nfil3 for its development is uterine ILC3, which participates in maintaining tissue homeostasis and barrier immunity during pregnancy (Doisne et al. 2015).

Nfil3 directs the differentiation of a committed ILC progenitor and acts transiently to enforce ILC lineage commitment. Nfil3 is required for the development of the earliest ILC lineage progenitors: the *Id2*⁺ CHILP and the $\alpha 4\beta 7^{\text{hi}}$ PLZF⁺ ILC progenitor (Xu et al. 2015, Yu et al. 2014). Geiger et al. (2014) generated *Nfil3*^{f/f1} × *Nkp46*^{Cre} mice and showed that they have normal numbers of ILC3, indicating that Nfil3 is not required for lineage maintenance. *Id2* has been reported to be a target of Nfil3 for NK cell development. Indeed, Nfil3 also directly binds to the *Id2* locus, promotes *Id2* expression in the CHILP, and orchestrates CHILP emergence from CLPs. Ectopic *Id2* expression in *Nfil3*^{-/-} progenitors also rescues all ILC lineage development. Recently, Belz and colleagues generated *Nfil3*^{f/f1} *Id2*-CreERT2^{+T} mice to spatiotemporally delete Nfil3 in *Id2*-expressing cells (Seillet et al. 2016). Their results show that all ILC lineages develop normally from those mice (Seillet et al. 2016). Thus, Nfil3 is a key factor for ILC lineage commitment, but its expression is only transiently required before *Id2* expression.

For DC lineages, Nfil3 was shown to be specifically required for cDC1 development at steady state. *Nfil3*^{-/-} mice display impaired cross-presentation to CD8⁺ T cells against cell-associated antigens (Kashiwada et al. 2011). However, a later study suggested that cDC1 can be induced in an Nfil3-independent manner in short-term bone marrow reconstitution (Seillet et al. 2013). Mechanically, *Nfil3*^{-/-} mice have normal numbers of pre-cDC progenitors, which have significantly reduced *Batf3* levels (Kashiwada et al. 2011). Our recent work with Nfil3 in cDC1 commitment shows that Nfil3 is required for early specification, perhaps initiation, of the cDC1 lineage (P. Bagadia, X. Huang, T. Liu, V. Durai, G. Grajales-Reyes, et al., submitted). As such, evidence for the role of Nfil3 in both ILC and DC lineages suggests that Nfil3 acts early in lineage specification.

Zeb2 is a zinc-finger transcription repressor that was first shown to be a regulator of epithelial-mesenchymal transition via interaction with Smad family proteins (Comijn et al. 2001, Remacle et al. 1999, van Grunsven et al. 2003, Verschueren et al. 1999). *Zeb2* has two

clusters of zinc fingers for DNA binding, one at each terminus. Both clusters bind to the CACCT sequence and are necessary for repression (Comijn et al. 2001, Remacle et al. 1999). Zeb2 can exert its repressive function by directly interacting with C-terminal binding proteins (CtBPs), a known corepressor family, via its CtBP interaction domain. Most notably, Zeb2 is a known partner of Smad family proteins and can bind with Smads 1, 2, 3, 5, and 8, known as R-Smads (van Grunsven et al. 2003). Germline deletion of Zeb2 leads to embryonic lethality in mice (Higashi et al. 2002, Van de Putte et al. 2003). Zeb2 performs a wide range of functions in multiple systems, ranging from dysregulation in several cancers (Vandewalle et al. 2009) to modulating myelination of oligodendrocytes (Weng et al. 2012). In 2011, the role of Zeb2 in the hematopoietic system was first demonstrated, as Zeb2 deletion using Tie-2-cre or Vav-cre resulted in defects in hematopoietic stem cell differentiation and homing to bone marrow (Goossens et al. 2011).

