

Immune modules shared by innate lymphoid cells and T cells



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1. To identify the key intracellular signaling intermediates, transcription factors, and cytokines for each of the 3 “immune modules.”
2. To name key differences between T-cell and innate lymphoid cell (ILC) populations within each immune module in terms of development or function.
3. To describe the concept of lineage stability and the relative degree of lineage stability in each of the immune modules.
4. To identify similarities between natural killer cells and CD8⁺ T cells within an immune module in terms of function and regulation.

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In recent years, innate lymphoid cells (ILCs) have emerged as innate correlates to T cells. The similarities between ILCs and T cells indicate that lymphocytes of fundamentally distinct lineages can share core “immune modules” that encompass transcriptional circuitry and effector functions while using nonredundant complementary mechanisms of pattern recognition to enact these functions. We review modules currently recognized to be shared between ILCs and T cells. (*J Allergy Clin Immunol* 2016;138:1243-51.)

Key words: Innate lymphoid cell, T cell, innate, adaptive, lymphocyte

The hematopoietic universe has rapidly expanded in recent years with the identification of a new major class of cells found in both human subjects and mice called innate lymphoid cells (ILCs).¹⁻⁷ ILCs belong to the lymphoid lineage because they derive from the common lymphoid progenitor and depend on the master lymphocyte cytokine receptor IL-2 receptor common γ chain.^{2,4} Yet their lack of recombined antigen-specific receptors and other lineage markers distinguish them from conventional T and B cells, as well as innate-like lymphocytes, such as natural killer (NK) T cells.¹ Remarkably, the functional specializations of ILCs, as well as their developmental programs, resemble those previously recognized in CD4⁺ T_H cell subsets²; therefore type 1 innate lymphoid cells (ILC1s), type 2 innate lymphoid cells (ILC2s), and type 3 innate lymphoid cells (ILC3s) are now considered the innate counterparts of T_H1, T_H2, and T_H17 cells, whereas NK cells are considered the innate counterpart to CD8⁺ cytotoxic T cells.^{2,8} To date, there is no recognized ILC counterpart to regulatory T (Treg) cells or follicular helper T cells. Furthermore, unlike CD4⁺ T-cell polarization from a multipotent naive cell in the periphery, ILC fate commitment occurs early in development (Fig 1).⁹⁻¹¹

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Abbreviations used

AHR:	Aryl hydrocarbon receptor
Eomes:	Eomesodermin
ILC:	Innate lymphoid cell
ILC1:	Type 1 innate lymphoid cell
ILC2:	Type 2 innate lymphoid cell
ILC3:	Type 3 innate lymphoid cell
NFAT:	Nuclear factor of activated T cells
NK:	Natural killer
ROR:	Retinoic acid–related orphan receptor
STAT:	Signal transducer and activator of transcription
T-bet:	T-box transcription factor
TCR:	T-cell receptor
TF:	Transcription factor
TRAIL:	TNF-related apoptosis-inducing ligand
Treg:	Regulatory T

ILC subtypes are grouped together based on shared developmental requirements and effector functions. Eomesodermin (Eomes)⁺ T-box transcription factor (T-bet)⁺ NK cells are cytotoxic and produce IFN- γ and TNF- α ; T-bet⁺ ILC1s produce IFN- γ and TNF- α , like NK cells; GATA-3^{hi} ILC2s produce IL-5, IL-13, IL-9, and amphiregulin; and retinoic acid–related orphan receptor (ROR) γ ^t ILC3s produce IL-22, GM-CSF and/or IL-17.

ILC1 and NK cell distinctions are controversial because developmental studies in mice separate these lineages, but their defining cell-surface markers vary between tissues and often overlap.^{12–15} Thus, mouse ILC1s are currently best defined by their lack of Eomes expression within NKp46⁺NK1.1⁺ cells.¹⁵ In human subjects, similar phenotypic heterogeneity in the absence of lineage tracing makes distinctions even more difficult, but 2 IFN- γ –producing subsets have been described: intraepithelial ILC1s express a CD103⁺CD56⁺CD94⁺NKp44⁺ phenotype, whereas CD127⁺ ILC1s express a CD127⁺CD161⁺ phenotype and do not express intraepithelial ILC1 markers.^{16–18}

ILC2s have been identified in many organs in mice and human subjects during homeostasis. Cells from both species express CD25, CD127, the IL-33 receptor ST2, and the inhibitory receptor KLRG1. Human ILC2s alone express the prostaglandin D₂ receptor–homologous molecule expressed on T_H2 cells, CRTH2.^{7,16,19,20}

ILC3s are a particularly diverse class of cells in both species. In adult mice these cells include 2 developmentally distinct lineages, one of which has many subsets. The first lineage, lymphoid tissue inducer–like cells or NKp46⁺CCR6⁺ ILC3s, expresses MHC class II and produces IL-22, IL-17a, IL-17f, and LT- α .^{21–26} The second lineage includes a sequence of cells that progressively differentiate and express different cytokines, cell-surface markers, and variable levels of T-bet: T-bet^{lo}NKp46⁺CCR6⁺ ILC3s express IL-22 and IL-17a^{27,28}; T-bet⁺NKp46⁺CCR6⁺ ILC3s express IL-22 and GM-CSF^{24,27–32}; and T-bet⁺NK1.1⁺NKp46⁺ “ex-ROR γ ” ILC3s produce IFN- γ and cannot be distinguished from ILC1 without lineage tracing.¹³ Recently, single-cell sequencing of human ILC3s has similarly identified 3 cell clusters based on shared and distinct transcriptional programs, including NKp44⁺ ILC3s, CD62L⁺NKp44⁺ ILC3s, and HLA-DR⁺ lymphoid tissue inducer–like ILC3s, reminiscent of diversity found among mouse ILC3s.³³ For additional phenotypic information, the cell-surface expression profiles of human and mouse ILCs have recently been reviewed.^{5,16}

Unlike other lymphocytes, ILCs respond directly to cytokine signals in the microenvironment without a need for antigen-specific receptor signaling or preactivation. Signaling specificity is regulated by the cytokine receptors expressed by ILCs, allowing distinct combinations of myeloid and/or tissue-produced cytokines to activate each ILC class. Although ILCs are a relatively small population of cells compared with adaptive lymphocytes, they appear to play major homeostatic roles, including through crosstalk with the epithelium. In mice ILCs are now recognized to constitutively produce “adaptive” cytokines, including IL-22, GM-CSF, and IL-5, at greater levels during steady state than conventional T cells.^{7,24,34–38} The similarities between ILCs and T cells indicate that lymphocytes of fundamentally distinct lineages can share core “immune modules” that encompass transcriptional circuitry and effector functions while using nonredundant complementary mechanisms of pattern recognition to enact these functions. We review modules currently recognized to be shared between T cells and ILCs.

CYTOTOXICITY

NK cells and CD8⁺ T cells are grouped together in the same immune module based on their shared function as professional killers. A core feature of this module is the presence of granular cytotoxicity, which is characterized in mice and human subjects by lytic granules that contain perforin and granzymes, which act together on target cells to induce cellular apoptosis (Fig 2). In human subjects cytotoxic granules also contain an additional antimicrobial factor, granulysin.³⁹ Cells in this module can also kill and induce other effector functions through shared expression of Fas ligand, TNF-related apoptosis-inducing ligand (TRAIL), TNF- α and IFN- γ .⁴⁰ Upstream, cytotoxic cells are activated by IL-12, IL-18, and IL-15.

