

The 3 major types of innate and adaptive cell-mediated effector immunity

Francesco Annunziato, PhD,^a Chiara Romagnani, MD, PhD,^b and Sergio Romagnani, MD^a Florence, Italy, and Berlin, Germany

The immune system has tailored its effector functions to optimally respond to distinct species of microbes. Based on emerging knowledge on the different effector T-cell and innate lymphoid cell (ILC) lineages, it is clear that the innate and adaptive immune systems converge into 3 major kinds of cell-mediated effector immunity, which we propose to categorize as type 1, type 2, and type 3. Type 1 immunity consists of T-bet⁺ IFN- γ -producing group 1 ILCs (ILC1 and natural killer cells), CD8⁺ cytotoxic T cells (T_C1), and CD4⁺ T_H1 cells, which protect against intracellular microbes through activation of mononuclear phagocytes. Type 2 immunity consists of GATA-3⁺ ILC2s, T_C2 cells, and T_H2 cells producing IL-4, IL-5, and IL-13, which induce mast cell, basophil, and eosinophil activation, as well as IgE antibody production, thus protecting against helminthes and venoms. Type 3 immunity is mediated by retinoic acid-related orphan receptor γ t⁺ ILC3s, T_C17 cells, and T_H17 cells producing IL-17, IL-22, or both, which activate mononuclear phagocytes but also recruit neutrophils and induce epithelial antimicrobial responses, thus protecting against extracellular bacteria and fungi. On the other hand, type 1 and 3 immunity mediate autoimmune diseases, whereas type 2 responses can cause allergic diseases. (J Allergy Clin Immunol 2015;135:626-35.)

Key words: Type 1 immunity, type 2 immunity, type 3 immunity, innate lymphoid cells, T_H1, T_C1, T_H2, T_C2, T_H17/T_H22, T_C17/T_C22

In 1986, Mosmann et al¹ demonstrated that murine CD4⁺ T_H cells can be classified into 2 major functionally different subsets on the basis of the different cytokines they produce (ie, T_H1 and T_H2). The first clear evidence for the existence of T_H1 and T_H2 cells in human subjects was provided only 5 years later.² As known, T_H1 cells produce IFN- γ and lymphotoxin (LT) α ,

Abbreviations used

APC:	Antigen-presenting cell
CRTH2:	Chemoattractant receptor-homologous molecule expressed on T _H 2 cells
DC:	Dendritic cell
Eomes:	Eomesodermin
IBD:	Inflammatory bowel disease
IL-7R:	IL-7 receptor
ILC:	Innate lymphoid cell
LT:	Lymphotoxin
MP:	Mononuclear phagocyte
MS:	Multiple sclerosis
NK:	Natural killer
NKp:	Natural killer progenitor
PB:	Peripheral blood
RA:	Rheumatoid arthritis
ROR:	Retinoic acid-related orphan receptor
STAT:	Signal transducer and activator of transcription
T _C :	Cytotoxic T
TSLP:	Thymic stromal lymphopoietin

whereas T_H2 cells produce IL-4, IL-5, and IL-13.³ Subsequently, a similar dichotomy within the CD8⁺ cytotoxic T (T_C) cell population was discovered in both mice and human subjects, and the 2 subsets were named T_C1 and T_C2, respectively.⁴ In 2005, a third subset of murine CD4⁺ T_H cells was identified and named T_H17 cells because of the unique ability of these cells to produce IL-17.⁵ Two years later, T_H17 cells were found to exist in human subjects.^{6,7} Likewise, CD8⁺ T cells producing IL-17 were identified and named T_C17 cells.⁸ In the last few years, the existence of innate lymphoid cells (ILCs), which differ from classic T cells because they lack the T-cell receptor, has been reported both in mice and human subjects.⁹ Because of their similarity to CD4⁺ and CD8⁺ T cells, it was recently proposed that ILCs can be classified into cytotoxic ILCs, namely natural killer (NK) cells, and helper ILCs, which, like CD4⁺ T_H cells, can be separated into the 3 main lineages ILC1s, ILC2s, and ILC3s, according to their ability to produce type 1, type 2, or type 17 cytokines, respectively.^{9,10} ILC3s are also present before birth in which case they are named lymphoid tissue inducer cells because of their crucial role in promoting lymph node and Peyer patch formation during fetal development.⁹ Although both T cells and ILCs originate from a common lymphoid progenitor, differentiation of naive CD8⁺ and CD4⁺ T cells from the T-cell precursor occurs in the thymus, and the different developmental steps have been elucidated clearly. Conversely, the location and stages of ILC differentiation are only beginning to be clarified. Helper-like ILCs and cytotoxic NK cells likely differentiate from a putative common innate lymphoid precursor, from which the “common helper-like

From ^athe Department of Experimental and Clinical Medicine and the DENOTHE Center, University of Florence, and ^bthe Innate Immunity, Deutsches Rheuma Forschungszentrum, Berlin.

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Corresponding author: Sergio Romagnani, MD, Department of Experimental and Clinical Medicine, Laboratory of Immunology, Allergology and Cellular Therapies, University of Florence, Viale Pieraccini 6, 50139 Firenze, Italy. E-mail: sergio.romagnani@unifi.it.