Zeb2 is required for NK cell terminal maturation, as shown through a NK cell-specific deletion of Zeb2 (*Ncr1^{icre}*) (van Helden et al. 2015). NK cell-specific Zeb2 deletion resulted in reduced survival for mature NK cells, in defects in their exit from BM, and in increased susceptibility to B16F10 melanomas (van Helden et al. 2015). T-bet was shown to be necessary and sufficient to induce Zeb2 expression in NK cells, and Zeb2-deficient mature NK cells phenocopied their T-bet-deficient counterparts.

Several studies have associated Zeb2 with T cell terminal differentiation and memory formation. In response to LCMV infection, Zeb2 is upregulated by KLRG1^{hi} effector CD8⁺ T cells, and loss of Zeb2 expression in these cells results in the loss of antigen-specific CD8⁺ effector cells and in the impairment of generation of effector memory cells, while the formation of central memory T cells was accelerated (Dominguez et al. 2015, Omilusik et al. 2015). Later studies further demonstrate that coordinated expression of Zeb2 and its family member, Zeb1, is critical for CD8⁺ T cell fate decision. Zeb2 promotes terminal T cell differentiation, whereas Zeb1 is critical for memory T cell survival and function, with TGF- β signaling selectively inducing Zeb1 and repressing Zeb2 (Guan et al. 2018).

Within the DC compartment, Zeb2 is required for pDC development (Scott et al. 2016, Wu et al. 2016). One study argued that Zeb2 is also required for cDC2 development (Scott et al. 2016), while another indicated that Zeb2 is dispensable for cDC2 development and is instead required to actively repress generation of cDC1 progenitors (Wu et al. 2016). Our recent work shows that Zeb2 forms a mutually repressive loop with Id2 and is repressed by Nfil3 in the CDP to allow for overall expression of Id2 for cDC1 specification (P. Bagadia, X. Huang, T. Liu, V. Durai, G. Grajales-Reyes, et al., submitted). The mechanisms by which Zeb2 influences ILC and DC lineage fates are less clear than the mechanisms by which Id2 and Nfil3 might influence fate, but work is currently being done in both fields to understand where and when Zeb2 acts.

CONCLUSION

Major questions remain regarding how ILC and DC subsets exert distinct effector functions and how transcription factors necessary for the development of each subset function at the

molecular and genetic levels. ILC and DC subsets share transcription factors, and a transcriptional network similar to the one that exists in DCs may exist in ILCs.