The transcription factors (TFs) Eomes and T-bet are essential regulators of the cytotoxicity module in mice and likely also in human subjects based on their conserved pattern of expression (Fig 2).⁴¹ As members of the same T-box family of TFs, Eomes and T-bet have somewhat redundant functions and can partially compensate for each other.^{42,43} Therefore the cytotoxic program fails to develop only in the absence of both molecules, leading to selective ablation of CD122^{hi} (marking IL-2/IL-15 receptor β) memory CD8⁺ T cells and NK cells and aberrant expression of IL-17 by remaining CD8⁺ T cells upon activation.^{44,45}

The regulation and specific functions of Eomes and T-bet appear to differ. In CD8⁺ T-cell effector differentiation, T-bet expression temporally precedes that of Eomes,⁴⁶ with the highest T-bet/Eomes ratio in early effector cells and the lowest ratio in memory cells. Although T-bet is better at inducing IFN- γ and the IL-12 coreceptor IL-12R β 2, Eomes results in superior induction of perforin and granzyme B expression.^{43,46,47} Initially, this developmental sequence appeared to be conserved in NK cell differentiation, with T-bet sustaining immature NK cells and Eomes sustaining mature cells.⁴⁵ Yet evaluation of mice deficient for T-bet and Eomes in addition to transfer studies have demonstrated that Eomes is uniquely required for NK cell development, whereas T-bet is in fact required for the development of ILC1s.^{13,48,49} Moreover, when ectopically expressed, Eomes skews ILC1s to a cytotoxic NK cell profile with enhanced Ly49 expression, whereas T-bet overexpression similarly results in increased production of Eomes⁺ phenotypic ILC1s.^{48,50} These data suggest that Eomes and T-bet might achieve balance through

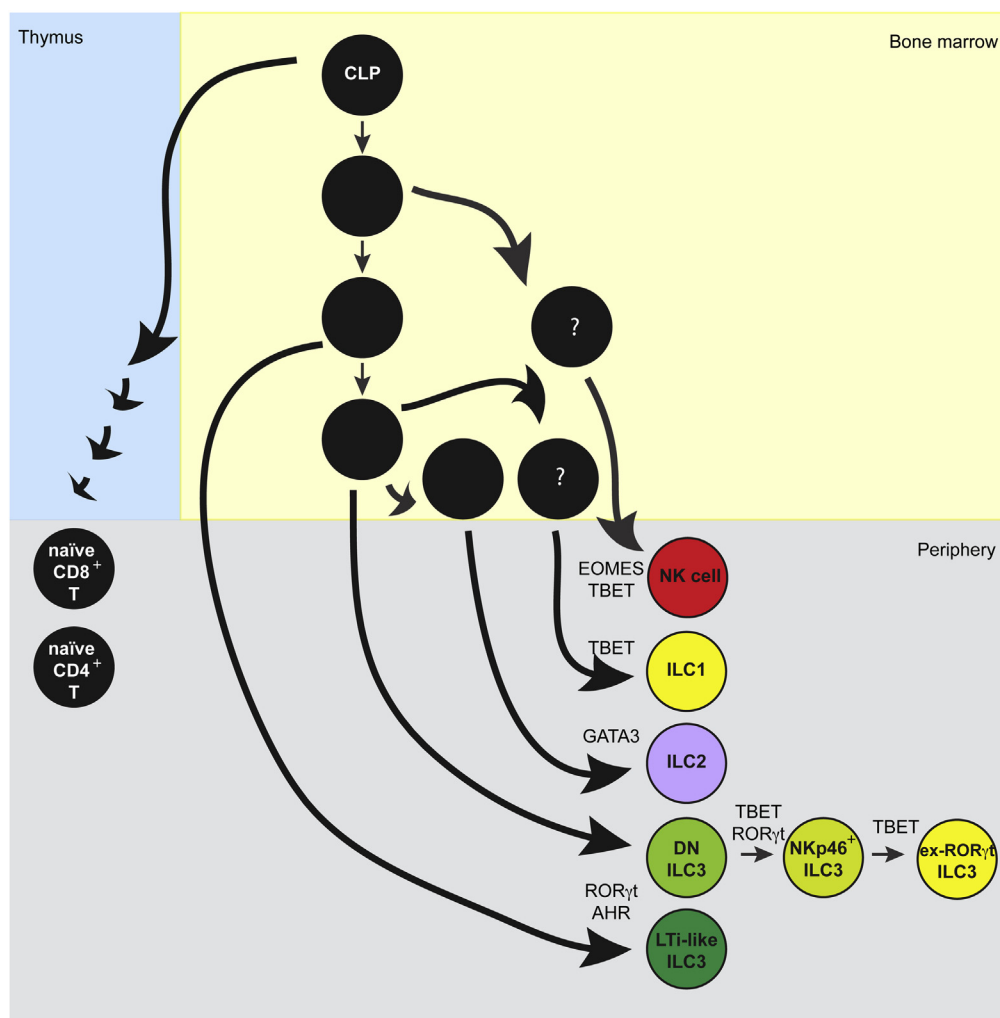


FIG 1. Development of T cells and ILCs. T cells and ILCs both develop downstream of the common lymphoid progenitor (CLP). T-cell progenitors (*left*) undergo progressive developmental stages in the thymus, which ultimately result in export of naïve CD8⁺ and CD4⁺ T cells to the periphery. In contrast, ILC generation (*right*) occurs in the bone marrow through a series of progenitors with increasingly restricted developmental potential, resulting in export of lineage-specified ILCs directly to the periphery. The sequences of recognized ILC progenitors are indicated in black in the bone marrow, whereas presumed progenitors are denoted by question marks.

mutual regulation. Developmentally, the exogenous factors that lead to differential regulation of Eomes and T-bet remain an active area of investigation. These factors likely include tissue factors, such as TGF- β , as recently demonstrated in a unique ILC1-like population in the salivary gland that is T-bet and Eomes independent.⁵¹ Nonetheless, in physiologic conditions both Eomes and T-bet together define the cytotoxic module, with Eomes particularly critical for NK cells.

MODULE 1: INTRACELLULAR PATHOGENS AND VIRUSES

ILC1s and T_H1 cells are grouped together based on their shared production of IFN- γ and TNF- α and their absent or reduced capacity for granular cytotoxicity compared with the cytotoxicity module, likely because of their absent or reduced levels of perforin and granzyme B (Fig 2).^{13,48} In mice some ILC1s

additionally appear to share expression of TRAIL.^{48,52,53} Under-scoring the similarity in cytokine production with cytotoxicity, module 1 is similarly defined by the TF T-bet.^{48,49,54} Cells in this module are also similarly regulated by the cytokines IL-12, IL-18, and IL-15, although in human subjects, CD127⁺ ILC1s preferentially respond to IL-12 and IL-18, whereas intraepithelial ILC1s respond to IL-15. Although IL-12-mediated signal transducer and activator of transcription (STAT) 4 activation causes T_H1 polarization *in vivo*,⁵⁵ this pathway is not required for ILC1 development.⁵⁶ However, it does provide a functional proliferative signal to mouse adipose tissue ILC1s in an inflammatory context.⁵⁶

Engagement of module 1 is physiologically associated with viral and intracellular pathogen immunity, but it is deregulated in patients with Crohn disease and some forms of autoimmunity, such as type 1 diabetes.⁴ Consistent with this, intraepithelial and CD127⁺ ILC1s have been reported to be increased in frequency