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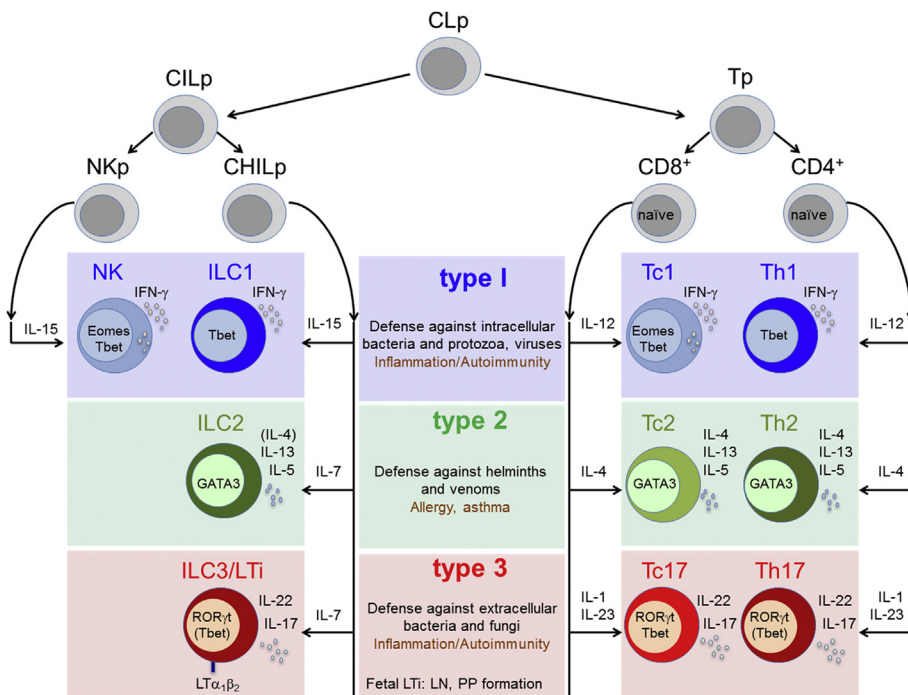


FIG 1. The 3 major types of innate and adaptive cell-mediated effector immunity. Type 1 immunity is composed of T-bet⁺ IFN- γ -producing CD4⁺ T_H1 cells and ILC1s and T-bet⁺ Eomes⁺ CD8⁺ T_C1 and NK cells. Type 2 immunity is composed of GATA-3⁺ CD4⁺ T_H2 cells, CD8⁺ T_C2 cells, and ILC2s, which produce IL-4, IL-5, and IL-13. Type 3 immunity is composed of ROR γ t (RORC)⁺ CD4⁺ T_H17 cells, CD8⁺ T_C17 cells, and ILC3s, producing IL-17, IL-22, or both. CILp, Common innate lymphoid precursor; CLp, common lymphoid precursor; LN, lymph node; LTI, lymphoid tissue inducer; PP, Peyer patch; Tp, T-cell progenitor.

ILC progenitor,” which was recently identified in the mouse,¹⁰ and the NK cell progenitor (NKp) might originate.

Taking into account this ontogenetic pathway, as well as the different effector functions and pathophysiologic effects, it is now possible to distinguish 3 major types of innate and adaptive cell-mediated effector immunity, which we propose to define as type 1, type 2, and type 3, respectively (Fig 1). These different types of cell-mediated immunity exist to ensure a tailored and maximally protective effect against the great variety of pathogenic microorganisms present in the environment. However, because of innate or acquired deficiencies, as well as abnormal or exaggerated responses, they can also generate different types of immune-mediated disorders. In this review we will discuss the 3 types of immunity, with particular focus on the main features of human cells and their respective role in protection and immunopathology.

TYPE 1 CELL-MEDIATED EFFECTOR IMMUNITY

Type 1 cell-mediated effector immunity provides an effective response against intracellular microbes, such as bacteria, protozoa, and some viruses, and it comprises T-bet⁺ IFN- γ -producing helper cells (ie, CD4⁺ T_H1 cells and ILC1s), as well as T-bet⁺ eomesodermin (Eomes)⁺ cytotoxic lymphocytes, namely CD8⁺ T cells and NK cells. The main features of the innate and adaptive cells involved in type 1 immunity are depicted in Fig 2.