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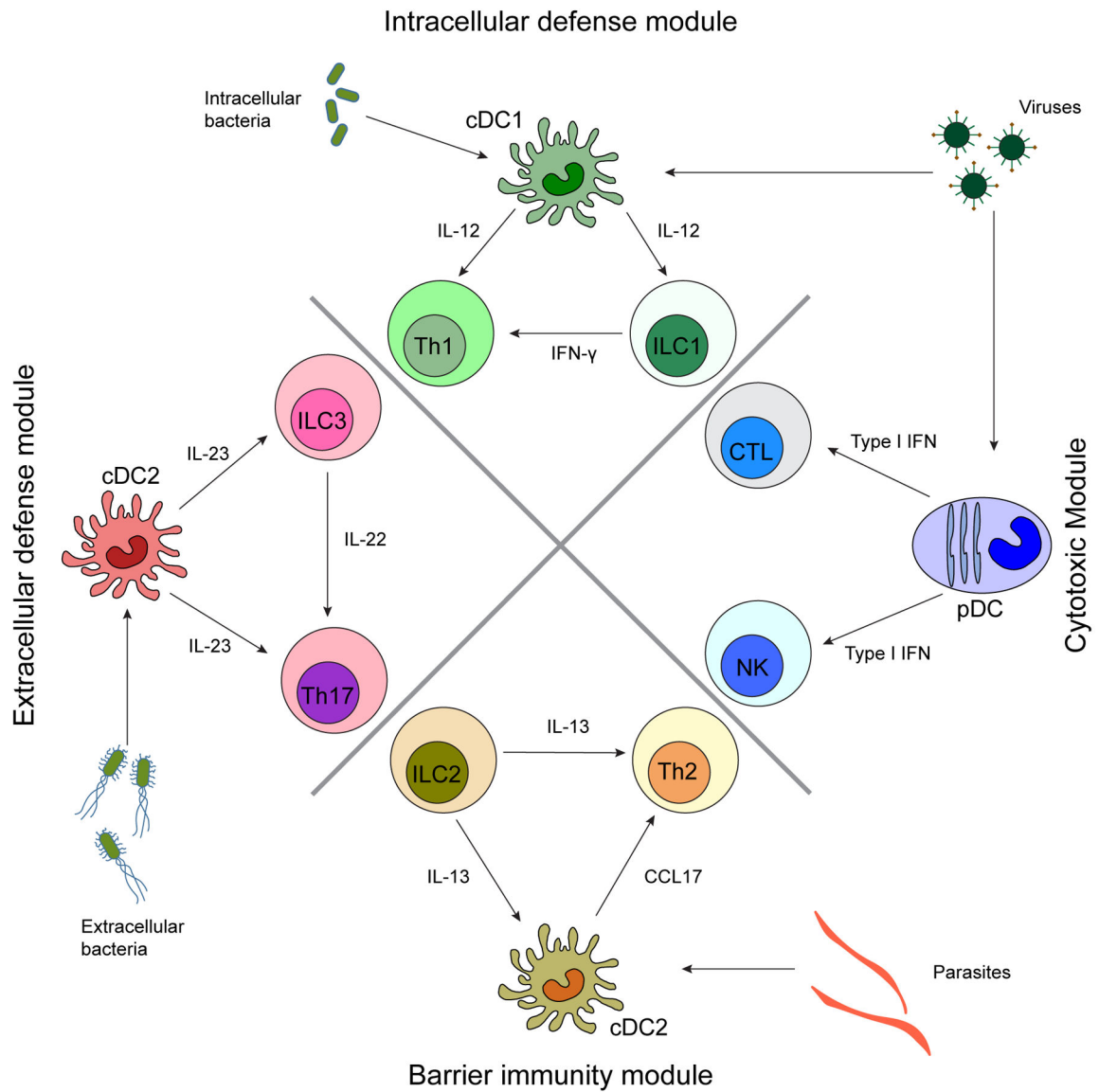


Figure 1. Four core immune modules shared between ILCs, DCs, and T cells. An immune response specific to a particular pathogen involves cross talk and collaboration between two innate cell lineages, ILCs and DCs, and an adaptive cell lineage, T cells, by secretion of cytokines and chemokines. Each cell type in this module is governed by specific transcription factors that influence the effector functions. Abbreviations: cDC, classical/conventional dendritic cell; CTL, cytotoxic T lymphocyte; DC, dendritic cell; IFN, interferon; ILC, innate lymphoid cell; pDC, plasmacytoid dendritic cell.