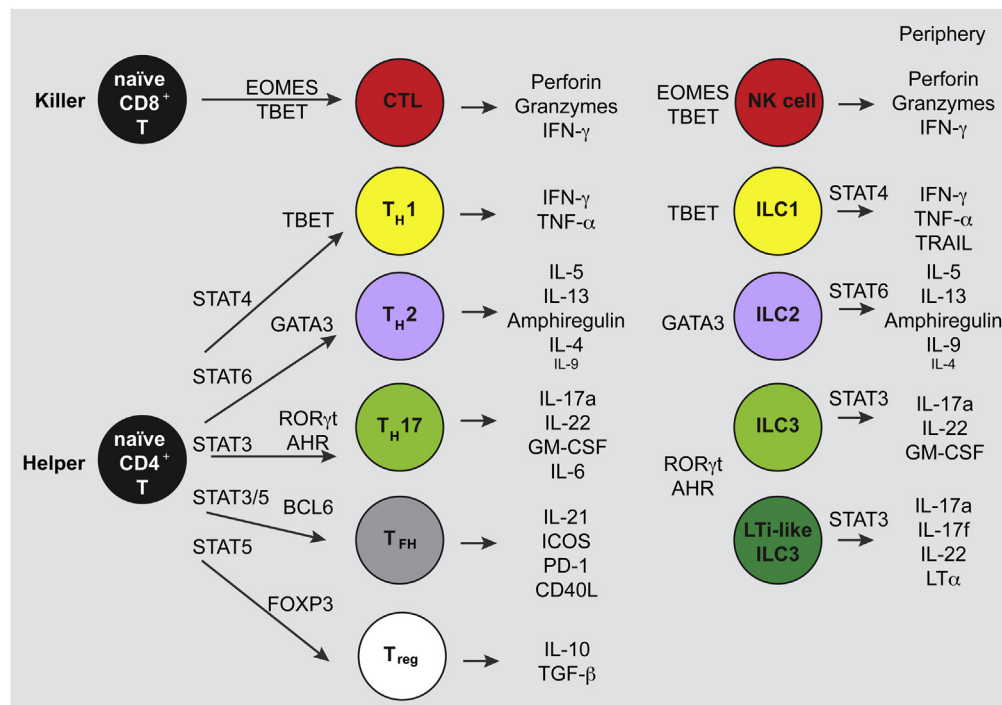


FIG 2. Effector modules of T cells and ILCs. In the periphery naive T cells (*left*) that recognize their specific antigen and are costimulated by antigen-presenting cells become activated and mature to effector cells. For CD4⁺ T cells, antigen-presenting cell-derived cytokines drive STAT activation and TF induction, leading to T_H polarization and the indicated effector functions. Meanwhile, ILCs in the periphery are already mature cells that do not require STAT activation to develop, although STATs are important for some ILC effector functions. The TFs required for T_H polarization and ILC development and the effector functions of cells in the same module are strikingly similar. ILC counterparts to follicular helper T (*T_{fh}*) and Treg cells are not currently recognized.

in patients with Crohn disease.^{17,18,57,58} Increased frequencies of ILC1s have also been reported to correlate with chronic obstructive pulmonary disease severity, presumably linked to viral infection.⁵⁹

T-bet has long been recognized as a key driver of T_H1 differentiation and was more recently recognized as a necessary factor for ILC1 differentiation.^{13,48,49,54,60} In the absence of T-bet, naive T cells do not produce IFN- γ and instead polarize to a Th2 effector program.⁶¹ Indeed, T-bet directly represses the development of T_H2.^{62,63} The fate of ILC precursors unable to engage T-bet is currently unclear. Functionally, T-bet drives module 1 effector cytokine production by binding to the promoter and regulatory elements of *Il12rb2* and *Ifng*.^{64,65} It also directly induces the expression of Runx3, an additional *Ifng*-activating TF. Supporting the role of Runx3 in module 1, Runx3-deficient mice also do not generate ILC1s.⁶⁶

Although T-bet clearly has an important role in module 1, the role of Eomes is more controversial. In mice, ILC1s are currently best defined by their lack of Eomes expression. However, in the absence of an Eomes fate-mapping mouse, it is unclear whether ILC1s always lack Eomes expression or whether they might sometimes express it. Recently, assay for transposase-accessible chromatin with high-throughput sequencing (ATACseq) data from mouse ILCs demonstrated graded expression of ATAC⁺ open chromatin surrounding *Eomes*, with the highest expression in NK cells, lower expression in ILC1s, and minimal expression in ILC2s and ILC3s,¹⁰ suggesting the potential to express Eomes

might not be absent in ILC1s. Furthermore, the “Eomes negative” definition of this module is not universally true because some T_H1 cells from both mice and human subjects express Eomes when activated.^{67,68} In human subjects, the 2 identified ILC1 subsets differ in their expression of Eomes and T-bet: CD127⁺ ILC1s exclusively express T-bet, whereas intraepithelial ILC1s express T-bet, as well as higher levels of Eomes, compared with CD127⁺ ILC1s and ILC3s.^{17,18,57} Notably, intraepithelial lymphocytes are well known to express highly activated phenotypes at the steady state because they are in direct contact with the epithelium and constitutively sense foreign metabolites and antigens.⁶⁹

Collectively, these data suggest that cells in module 1 critically rely on T-bet, likely for this TF's preferential induction of cytokine versus cytotoxic machinery, but might express Eomes in some circumstances, such as activation. Yet, unlike T-bet, Eomes is not required for the development of T_H1 cells or ILC1s and is unlikely to be a major functional regulator of this module.

MODULE 2: BARRIER MAINTENANCE AND HELMINTHS

ILC2s, T_H2 cells, and T_H9 cells share the same functional module based on their mutual production of the signature cytokines IL-5 and IL-13 (Fig 2).⁷⁰ IL-25, IL-33, and thymic stromal lymphopoietin are conserved cytokine regulators. Other

factors associated with this module include IL-4, IL-9, GM-CSF, and the epidermal growth factor family member amphiregulin.^{71,72} In particular, the common γ chain family cytokines IL-4 and IL-9 seem to be differently regulated in this module because T_H2 cells produce greater quantities of IL-4,⁷³⁻⁷⁵ whereas ILC2s and T_H9 cells produce IL-9 more readily.⁷² IL-4 signaling through STAT6 is also an important factor for T_H2 and T_H9 cell polarization *in vitro*, but this pathway is not universally required *in vivo* and is not required for the development of ILC2s.^{38,76} However, STAT6 has a postdevelopmental role in ILC2 function because STAT6-deficient ILC2s produce less IL-13.³⁸ Type 2 cytokines support tissue remodeling and the response to helminth infections but are deregulated in the development of allergy and asthma.^{4,77-79} Indeed, ILC2s are a rare population in normal human tissues^{33,57} but are expanded in nasal polyps of allergic patients with chronic rhinosinusitis and the skin of patients with atopic dermatitis.^{20,80,81}

GATA-3 is the master TF regulating module 2 and is required for the development of ILC2s and T_H2 cells.^{20,65,82-84} In both human subjects and mice, *Il4*, *Il5*, and *Il13* are located in a gene cluster on the same chromosome and are mutually regulated by the locus control region within an intervening gene, *Rad50*^{70,85,86}; *Csf2* (encoding GM-CSF) is also located nearby on the same chromosome. GATA-3 binds regulatory elements within this gene cluster and in the *Rad50* locus control region, as well as binding directly to the promoter of IL-5 and IL-13.⁸⁷ Consistent with the minimal expression of IL-4 by ILC2s, GATA-3 does not appear to bind directly to the IL-4 promoter, and conditional deletion experiments demonstrate that it is not required for expression after T_H2 development.^{87,88} However, GATA-3 conditional deletion demonstrates a common role for this TF in module 2 production of IL-5, IL-13, and amphiregulin.^{88,89}