CD4⁺ T_H1 cells

As mentioned above, in both mice and human subjects, T_H1 cells make IFN- γ and LT- α as their signature cytokines^{1,2} but

can also produce TNF and IL-2 and mediate mononuclear phagocyte (MP) activation. Moreover, T_H1 cells are able to help the production by B lymphocytes of antibodies of the IgG_{2a} isotype in mice¹ and of IgM, IgG, and IgA, but not IgE, in human subjects.³ The environmental cytokine mainly responsible for human T_H1 cell differentiation is IL-12,¹¹ which is produced by dendritic cells (DCs) in response to the interaction of pattern recognition receptors with bacterial or viral conserved structures. IFN- γ also contributes to T_H1 cell differentiation, whereas IFN- α is involved in human subjects but not in mice.¹² More recently, 2 other cytokines, IL-23 and IL-27, have been found to have a T_H1-polarizing activity.¹³ Activation of signal transducer and activator of transcription (STAT) 1 by IFN- γ and of STAT4 by IL-12 is critical for the induction of T-bet, which is considered the hallmark transcription factor for T_H1 cells.¹² In addition to the production of IFN- γ and expression of T-bet, T_H1 cells are also characterized by the expression of chemokine receptors, which allow their recruitment to inflammatory sites. The main chemokine receptors of T_H1 cells are CXCR3A and CCR5.¹⁴ Thus the CXCR3 ligands CXCL9, CXCL10, and CXCL11 and the CCR5 ligands CCL3, CCL4, and CCL5 mainly contribute to T_H1 cell recruitment.¹⁴ More recently, an important link between T_H1 responses and epithelial tissues has been discovered. IFN- γ produced by T_H1 cells seems to be very important in inducing a defect in the epithelial barrier by downregulating tight junctions,¹⁵ as well as by increasing the apoptosis of keratinocytes in the skin.¹⁶ On the other hand, it is known that both keratinocytes and epithelial cells produce CXCL9, CXCL10, and CXCL11 in response to IFN- γ , thus favoring recruitment of T_H1 cells.¹⁷

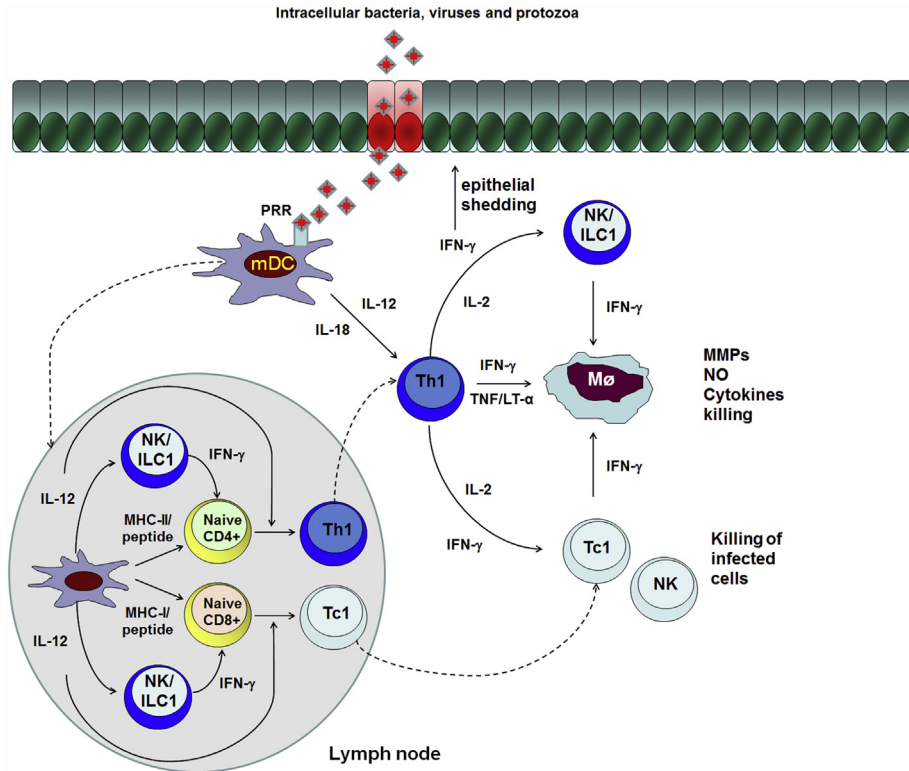


FIG 2. Cells, cytokines, and effectors of type 1 immunity. Intracellular microbes interacting with pathogen recognition receptors (*PRR*) on DCs in the presence of DC-derived IL-12 and IL-18 and of NK/ILC1-derived IFN- γ induce T_H1 or T_C1 development from naive T cells. T_C1 and NK cells kill virus-infected cells. T_H1 cell-, T_C1 cell-, and ILC1-derived cytokines activate MPs to produce the matrix metalloproteinase (*MMPs*), nitric oxide (*NO*), and cytokines that allow engulfment and killing of microbial invaders. *mDC*, Myeloid dendritic cell.

CD8⁺ T_{C1} cells

CD8⁺ T cells generally produce IFN- γ , TNF and LT- α . However, after the discovery of T_H1 and T_H2 cells, the existence of CD8⁺ T cells able to produce IL-4 and IL-5 instead of IFN- γ was reported, and therefore IFN- γ -producing CD8⁺ T cells were renamed T_C1 cells.⁴ Like CD4⁺ T_H1 differentiation, IFN- γ and IL-12 promote differentiation toward T_C1 cells.¹⁸ However, in response to antigen, T_C1 cells can be induced to produce IFN- γ independently of IL-12 and STAT4 activation.¹⁹ T-bet activation in T_C1 cells is required for both IFN- γ production and cytolytic potential. In the same cells both these activities are also under the control of another T-box transcription factor, Eomes.¹⁹ As has been shown for T_H1 cells, CCR5 and CXCR3 are the main chemokine receptors for T_C1 cells.²⁰