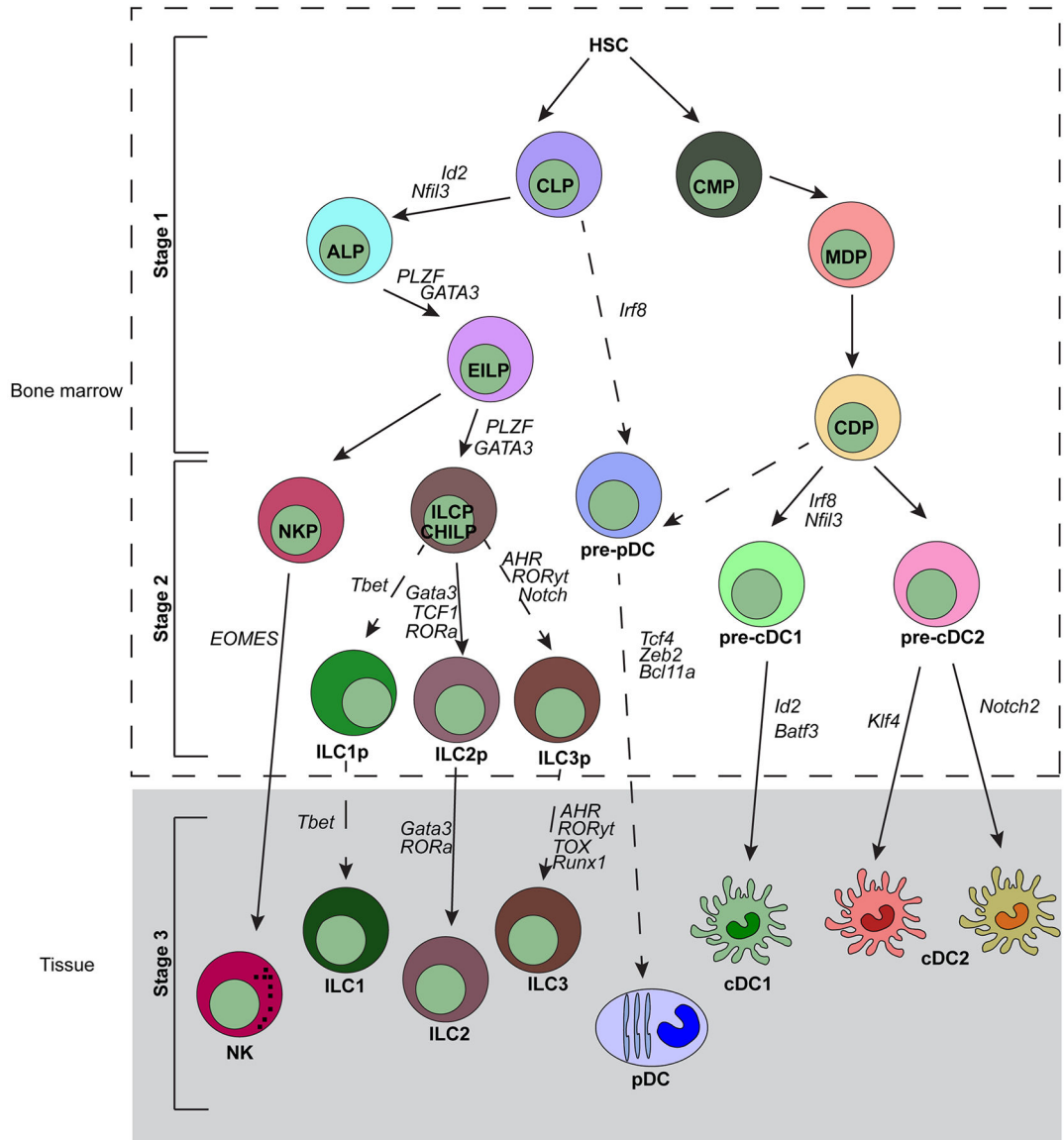


Figure 2. ILC and DC development can be divided into three stages. Stage 1 refers to specification of common precursors from multipotent progenitors that have not yet excluded other cell lineage fates. Stage 2 is the commitment of those common precursors to the mature cell. Stage 3 is the maintenance of those cells in tissues. Many transcription factors influence either specification or commitment, and the precise roles for those factors are still unknown. Abbreviations: ALP, all-lymphoid progenitor; cDC, classical/conventional dendritic cell; CDP, common dendritic progenitor; CHILP, common helper-like ILC progenitor; CLP, common lymphoid progenitor; CMP, common myeloid progenitor; EILP, early innate lymphoid progenitor; HSC, hematopoietic stem cell; ILC, innate lymphoid cell; ILCP, ILC progenitor; MDP, macrophage/DC progenitor; NKP, NK progenitor; pDC, plasmacytoid dendritic cell.