Module 2 is a feed-forward module with a high degree of lineage stability, which in certain conditions can be overcome to generate plasticity toward module 1. Feed-forward loops depend on module 2 cytokines and, at least for T cells, cell-intrinsic signaling. For T cells, IL-4 production by T_H2 facilitates the polarization of more T_H2 through STAT6 induction of GATA-3.⁷⁶ Lineage stability is then enhanced by means of autoactivation of GATA-3 once it overcomes a threshold mediated by the transcriptional regulator FOG-1.^{90,91} Although ILCs appear to develop in the absence of polarizing cytokines in bone marrow, their activation in the periphery is similarly feed-forward. In mice, ILC2-generated IL-13 acts on the epithelium to drive the differentiation of tuft cells from LGR5⁺ stem cells, which in turn generate IL-25, which activates ILC2s to produce more IL-5 and IL-13.³⁴⁻³⁶

Despite module 2 lineage stability, strong module 1 stimuli can induce plasticity. For example, viral infection with lymphocytic choriomeningitis virus causes T_H2 to upregulate T-bet and subsequently produce IFN- γ in conjunction with IL-4.⁹² Recently, mouse ILC2s in the lung were also shown to undergo similar T-bet-mediated plasticity in response to infection with respiratory syncytial virus, influenza virus, *Haemophilus influenzae*, and *Staphylococcus aureus*.⁵⁹ Likewise, human ILC2s cultured *in vitro* with the danger cytokine IL-1 upregulate T-bet and IL-12R β 2, prompting responsiveness to IL-12 and the development of IFN- γ and IL-13 dual-producing cells.⁹³ Thus module 2 is typically self-perpetuating but can occasionally be redirected toward module 1.

MODULE 3: EXTRACELLULAR BACTERIA AND FUNGI

All ILC3 cell subsets and T_H17 and T_H22 cells belong to module 3 based on production of the cytokines IL-22, IL-17a, and/or IL-17f (Fig 2). IL-26 is additionally produced in human subjects but is not conserved in mice. In the T-cell lineage T_H22 cells also produce IL-10, which is not made in substantial quantities by other cells.⁹⁴ Yet module 3 shares additional factors, including inherent plasticity to module 1 and regulation by the cytokines IL-23 and IL-1. IL-23 activation of STAT3 drives T_H17 and T_H22 polarization but is not required for ILC3 development. However, STAT3-deficient ILC3s are unable to respond appropriately to IL-23 and are functionally impaired.^{95,96}

Module 3 is conventionally associated with immunity to extracellular pathogens and fungi, but this module is also recognized to have a role in tissue homeostasis. It is deregulated in the development of psoriasis, Crohn disease, and other forms of autoimmunity, such as the multiple sclerosis model experimental autoimmune encephalomyelitis. Consistent with this, investigators have reported ILC3 expansion in skin and blood of patients with psoriasis⁹⁷⁻⁹⁹; blood, gut, synovial fluid, and bone marrow of patients with ankylosing spondylitis¹⁰⁰; and blood, lung, and gut of patients with common variable immunodeficiency.¹⁰¹ Interestingly, several laboratories have reported that ILC3 numbers are reduced rather than increased in patients with Crohn disease relative to ILC1s^{17,18,57,58} and that remaining ILC3s are phenotypically altered and express less MHC class II.¹⁰²

The master TF regulating module 3 identity is ROR γ t because in its absence T_H17 cells and ILC3s do not develop.^{24,103} After development, however, ROR γ t directly regulates few genes, although in T_H17 cells, these include the signature cytokines IL-17a and IL-17f, as well as receptors for the activating cytokines IL-23 and IL-1.¹⁰⁴ In ILC3s, ROR γ t may have an even smaller effect because conditional deletion of ROR γ t, as well as pharmacologic blockade, revealed no difference in IL-17a production by ILC3 but reduced IL-17a production in T_H17 cells.¹⁰⁵ Many other factors have been shown to regulate T_H17 , but the TF aryl hydrocarbon receptor (AHR) in particular appears to be shared by ILC3s.^{30,106,107} AHR is a ligand-dependent TF that binds pollutants, dietary metabolites, and bacterial metabolic byproducts.¹⁰⁸ In conjunction with ROR γ t, AHR is required for the development of T_H22 cells and postnatal ILC3s and also directly controls IL-22 production.^{30,106,107,109}

Both human and mouse T_H17 cells, as well as most ILC3s, are further characterized by substantial plasticity to module 1 through acquisition of T-bet and reduction of ROR γ t expression. This was originally discovered in patients with Crohn disease, who harbor a population of ROR γ t⁺T-bet⁺ cells that produce both IL-17 and IFN- γ .¹¹⁰ Later, mouse lineage tracing experiments of ROR γ t expression demonstrated that T_H17 cells lose ROR γ t and IL-17 in IL-12-rich inflammatory environments but retain the module 1 TF T-bet and IFN- γ effector profile.¹¹¹ For the mouse CCR6⁺ lineage of ILC3s, similar lineage tracing experiments revealed that plasticity occurs at steady state.¹³ Unlike transitioning T_H17 , however, ROR γ t⁺T-bet⁺NKp46⁺ ILC3s have lost the capacity to produce IL-17 and instead produce IL-22 and IFN- γ .^{24,27-32} Mouse ILC3 plasticity is enhanced in certain microenvironments, such as the colon, in part through higher levels of IL-23.²⁷ Human

NKp44⁺ ILC3s also exhibit substantial plasticity *in vitro*, which is induced by several cytokines, including IL-12, IL-2, and IL-23.^{18,57,112} Consequently, the reduction in ILC3 numbers and increase in ILC1 numbers in patients with Crohn disease might reflect increased ILC3 plasticity that occurs in the inflammatory microenvironment.

CONCLUDING REMARKS

The identification of ILCs was a surprise in part because an entire lineage of cells was missed for many years but also because it suggested that cytokines conventionally thought to be produced only by T cells could also be expressed by innate immune cells.¹¹³ Over recent years, the similarity between T-cell and ILC development and effector programs has been increasingly appreciated. For ILCs, engagement of master TFs necessary for T_H cell polarization explains the convergent function of these cells in a single module, which notably each directly activate module-defining effector cytokines. In the future, emerging unique functions for ILCs are likely to be mediated by lineage-defining TFs, such as the master ILC regulator Id2 and Ets family members,¹¹⁴ either directly or through reorganization of the accessible chromatin landscape.

Can ILCs perform all the functions of T cells? Thus far, there appear to be 3 functions that ILCs lack. First, ILCs by definition do not express the T-cell receptor (TCR) and therefore cannot signal through it. Although obvious, this point is notable because gene expression and regulatory differences between ILCs and T cells might involve signaling factors differentially associated with TCRs but not cytokine receptors. Consistent with this, we recently reported that the regulomes of human T_H cells were characterized by activator protein 1 (AP-1) and nuclear factor of activated T cells (NFAT) TF motifs, core pathways activated by TCR signaling.¹¹⁵ Indeed, *Ii4* expression, which is increased in T_H2 cells compared with ILC2s, is well known to be regulated by activator protein 1 and NFAT.¹¹⁶

Second, as immediately functional cells, ILCs lack the capacity for naivety, leading one group to propose that the naive state is the defining feature of adaptive immune cells rather than any particular effector function.¹¹⁷ As ILCs develop, they appear to acquire modular pathways *de novo* in the bone marrow, whereas naive CD4⁺ T cells uniquely require TCR signaling and cytokine-mediated STAT activation to generate chromatin landscapes supportive of T_H polarization (Fig 1). Interestingly, *in vitro*-generated T_H cells also have the capacity to respond directly to cytokines through innate-like STAT- and nuclear factor κ B (NF- κ B)-dependent and NFAT-independent mechanisms.¹¹⁸⁻¹²² *In vivo* tissue-resident memory CD4⁺ T-cell populations can also demonstrate similar innate-like cytokine activation.^{123,124} Future comparisons between effector profiles of *in vivo*-generated T cells of different stages of maturity/tissue residence and ILCs will likely be informative to further define the scope of shared immune modules.