Group 1 ILCs

Group 1 ILCs were defined to include ILCs expressing T-bet and producing IFN- γ and originally were composed of only NK cells. NK cells are NKp46⁺ cytotoxic lymphocytes producing IFN- γ in response to cytokines and/or activating receptor engagement and depend on IL-15 and E4bp4 (a member of the bZIP family of DNA-binding proteins) for their development. NK cells have been mostly characterized in human peripheral blood (PB), where they represent around 5% to 15% of circulating lymphocytes, and in mouse spleens, where they coexpress the transcription factors T-bet and Eomes, which is similar to

CD8⁺ T cells.²¹ However, it was recently shown that among NKp46⁺ cells resident in various tissues, a large heterogeneity can be appreciated concerning phenotype, expression of master transcription factors, and developmental dependence, and in some reports these cells have been designated as distinct lineages from NK cells termed ILC1s.^{10,22-25}

ILC1s appear to be functionally characterized by the ability to produce IFN- γ , TNF, GM-CSF, and even IL-2 in response to cytokine stimulation but have low or no cytotoxic ability.^{10,22-24} However, in some cases cells described as ILC1-like populations rather represent retinoic acid-related orphan receptor (*ROR*) γ t (*RORC*)⁺ ILC3s, which, because of their plasticity, have lost the expression of *ROR* γ t while acquiring many features of other group 1 ILC cell subsets.^{22,25} Interestingly, a mouse $\alpha_4\beta_7$ ⁺ progenitor has been recently identified, giving rise to NKp46⁺T-bet⁺Eomes⁻ ILC1s (as well as ILC2s and ILC3s) but not to NKp46⁺T-bet⁺Eomes⁺ NK cells.¹⁰ Based on all these observations, it was thus proposed that NKp46⁺ IL-7 receptor (IL-7R)⁺ T-bet⁺Eomes⁻ ILC1s (depending on T-bet but not on Eomes or *ROR* γ t for their development) could correspond to IFN- γ -producing helper ILCs. Conversely, cytotoxic T-bet⁺Eomes⁺ NK cells (depending on Eomes but not on *ROR* γ t for their development) might represent a distinct lineage, acting as the innate counterpart of CD8⁺ T cells.¹⁰ However, following these criteria, not all the NKp46⁺ cells described to date in different tissues can be categorized as NK cells or ILC1s.^{23,24} Therefore further characterization of the large heterogeneity

TABLE I. Main features of murine and human ILCs

	Murine					Human				
	NK cells ^{9,21,26}	ILC1s ¹⁰	ILC2s ^{25,27-31}	NCR ⁻ ILC3s ^{9,25,26}	NCR ⁺ ILC3s ^{9,25,26}	NK cells ^{9,26}	ILC1s ²²	ILC2s ^{31,32}	NCR ⁻ ILC3s ^{26,33-35}	NCR ⁺ ILC3s ^{26,33-35}
Surface markers										
CD127 (IL-7R α)	-	+	+	+	+	-/lo	+	+	+	+
CD117 (cKit)	-/lo	+	+	+	+	-/lo	-	+/-	+	+
NK1.1/CD161	+	+	-	-	lo	+	+	+	+	+
CCR6	-	ND	-	+/-	-	-	-	+	+	+
CRT2	ND	ND	ND	ND	ND	-	-	+	-	-
NKp44	NA	NA	NA	NA	NA	+/-	-	-	-	+
NKp46	+	+	+	-	+	+	-	-	-	+
CD56	NA	NA	NA	NA	NA	+	-	-	+/-	+/-
Perforin	+	lo	-	-	-	+	-	-	-	-
CD16	+	ND	-	-	-	+/-	-	-	-	-
Ly49/KIR	+/-	lo	-	-	-	+/-	-	-	-	-
CD94	+	ND	+/-	-	+/-	+	-	-	-	-
Cytokines										
IFN- γ	+	+	-/lo	-/lo	-/lo	+	+	-	-/lo	-/lo
IL-17	-	-	-	+/-	-	-	-	-	-/lo	-/lo
IL-22	-	-	+	+	+	-	-	-/lo	-	+
IL-13, IL-5	-	-	+	-	-	-	-	+	-/lo	-/lo
Transcription factors										
T-bet	+	+	-	+/-	+	+	+	-	-	-
Eomes	+	-	-	-	-	+	-	-	-	-
ROR γ t	-	-	lo	+	+	-	lo	-/lo	+	+
GATA-3	-	lo	+	lo	lo	-/lo	-/lo	-/lo	-/lo	-/lo
Location	Spleen, lung	Gut LP	Gut LP, lung	Gut LP	Gut LP	PB	Gut LP	PB, tonsil	Tonsil, gut LP	Tonsil, gut LP

CRT2, Chemoattractant receptor-homologous molecule expressed on T_H2 cells; lo, low expression; LP, lamina propria; NA, not applicable; NCR, natural cytotoxicity receptor; ND, not determined.

displayed by NKp46⁺ cells in different tissues and understanding of their developmental requirements and specific functions will enable us to have more insight to better dissect group 1 ILCs.

Markers expressed by murine splenic or human PB NK cells versus ILC1s are shown in Table I.^{9,10,21,22,25-35} Because of their large heterogeneity and the still poor characterization of ILC1s from different tissues, for simplicity, only markers of murine¹⁰ and human²² ILC1s identified in the gut lamina propria have been described.

Type 1 cell-mediated effector immunity in protection and immunopathology

The essential physiologic role of type 1 immunity is protection against intracellular microbes, such as *Mycobacterium tuberculosis*, *Leishmania Major*, *Toxoplasma gondii*, and many others. Intracellular bacteria or protozoans are endowed with the capacity to survive and replicate inside MPs and sometimes within certain other host cells. MPs are potent effector cells that are able to engulf and kill many bacterial invaders. Therefore intracellular bacteria had to exploit potent evasion mechanisms that allow their survival in this hostile environment.³ During intracellular persistence, microbial proteins are processed and presented, thus initiating T-cell activation. By secreting IFN- γ and TNF, T_H1, T_C1, and group 1 ILCs activate MPs, converting them to potent effector cells. T_C1 cells are even more important than T_H1 cells for protection against viruses because in addition to the ability to produce IFN- γ and TNF, they exhibit a high specific cytolytic potential against infected cells. In particular, a specific role for NK cells in the defense against herpesvirus has been long established³⁶ and more recently revisited.³⁷ However,

although it has been shown that newly identified ILC1s are the main producers of IFN- γ and other cytokines during *Toxoplasma gondii* infection,¹⁰ the specific contribution of distinct group 1 ILCs in other intracellular pathogen infections needs to be further investigated. However, type 1 immunity might also play some pathogenic role in several human diseases, including autoimmune organ-specific disorders, such as rheumatoid arthritis (RA), multiple sclerosis (MS), Hashimoto thyroiditis, insulin-dependent diabetes mellitus, autoimmune gastritis, and other chronic inflammatory disorders, such as inflammatory bowel diseases (IBDs), atherosclerosis, and sarcoidosis, as had already been suggested on the basis of studies performed on T_H1 cells.³⁸

TYPE 2 CELL-MEDIATED EFFECTOR IMMUNITY

Type 2 immunity is mainly devoted to protection against helminths and venoms and is composed of GATA-3⁺ lymphocytes producing IL-4, IL-5, and IL-13, namely CD4⁺ T_H2 cells, CD8⁺ T_C2 cells, and ILC2s. The main features of innate and adaptive cells involved in type 2 immunity are depicted in Fig 3.

CD4⁺ T_H2 cells

CD4⁺ T_H2 cells fundamentally differ from T_H1 cells because they are unable to secrete IFN- γ and LT- α but produce other cytokines, such as IL-4, IL-5, and IL-13.³ Both IL-4 and IL-13 are essential for the switching process of B cells to the production of IgG₁ and IgE in mice¹ and of all immunoglobulin classes, including IgE, in human subjects,³ whereas IL-5 plays an important role in the differentiation, activation, and survival of eosinophils in both mice and human subjects.¹⁻³ The presence