Finally, to date, no NKT or ILC subset has been discovered to express the master regulatory TF forkhead box P3 (FOXP3), which drives Treg cell development. In the future, it will be interesting to determine whether a regulatory module driven by FOXP3 expression is incompatible with NKT and ILC lineage and, if so, the mechanism through which this occurs.

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What do we know?

- ILCs and T cells share key TFs and effector functions.
- TFs drive effector functions and define ILC and T-cell subtypes.
- T_H cells go through a naive state while ILCs do not.
- ILC and T-cell functions are similar but not identical.

What is still unknown?

- To what extent do differences in cell surface receptor signaling produce functional differences between ILCs and T cells?
- How do effector programs of ILCs compare with those of naive, effector, and memory T cell subsets?
- Are there ILC counterparts to follicular helper T cells and Treg cells, and if not, why not?
- What is the contribution of ILCs to human biology in homeostasis and disease?

REFERENCES

- Spits H, Artis D, Colonna M, Diefenbach A, Di Santo JP, Eberl G, et al. Innate lymphoid cells—a proposal for uniform nomenclature. *Nat Rev Immunol* 2013; 13:145-9.
- Diefenbach A, Colonna M, Koyasu S. Development, differentiation, and diversity of innate lymphoid cells. *Immunity* 2014;41:354-65.
- Cortez VS, Robinette ML, Colonna M. Innate lymphoid cells: new insights into function and development. *Curr Opin Immunol* 2015;32:71-7.
- Eberl G, Colonna M, Di Santo JP, McKenzie AN. Innate lymphoid cells. Innate lymphoid cells: a new paradigm in immunology. *Science* 2015;348aaa6566.
- Seraphin N, Voshchenrich CA, Di Santo JP. Transcriptional regulation of innate lymphoid cell fate. *Nat Rev Immunol* 2015;15:415-28.
- Cording S, Medvedovic J, Aychek T, Eberl G. Innate lymphoid cells in defense, immunopathology and immunotherapy. *Nat Immunol* 2016;17:755-7.
- Klose CS, Artis D. Innate lymphoid cells as regulators of immunity, inflammation and tissue homeostasis. *Nat Immunol* 2016;17:765-74.
- Sun JC, Lanier LL. NK cell development, homeostasis and function: parallels with CD8(+) T cells. *Nat Rev Immunol* 2011;11:645-57.
- Ishizuka IE, Chea S, Gudjonson H, Constantinides MG, Dinner AR, Bendelac A, et al. Single-cell analysis defines the divergence between the innate lymphoid cell lineage and lymphoid tissue-inducer cell lineage. *Nat Immunol* 2016;17:269-76.
- Shih HY, Sciume G, Mikami Y, Guo L, Sun HW, Brooks SR, et al. Developmental acquisition of regulomes underlies innate lymphoid cell functionality. *Cell* 2016; 165:1120-33.
- Bando JK, Liang HE, Locksley RM. Identification and distribution of developing innate lymphoid cells in the fetal mouse intestine. *Nat Immunol* 2015;16:153-60.
- Constantinides MG, McDonald BD, Verhoeve PA, Bendelac A. A committed precursor to innate lymphoid cells. *Nature* 2014;508:397-401.
- Klose CS, Flach M, Mohle L, Rogell L, Hoyler T, Ebert K, et al. Differentiation of type 1 ILCs from a common progenitor to all helper-like innate lymphoid cell lineages. *Cell* 2014;157:340-56.
- Constantinides MG, et al. PLZF expression maps the early stages of ILC1 lineage development. *Proc Natl Acad Sci U S A* 2015;112:5123-8.
- Spits H, Bernink JH, Lanier L. NK cells and type 1 innate lymphoid cells: partners in host defense. *Nat Immunol* 2016;17:758-64.
- Juelke K, Romagnani C. Differentiation of human innate lymphoid cells (ILCs). *Curr Opin Immunol* 2016;38:75-85.
- Fuchs A, Vermi W, Lee JS, Lonardi S, Gilfillan S, Newberry RD, et al. Intraepithelial type 1 innate lymphoid cells are a unique subset of IL-12- and IL-15-responsive IFN-gamma-producing cells. *Immunity* 2013;38:769-81.
- Bernink JH, Peters CP, Munneke M, te Velde AA, Meijer SL, Weijer K, et al. Human type 1 innate lymphoid cells accumulate in inflamed mucosal tissues. *Nat Immunol* 2013;14:221-9.
- Molofsky AB, Nussbaum JC, Liang HE, Van Dyken SJ, Cheng LE, Mohapatra A, et al. Innate lymphoid type 2 cells sustain visceral adipose tissue eosinophils and alternatively activated macrophages. *J Exp Med* 2013;210:535-49.
- Mjosberg J, Bernink J, Golebski K, Karrich JJ, Peters CP, Blom B, et al. The transcription factor GATA3 is essential for the function of human type 2 innate lymphoid cells. *Immunity* 2012;37:649-59.