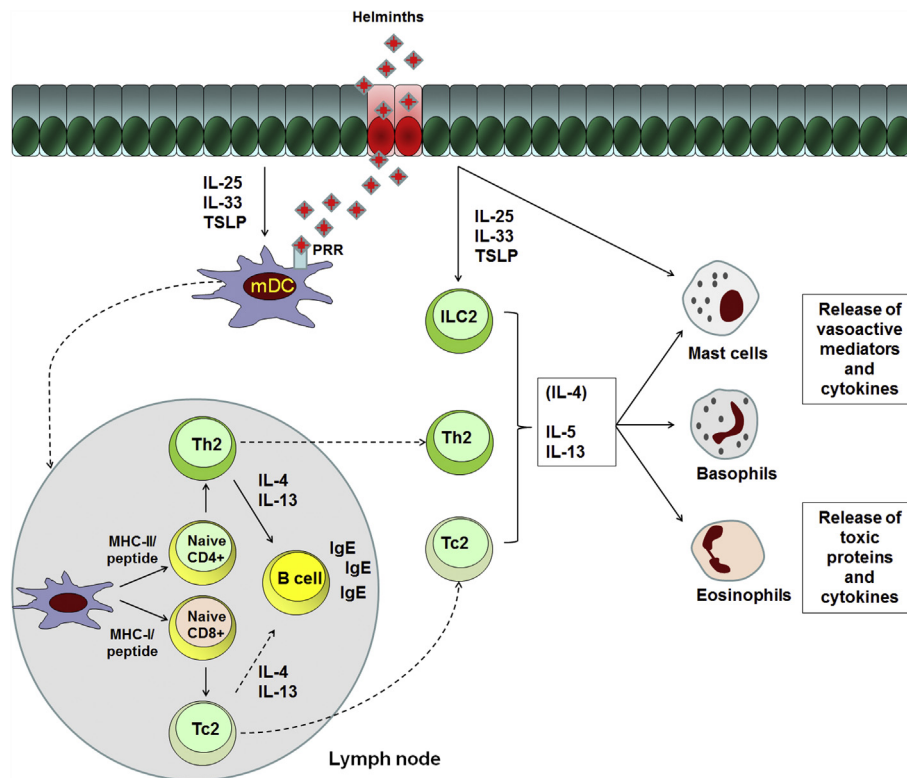


FIG 3. Cells, cytokines, and effectors of type 2 immunity. Helminths induce IL-25, IL-33, and thymic stromal lymphopoietin (*TSLP*) release by epithelial cells, which might directly activate mast cells, eosinophils, basophils, and ILC2s to produce IL-5, IL-13, and perhaps small amounts of IL-4. Activated DCs in the presence of IL-4 induce naive T cells to develop into T_H2 and T_C2 cells producing IL-4, IL-5, and IL-13. IL-4 and IL-13 allow IgE production by B lymphocytes, whereas IL-5 promotes eosinophil recruitment. *mDC*, Myeloid dendritic cell; *PRR*, pathogen recognition receptors.

of IL-4 in the microenvironment of antigen-presenting cell (APC)–naive T_H cell interaction has been found to be critical for T_H2 cell differentiation in both mice³⁹ and human subjects,³ but the nature of the cell responsible for this early IL-4 production is still controversial. It was reported that basophils can act as T_H2 -inducing APCs because these cells express MHC class II and CD80/CD86 and produce large amounts of IL-4⁴⁰; however, these findings were challenged by the observation that only inflammatory DCs were necessary and sufficient for the induction of T_H2 immunity, whereas basophils could not act as APCs and were not required.⁴¹ Whatever the source of early IL-4, this cytokine is critical for inducing the subsequent steps allowing T_H2 differentiation.

The interaction between IL-4 and its receptor results in STAT6 activation, which, in turn, promotes the expression of GATA-3. GATA-3 induces transactivation of the *IL4* promoter and also directly regulates *IL5* and *IL13* gene expression.¹² Human T_H2 cells have also been found to express chemokine receptors different from those expressed by T_H1 cells, such as CCR3 (which binds to CCL11), CCR4 (which binds to CCL22 and CCL17), and CCR8 (which binds to CCL1).¹⁴ On the other hand, it is now known that the 2 CCR4 ligands CCL17 and CCL22 are expressed by airway epithelial cells, that their expression in atopic subjects is strongly upregulated after allergen challenge, and that IL-4 in combination with TNF- α upregulates CCL17 production by airway epithelial cells, thus favoring the recruitment of T_H2 cells.^{42,43} However, the most selective marker of human T_H2 cells is the chemoattractant

receptor-homologous molecule expressed on T_H2 cells (CRTH2), which is one of the 2 receptors of prostaglandin D₂.⁴⁴ Interestingly, human T_H2 cells also express the β_2 -chain of the IL-12 receptor, which is the reason why even established allergen-specific T_H2 cells can be reversed to the production of IFN- γ in the presence of IL-12,⁴⁵ thus suggesting the possibility of the plasticity of T_H cell subsets.

CD8⁺ T_C2 cells

CD8⁺ T cells able to produce type 2 cytokines have been defined as T_C2 cells.⁴ T_C2 cells secrete IL-4, IL-5, and IL-13, but not IFN- γ , and exhibit reduced cytotoxic activity in comparison with T_C1 cells. This finding is consistent with the observations that T_C2 cells still express the perforin pathway and that CD95 ligand and can provide partial help for immunoglobulin production.⁴⁶ T_C2 cells were then isolated from the skin and PB of HIV-infected subjects, particularly those affected by hyper-IgE syndrome. These T_C2 cells exhibited strongly reduced cytolytic potential, were able to help immunoglobulin production (including IgE) by normal B cells, and expressed higher levels of CD30, CD28, and CD40 ligand on their surfaces than T_C1 cells.⁴⁶ As for CD4⁺ T_H2 cells, IL-4 is essential for T_C2 cell development, and the interaction of IL-4 with its receptor also results in STAT6 phosphorylation.⁴⁷ Thus although the subsequent steps leading to type 2 cytokine production have not been investigated, it is likely that GATA-3 represents the hallmark transcription factor also for T_C2 differentiation.

Group 2 ILCs

An innate lymphoid source of type 2 cytokines was already identified in 2001.²⁸ However, it was only in 2010 that these cells, later defined as group 2 ILCs or ILC2s, were clearly characterized in mice.^{27,29-31} ILC2s are present in very low percentages in the lungs, skin, and gut, as well as in mesenteric fat. They are characterized by high expression of the master transcription factor GATA-3 and of the IL-7R, CD25, IL-33 receptor (T1/ST2), and IL-25 receptor.^{9,31} In addition to these markers, human ILC2s also express CCR2 and CD161 and can be also found in extremely low percentages in PB.³² ILC2 development requires GATA-3 and ROR α , whereas it is independent of ROR γ t. ILC2s produce IL-5, IL-13, IL-9, and amphiregulin, a member of the epidermal growth factor family.^{9,31,32} As assessed by using reporter mice, ILC2s represent a predominant source of IL-5 in almost all organs analyzed. Gut ILC2s constitutively express both IL-5 and IL-13, which are regulated in response to feeding through production of vasoactive intestinal peptide. Serum IL-5 levels correlate with the circadian variation in blood eosinophils, which are strongly dependent on ILC2s. Conversely, lung ILC2s produce IL-13 only after cytokine stimulation, helminth infection, or both.⁴⁸ IL-25, IL-33, and thymic stromal lymphopoietin (TSLP) are the main cytokines produced by epithelial cells after tissue damage during allergic inflammation or helminth infections and have all been shown to enhance cytokine production in ILC2s.^{9,31,32} Moreover, it has been shown that TL1A, a TNF superfamily member binding to DR3, prostaglandin D₂, and leukotriene D₄, also contributes to the induction of cytokine expression in ILC2s.⁴⁹ Although ILC2s are considered to be low IL-4 producers, expression of IL-4 by ILC2s was reported, especially in response to TSLP and leukotriene D₄ rather than IL-33.⁴⁹ Markers of murine and human ILC2s are shown in Table 1.

Type 2 cell-mediated effector immunity in protection and immunopathology

Type 2 immunity has long been associated with protection against intestinal nematodes, which is dependent on the IL-13 pathway provided by T_H2 cells and ILC2s. The protective mechanisms of type 2 immunity are different and might include the enhancement of intestinal smooth muscle cell contractility, changes in epithelial cell function, and increased intestinal mucus secretion, as well as induction of intestinal mastocytosis, which favor parasite expulsion.⁵⁰ Moreover, a protective role for IgG₄ antibodies, which are secreted by a particular subset of IL-10-producing regulatory B cells,⁵¹ should be considered. More recently, however, the protective role of type 2 immunity has been extended to noxious xenobiotics, venoms from a variety of ectoparasites (including ticks and mosquitoes), hematophagous fluids, and environmental irritants.⁵² The hallmark human pathologic disorders related to type 2 immunity are allergy and asthma.⁵³

According to the initial view on the protective function of type 2 immunity, allergy arises when this type of response is inadvertently activated by noninfectious environmental antigens. Thus the allergic response was considered a misdirected and unintended type 2 immune response. The most recent view that type 2 immunity can provide protection against different types of noninfectious noxious environmental factors allows the

suggestion that allergens are not really innocuous environmental antigens, as previously believed. This hypothesis is consistent with the recent demonstration that phospholipase A₂, the major allergen in bee venom, induces a primary type 2 response through the enzymatic cleavage of membrane phospholipids and release of IL-33.⁵⁴ Very recent and interesting new progress in the field of T_H2-mediated inflammatory disorders, such as bronchial asthma and chronic rhinosinusitis, has included the definition of different disease “endotypes.” An endotype is proposed to be a subtype of a condition defined by a distinct pathophysiologic mechanism that might be identified by corresponding biomarkers.^{55,56} Identification of endotypes allows us to envisage more personalized therapies based on targeting the predominant pathophysiologic process characterizing the endotype with presently available biological agents (anti-IgE, anti-IL-5, anti-IL-13, anti-IL-4/IL-13, and anti-TNF) with potential for more effective treatment and better patient outcomes.⁵⁷

TYPE 3 CELL-MEDIATED EFFECTOR IMMUNITY

Type 3 immunity is devoted to protection against extracellular bacteria and fungi and is composed of ROR γ t⁺ lymphocytes, producing IL-17 alone or in combination with IL-22 as signature cytokines (ie, CD4⁺ T_H17 cells, CD8⁺ T_C17 cells, and ILC3s). The major features of innate and adaptive cells involved in type 3 immunity are depicted in Fig 4.

CD4⁺ T_H17 cells

A third type of CD4⁺ T_H cells has recently been identified in both mice and human subjects and named T_H17 cells because of their ability to produce IL-17A and IL-17F.⁵⁻⁷ IL-17A and IL-17F are similar in their biological activity because both cytokines target either immune or nonimmune cell types and are also key cytokines for the recruitment, activation, and migration of neutrophils. In addition, T_H17 cells produce IL-22 and IL-26,⁵⁸ and IL-22 promotes epithelial cell homeostasis and antimicrobial defense⁵⁹ but seems to be particularly important by having many roles in tissue repair.⁶⁰ The role of IL-26, which has no murine homolog and can be produced by both T_H17 and T_H1 cells, is still unclear, although IL-26 levels are increased during intestinal inflammation,⁶¹ as well as by synovial cells of patients with RA.⁶² Similar to mice, human T_H17 cells produce TNF and GM-CSF, which also contribute to the activation, survival, and recruitment of neutrophils.⁵⁸