21. Crellin NK, Trifari S, Kaplan CD, Cupedo T, Spits H. Human NKp44+IL-22+ cells and LT α -like cells constitute a stable RORC+ lineage distinct from conventional natural killer cells. *J Exp Med* 2010;207:281-90.
22. Cella M, Fuchs A, Vermi W, Facchetti F, Otero K, Lennerz JK, et al. A human natural killer cell subset provides an innate source of IL-22 for mucosal immunity. *Nature* 2009;457:722-5.
23. Hepworth MR, Monticelli LA, Fung TC, Ziegler CG, Grunberg S, Sinha R, et al. Innate lymphoid cells regulate CD4+ T-cell responses to intestinal commensal bacteria. *Nature* 2013;498:113-7.
24. Sawa S, Cherrier M, Lochner M, Satoh-Takayama N, Fehling HJ, Langa F, et al. Lineage relationship analysis of RORgammat+ innate lymphoid cells. *Science* 2010;330:665-9.
25. Vonarbourg C, Mortha A, Bui VL, Hernandez PP, Kiss EA, Hoyler T, et al. Regulated expression of nuclear receptor RORgammat confers distinct functional fates to NK cell receptor-expressing RORgammat(+) innate lymphocytes. *Immunity* 2010;33:736-51.
26. Buonocore S, Ahern PP, Uhlig HH, Ivanov II, Littman DR, Maloy KJ, et al. Innate lymphoid cells drive interleukin-23-dependent innate intestinal pathology. *Nature* 2010;464:1371-5.
27. Klose CS, Kiss EA, Schwierzeck V, Ebert K, Hoyler T, d'Hargues Y, et al. A T-bet gradient controls the fate and function of CCR6-RORgammat+ innate lymphoid cells. *Nature* 2013;494:261-5.
28. Song C, Lee JS, Gilfillan S, Robinette ML, Newberry RD, Stappenbeck TS, et al. Unique and redundant functions of NKp46+ ILC3s in models of intestinal inflammation. *J Exp Med* 2015;212:1869-82.
29. Satoh-Takayama N, Vosschenrich CA, Lesjean-Pottier S, Sawa S, Lochner M, Rattis F, et al. Microbial flora drives interleukin 22 production in intestinal NKp46+ cells that provide innate mucosal immune defense. *Immunity* 2008;29:958-70.
30. Lee JS, Cella M, McDonald KG, Garlanda C, Kennedy GD, Nukaya M, et al. AHR drives the development of gut ILC22 cells and postnatal lymphoid tissues via pathways dependent on and independent of Notch. *Nat Immunol* 2012;13:144-51.
31. Sciume G, Hirahara K, Takahashi H, Laurence A, Villarino AV, Singleton KL, et al. Distinct requirements for T-bet in gut innate lymphoid cells. *J Exp Med* 2012;209:2331-8.
32. Rankin LC, Groom JR, Chopin M, Herold MJ, Walker JA, Mielke LA, et al. The transcription factor T-bet is essential for the development of NKp46+ innate lymphocytes via the Notch pathway. *Nat Immunol* 2013;14:389-95.
33. Bjorklund AK, Forkel M, Picelli S, Konya V, Theorell J, Friberg D, et al. The heterogeneity of human CD127(+) innate lymphoid cells revealed by single-cell RNA sequencing. *Nat Immunol* 2016;17:451-60.
34. Gerbe F, Sidot E, Smyth DJ, Ohmoto M, Matsumoto I, Dardalhon V, et al. Intestinal epithelial tuft cells initiate type 2 mucosal immunity to helminth parasites. *Nature* 2016;529:226-30.
35. Howitt MR, Lavoie S, Michaud M, Blum AM, Tran SV, Weinstock JV, et al. Tuft cells, taste-chemosensory cells, orchestrate parasite type 2 immunity in the gut. *Science* 2016;351:1329-33.
36. von Moltke J, Ji M, Liang HE, Locksley RM. Tuft-cell-derived IL-25 regulates an intestinal ILC2-epithelial response circuit. *Nature* 2016;529:221-5.
37. Mortha A, Chudnovskiy A, Hashimoto D, Bogunovic M, Spencer SP, Belkaid Y, et al. Microbiota-dependent crosstalk between macrophages and ILC3 promotes intestinal homeostasis. *Science* 2014;343:1249288.
38. Nussbaum JC, Van Dyken SJ, von Moltke J, Cheng LE, Mohapatra A, Molofsky AB, et al. Type 2 innate lymphoid cells control eosinophil homeostasis. *Nature* 2013;502:245-8.
39. Voskoboinik I, Whisstock JC, Trapani JA. Perforin and granzymes: function, dysfunction and human pathology. *Nat Rev Immunol* 2015;15:388-400.
40. Berke G. The binding and lysis of target cells by cytotoxic lymphocytes: molecular and cellular aspects. *Annu Rev Immunol* 1994;12:735-73.
41. McLane LM, Banerjee PP, Cosma GL, Makedonas G, Wherry EJ, Orange JS, et al. Differential localization of T-bet and Eomes in CD8 T cell memory populations. *J Immunol* 2013;190:3207-15.
42. Kaech SM, Cui W. Transcriptional control of effector and memory CD8+ T cell differentiation. *Nat Rev Immunol* 2012;12:749-61.
43. Pearce EL, Mullen AC, Martins GA, Krawczyk CM, Hutchins AS, Zediak VP, et al. Control of effector CD8+ T cell function by the transcription factor Eomesodermin. *Science* 2003;302:1041-3.
44. Intlekofer AM, Takemoto N, Wherry EJ, Longworth SA, Northrup JT, Palanivel VR, et al. Effector and memory CD8+ T cell fate coupled by T-bet and eomesodermin. *Nat Immunol* 2005;6:1236-44.
45. Gordon SM, Chaix J, Rupp LJ, Wu J, Madera S, Sun JC, et al. The transcription factors T-bet and Eomes control key checkpoints of natural killer cell maturation. *Immunity* 2012;36:55-67.
46. Cruz-Guilloty F, Pipkin ME, Djuretic IM, Levanon D, Lotem J, Lichtenheld MG, et al. Runx3 and T-box proteins cooperate to establish the transcriptional program of effector CTLs. *J Exp Med* 2009;206:51-9.
47. Townsend MJ, Weinmann AS, Matsuda JL, Salomon R, Farnham PJ, Biron CA, et al. T-bet regulates the terminal maturation and homeostasis of NK and Valpha14i NKT cells. *Immunity* 2004;20:477-94.
48. Daussy C, Faure F, Mayol K, Viel S, Gasteiger G, Charrier E, et al. T-bet and Eomes instruct the development of two distinct natural killer cell lineages in the liver and in the bone marrow. *J Exp Med* 2014;211:563-77.
49. Sojka DK, Plougastel-Douglas B, Yang L, Pak-Wittel MA, Artyomov MN, Ivanova Y, et al. Tissue-resident natural killer (NK) cells are cell lineages distinct from thymic and conventional splenic NK cells. *Elife* 2014;3:e01659.
50. Pikovskaya O, Chaix J, Rothman NJ, Collins A, Chen YH, Scipioni AM, et al. Cutting edge: eomesodermin is sufficient to direct type 1 innate lymphocyte development into the conventional NK lineage. *J Immunol* 2016;196:1449-54.
51. Cortez VS, Cervantes-Barragan L, Robinette ML, Bando JK, Wang Y, Geiger TL, et al. Transforming growth factor-beta signaling guides the differentiation of innate lymphoid cells in salivary glands. *Immunity* 2016;44:1127-39.
52. Seillet C, Rankin LC, Groom JR, Mielke LA, Tellier J, Chopin M, et al. Nfil3 is required for the development of all innate lymphoid cell subsets. *J Exp Med* 2014;211:1733-40.
53. Robinette ML, Fuchs A, Cortez VS, Lee JS, Wang Y, Durum SK, et al. Transcriptional programs define molecular characteristics of innate lymphoid cell classes and subsets. *Nat Immunol* 2015;16:306-17.
54. Szabo SJ, Kim ST, Costa GL, Zhang X, Fathman CG, Glimcher LH. A novel transcription factor, T-bet, directs Th1 lineage commitment. *Cell* 2000;100:655-69.
55. Hsieh CS, et al. Development of TH1 CD4+ T cells through IL-12 produced by Listeria-induced macrophages. *Science* 1993;260:547-9.
56. O'Sullivan TE, Rapp M, Fan X, Weizman OE, Bhardwaj P, Adams NM, et al. Adipose-resident group 1 innate lymphoid cells promote obesity-associated insulin resistance. *Immunity* 2016;45:428-41.
57. Bernink JH, Krabbendam L, Germar K, de Jong E, Gronke K, Kofoed-Nielsen M, et al. Interleukin-12 and -23 control plasticity of CD127(+) group 1 and group 3 innate lymphoid cells in the intestinal lamina propria. *Immunity* 2015;43:146-60.
58. Li J, Doty AL, Iqbal A, Glover SC. The differential frequency of Lineage(-) CRTH2(-)CD45(+)NKp44(-)CD117(-)CD127(+)ILC subset in the inflamed terminal ileum of patients with Crohn's disease. *Cell Immunol* 2016;304:305:63-8.
59. Silver JS, Kearley J, Copenhaver AM, Sanden C, Mori M, Yu L, et al. Inflammatory triggers associated with exacerbations of COPD orchestrate plasticity of group 2 innate lymphoid cells in the lungs. *Nat Immunol* 2016;17:626-35.
60. Peng H, Jiang X, Chen Y, Sojka DK, Wei H, Gao X, et al. Liver-resident NK cells confer adaptive immunity in skin-contact inflammation. *J Clin Invest* 2013;123:1444-56.
61. Szabo SJ, Sullivan BM, Stemmann C, Satoskar AR, Sleckman BP, Glimcher LH. Distinct effects of T-bet in Th1 lineage commitment and IFN-gamma production in CD4 and CD8 T cells. *Science* 2002;295:338-42.
62. Hwang ES, Szabo SJ, Schwartzberg PL, Glimcher LH. T helper cell fate specified by kinase-mediated interaction of T-bet with GATA-3. *Science* 2005;307:430-3.
63. Zhu J, Jankovic D, Oler AJ, Wei G, Sharma S, Hu G, et al. The transcription factor T-bet is induced by multiple pathways and prevents an endogenous Th2 cell program during Th1 cell responses. *Immunity* 2012;37:660-73.
64. Djuretic IM, Levanon D, Negreanu V, Groner Y, Rao A, Ansel KM. Transcription factors T-bet and Runx3 cooperate to activate Ifng and silence Il4 in T helper type 1 cells. *Nat Immunol* 2007;8:145-53.
65. Zhu J, Yamane H, Cote-Sierra J, Guo L, Paul WE. GATA-3 promotes Th2 responses through three different mechanisms: induction of Th2 cytokine production, selective growth of Th2 cells and inhibition of Th1 cell-specific factors. *Cell Res* 2006;16:3-10.
66. Ebihara T, Song C, Ryu SH, Plougastel-Douglas B, Yang L, Levanon D, et al. Runx3 specifies lineage commitment of innate lymphoid cells. *Nat Immunol* 2015;16:1124-33.
67. Knox JJ, Cosma GL, Betts MR, McLane LM. Characterization of T-bet and eomes in peripheral human immune cells. *Front Immunol* 2014;5:217.
68. Lupa E, Brack M, Garnier L, Laffont S, Rauch KS, Schachtrup K, et al. Eomesodermin Expression in CD4+ T cells restricts peripheral Foxp3 induction. *J Immunol* 2015;195:4742-52.
69. Cheroutre H, Lambolez F, Mucida D. The light and dark sides of intestinal intra-epithelial lymphocytes. *Nat Rev Immunol* 2011;11:445-56.

70. Zhu J. T helper 2 (Th2) cell differentiation, type 2 innate lymphoid cell (ILC2) development and regulation of interleukin-4 (IL-4) and IL-13 production. *Cytokine* 2015;75:14-24.
71. Monticelli LA, Sonnenberg GF, Abt MC, Alenghat T, Ziegler CG, Doering TA, et al. Innate lymphoid cells promote lung-tissue homeostasis after infection with influenza virus. *Nat Immunol* 2011;12:1045-54.
72. Turner JE, Morrison PJ, Wilhelm C, Wilson M, Ahlfors H, Renauld JC, et al. IL-9-mediated survival of type 2 innate lymphoid cells promotes damage control in helminth-induced lung inflammation. *J Exp Med* 2013;210:2951-65.
73. Moro K, Yamada T, Tanabe M, Takeuchi T, Ikawa T, Kawamoto H, et al. Innate production of T(H)2 cytokines by adipose tissue-associated c-Kit(+)Sca-1(+) lymphoid cells. *Nature* 2010;463:540-4.
74. Neill DR, Wong SH, Bellosi A, Flynn RJ, Daly M, Langford TK, et al. Nuocytes represent a new innate effector leukocyte that mediates type-2 immunity. *Nature* 2010;464:1367-70.
75. Price AE, Liang HE, Sullivan BM, Reinhardt RL, Eisle CJ, Erle DJ, et al. Systemically dispersed innate IL-13-expressing cells in type 2 immunity. *Proc Natl Acad Sci U S A* 2010;107:11489-94.
76. Paul WE. What determines Th2 differentiation, in vitro and in vivo? *Immunol Cell Biol* 2010;88:236-9.
77. Gold MJ, Antignano F, Halim TY, Hirota JA, Blanchet MR, Zaph C, et al. Group 2 innate lymphoid cells facilitate sensitization to local, but not systemic, TH2-inducing allergen exposures. *J Allergy Clin Immunol* 2014;133:1142-8.
78. Halim TY, Krauss RH, Sun AC, Takei F. Lung natural helper cells are a critical source of Th2 cell-type cytokines in protease allergen-induced airway inflammation. *Immunity* 2012;36:451-63.
79. Halim TY, Steer CA, Matha L, Gold MJ, Martinez-Gonzalez I, McNagny KM, et al. Group 2 innate lymphoid cells are critical for the initiation of adaptive T helper 2 cell-mediated allergic lung inflammation. *Immunity* 2014;40:425-35.
80. Kim BS, Siracusa MC, Saenz SA, Noti M, Monticelli LA, Sonnenberg GF, et al. TSLP elicits IL-33-independent innate lymphoid cell responses to promote skin inflammation. *Sci Transl Med* 2013;5:170ra116.
81. Salimi M, Barlow JL, Saunders SP, Xue L, Gutowska-Owsiak D, Wang X, et al. A role for IL-25 and IL-33-driven type-2 innate lymphoid cells in atopic dermatitis. *J Exp Med* 2013;210:2939-50.
82. Hoyler T, Klose CS, Souabni A, Turqueti-Neves A, Pfeifer D, Rawlins EL, et al. The transcription factor GATA-3 controls cell fate and maintenance of type 2 innate lymphoid cells. *Immunity* 2012;37:634-48.
83. Zhang DH, Cohn L, Ray P, Bottomly K, Ray A. Transcription factor GATA-3 is differentially expressed in murine Th1 and Th2 cells and controls Th2-specific expression of the interleukin-5 gene. *J Biol Chem* 1997;272:21597-603.
84. Zheng W, Flavell RA. The transcription factor GATA-3 is necessary and sufficient for Th2 cytokine gene expression in CD4 T cells. *Cell* 1997;89:587-96.
85. Smirnov DV, Smirnova MG, Korobko VG, Frolova EI. Tandem arrangement of human genes for interleukin-4 and interleukin-13: resemblance in their organization. *Gene* 1995;155:277-81.
86. Lee DU, Rao A. Molecular analysis of a locus control region in the T helper 2 cytokine gene cluster: a target for STAT6 but not GATA3. *Proc Natl Acad Sci U S A* 2004;101:16010-5.
87. Yagi R, Zhu J, Paul WE. An updated view on transcription factor GATA3-mediated regulation of Th1 and Th2 cell differentiation. *Int Immunol* 2011;23:415-20.
88. Zhu J, Min B, Hu-Li J, Watson CJ, Grinberg A, Wang Q, et al. Conditional deletion of Gata3 shows its essential function in T(H)1-T(H)2 responses. *Nat Immunol* 2004;5:1157-65.
89. Yagi R, Zhong C, Northrup DL, Yu F, Bouladoux N, Spencer S, et al. The transcription factor GATA3 is critical for the development of all IL-7Ralpha-expressing innate lymphoid cells. *Immunity* 2014;40:378-88.
90. Zhou M, Ouyang W, Gong Q, Katz SG, White JM, Orkin SH, et al. Friend of GATA-1 represses GATA-3-dependent activity in CD4+ T cells. *J Exp Med* 2001;194:1461-71.
91. Ouyang W, Lohning M, Gao Z, Assenmacher M, Ranganath S, Radbruch A, et al. Stat6-independent GATA-3 autoactivation directs IL-4-independent Th2 development and commitment. *Immunity* 2000;12:27-37.
92. Hegazy AN, Peine M, Helmstetter C, Panse I, Frohlich A, Bergthaler A, et al. Interferons direct Th2 cell reprogramming to generate a stable GATA-3(+)Tbet(+) cell subset with combined Th2 and Th1 cell functions. *Immunity* 2010;32:116-28.
93. Ohne Y, Silver JS, Thompson-Snipes L, Collet MA, Blanck JP, Cantarel BL, et al. IL-1 is a critical regulator of group 2 innate lymphoid cell function and plasticity. *Nat Immunol* 2016;17:646-55.
94. Eyerich S, Eyerich K, Pennino D, Carbone T, Nasorri F, Pallotta S, et al. Th22 cells represent a distinct human T cell subset involved in epidermal immunity and remodeling. *J Clin Invest* 2009;119:3573-85.
95. Guo X, Qiu J, Tu T, Yang X, Deng L, Anders RA, et al. Induction of innate lymphoid cell-derived interleukin-22 by the transcription factor STAT3 mediates protection against intestinal infection. *Immunity* 2014;40:25-39.
96. Rankin LC, Girard-Madoux MJ, Seillet C, Mielke LA, Kerdeles Y, Fenis A, et al. Complementarity and redundancy of IL-22-producing innate lymphoid cells. *Nat Immunol* 2016;17:179-86.
97. Teunissen MB, Munneke JM, Bernink JH, Spuls PI, Res PC, Te Velde A, et al. Composition of innate lymphoid cell subsets in the human skin: enrichment of NCR(+) ILC3 in lesional skin and blood of psoriasis patients. *J Invest Dermatol* 2014;134:2351-60.
98. Villanova F, Flutter B, Tosi I, Grys K, Sreeneebus H, Perera GK, et al. Characterization of innate lymphoid cells in human skin and blood demonstrates increase of NKp44+ ILC3 in psoriasis. *J Invest Dermatol* 2014;134:984-91.
99. Dyring-Andersen B, Geisler C, Agerbeck C, Lauritsen JP, Gudjonsdottir SD, Skov L, et al. Increased number and frequency of group 3 innate lymphoid cells in nonlesional psoriatic skin. *Br J Dermatol* 2014;170:609-16.
100. Ciccia F, Guggino G, Rizzo A, Saieva L, Peralta S, Giardina A, et al. Type 3 innate lymphoid cells producing IL-17 and IL-22 are expanded in the gut, in the peripheral blood, synovial fluid and bone marrow of patients with ankylosing spondylitis. *Ann Rheum Dis* 2015;74:1739-47.
101. Cols M, Rahman A, Maglione PJ, Garcia-Carmona Y, Simchoni N, Ko HB, et al. Expansion of inflammatory innate lymphoid cells in patients with common variable immune deficiency. *J Allergy Clin Immunol* 2016;137:1206-15.
102. Hepworth MR, Fung TC, Masur SH, Kelsen JR, McConnell FM, Dubrot J, et al. Immune tolerance. Group 3 innate lymphoid cells mediate intestinal selection of commensal bacteria-specific CD4(+) T cells. *Science* 2015;348:1031-5.
103. Ivanov II, McKenzie BS, Zhou L, Tadokoro CE, Lepelley A, Lafaille JJ, et al. The orphan nuclear receptor RORgamma directs the differentiation program of proinflammatory IL-17+ T helper cells. *Cell* 2006;126:1121-33.
104. Ciofani M, Madar A, Galan C, Sellars M, Mace K, Pauli F, et al. A validated regulatory network for Th17 cell specification. *Cell* 2012;151:289-303.
105. Withers DR, Hepworth MR, Wang X, Mackley EC, Halford EE, Dutton EE, et al. Transient inhibition of ROR-gamma therapeutically limits intestinal inflammation by reducing Th17 cells and preserving group 3 innate lymphoid cells. *Nat Med* 2016;22:319-23.
106. Kiss EA, Vonarbourg C, Kopfmann S, Hobeika E, Finke D, Esser C, et al. Natural aryl hydrocarbon receptor ligands control organogenesis of intestinal lymphoid follicles. *Science* 2011;334:1561-5.
107. Qiu J, Heller JJ, Guo X, Chen ZM, Fish K, Fu YX, et al. The aryl hydrocarbon receptor regulates gut immunity through modulation of innate lymphoid cells. *Immunity* 2012;36:92-104.
108. Cella M, Colonna M. Aryl hydrocarbon receptor: Linking environment to immunity. *Semin Immunol* 2015;27:310-4.
109. Basu R, O'Quinn DB, Silberger DJ, Schoeb TR, Fouser L, Ouyang W, et al. Th22 cells are an important source of IL-22 for host protection against enteropathogenic bacteria. *Immunity* 2012;37:1061-75.
110. Annunziato F, Cosmi L, Santarlasci V, Maggi L, Liotta F, Mazzinghi B, et al. Phenotypic and functional features of human Th17 cells. *J Exp Med* 2007;204:1849-61.
111. Lee YK, Turner H, Maynard CL, Oliver JR, Chen D, Elson CO, et al. Late developmental plasticity in the T helper 17 lineage. *Immunity* 2009;30:92-107.
112. Cella M, Otero K, Colonna M. Expansion of human NK-22 cells with IL-7, IL-2, and IL-1beta reveals intrinsic functional plasticity. *Proc Natl Acad Sci U S A* 2010;107:10961-6.
113. Walker JA, Barlow JL, McKenzie AN. Innate lymphoid cells—how did we miss them? *Nat Rev Immunol* 2013;13:75-87.
114. Zook EC, Kee BL. Development of innate lymphoid cells. *Nat Immunol* 2016;17:775-82.
115. Koues OI, Collins PL, Cella M, Robinette ML, Porter SI, Pyfrom SC, et al. Distinct gene regulatory pathways for human innate versus adaptive lymphoid cells. *Cell* 2016;165:1134-46.
116. Li-Weber M, Krammer PH. Regulation of IL4 gene expression by T cells and therapeutic perspectives. *Nat Rev Immunol* 2003;3:534-43.
117. Bedoui S, Gebhardt T, Gasteiger G, Kastenmuller W. Parallels and differences between innate and adaptive lymphocytes. *Nat Immunol* 2016;17:490-4.
118. Guo L, Wei G, Zhu J, Liao W, Leonard WJ, Zhao K, et al. IL-1 family members and STAT activators induce cytokine production by Th2, Th17, and Th1 cells. *Proc Natl Acad Sci U S A* 2009;106:13463-8.

119. Robinson D, Shibuya K, Mui A, Zonin F, Murphy E, Sana T, et al. IGIF does not drive Th1 development but synergizes with IL-12 for interferon-gamma production and activates IRAK and NFkappaB. *Immunity* 1997;7:571-81.
120. Yang J, Zhu H, Murphy TL, Ouyang W, Murphy KM. IL-18-stimulated GADD45 beta required in cytokine-induced, but not TCR-induced, IFN-gamma production. *Nat Immunol* 2001;2:157-64.
121. Chung Y, Chang SH, Martinez GJ, Yang XO, Nurieva R, Kang HS, et al. Critical regulation of early Th17 cell differentiation by interleukin-1 signaling. *Immunity* 2009;30:576-87.
122. Meisel C, Bonhagen K, Lohning M, Coyle AJ, Gutierrez-Ramos JC, Radbruch A, et al. Regulation and function of T1/ST2 expression on CD4+ T cells: induction of type 2 cytokine production by T1/ST2 cross-linking. *J Immunol* 2001;166:3143-50.
123. Coquet JM, Schuijs MJ, Smyth MJ, Deswarte K, Beyaert R, Braun H, et al. Interleukin-21-producing CD4(+) T cells promote type 2 immunity to house dust mites. *Immunity* 2015;43:318-30.
124. Guo L, Huang Y, Chen X, Hu-Li J, Urban JF Jr, Paul WE. Innate immunological function of TH2 cells in vivo. *Nat Immunol* 2015;16:1051-9.