Although murine T_H17 cells originate from naive T_H cells in response to the combined activity of IL-6 and TGF- β ,⁵ the latter cytokine has not been found to be essential for the differentiation of human T_H17 cells.^{63,64} More importantly, it was found that all memory human T_H17 cells express the NK and NKT marker CD161, and the existence of T_H17 precursors was identified in both umbilical cord blood (UCB) and newborn thymus.⁶⁴ These CD161⁺ T-cell precursors, which are absent from adult PB, expressed RORC, IL-23 receptor, and CCR6 (see below) and were able to differentiate into mature IL-17A-producing cells only when cultured in the presence of IL-1 β and IL-23, even in the absence of TGF- β .⁶⁴ These findings suggest that human T_H17 cells originate from a distinct lineage of CD161⁺ RORC-expressing T-cell precursors already present in the human thymus, which then directly migrate to lymphoid tissues, where they can develop into mature T_H17 cells under the combined

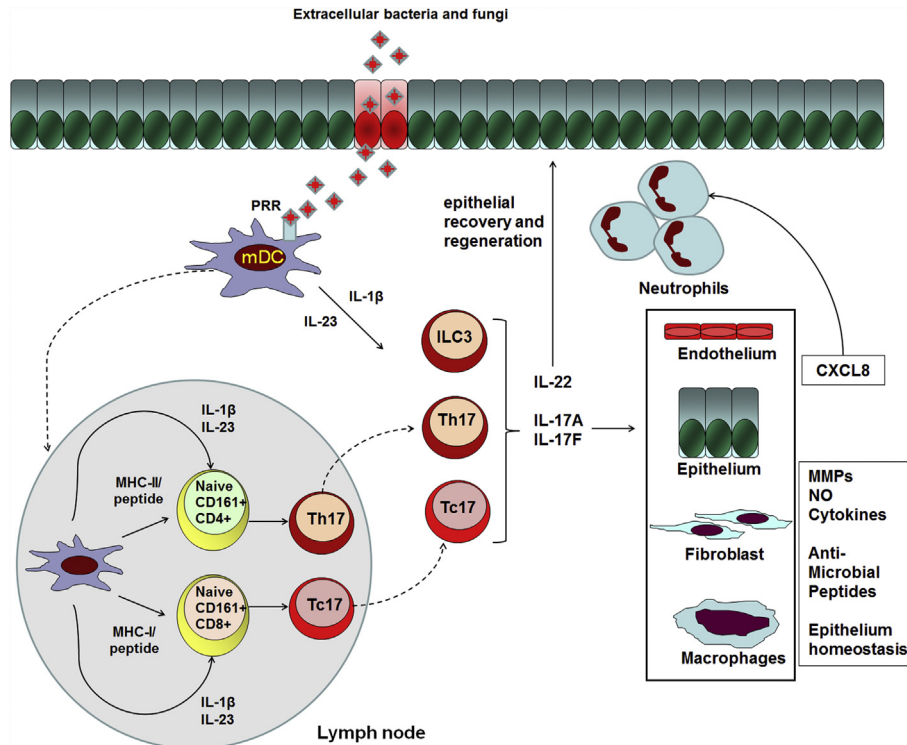


FIG 4. Cells, cytokines, and effectors of type 3 immunity. Extracellular bacteria and fungi induce myeloid dendritic cells (*mDC*) to produce IL-1 β and IL-23, which allow T_H17 or T_C17 development from naive $CD161^+$ T cells and trigger cytokine production by ILC3s. IL-17A, IL-17F, and IL-22 from ILC3s and T_H17 and T_C17 cells activate nonimmune and immune cells to produce matrix metalloproteinases (MMPs), nitric oxide (NO), cytokines, antimicrobial peptides, and the neutrophil recruiter CXCL8. IL-22, especially that produced by ILC3s, promotes epithelial proliferation and restrains the gut microflora. PRR, Pathogen recognition receptors.

activity of IL-1 β and IL-23.⁶⁴ More recent studies performed in mice have also shown the dispensability of TGF- β , as well as the essential role of IL-1 β and IL-23, in the orchestration of T_H17 cell differentiation.^{65,66} Murine T_H17 cells express neither T-bet nor GATA-3, but they express ROR γ t, which is a hallmark transcription factor for T_H17 cells.⁶⁷ *RORC* is also expressed in human T_H17 cells.⁶⁷

Another transcription factor important for both murine and human T_H17 differentiation is STAT3. Deletion of STAT3 in murine T cells abrogates T_H17 differentiation, whereas retroviral overexpression of constitutively active STAT3 is sufficient to induce IL-17 production.⁶⁸ The requirement for STAT3 in human subjects was unraveled in patients with hyper-IgE syndrome, a primary immunodeficiency disorder caused by dominant negative mutations of STAT3 and severely impaired production of T_H17 cells, which might explain the inability of these patients to clear some bacterial and fungal infections.⁶⁹ Human T_H17 cells express the chemokine receptors CCR6 and CCR4.^{6,7} Most T_H17 cells express CCR6, but not CXCR3, whereas most T_H1 cells express CXCR3, but not CCR6, and thus CCR6 in the absence of CXCR3 expression appears to be a marker of the human memory T_H17 phenotype.^{6,7} CCR6 expression is not restricted to human memory T_H17 cells but is also present in their UCB and thymic precursors,⁶⁴ suggesting that when it is expressed in combination with *RORC*, IL-23R, CD161, and IL-4–induced gene 1 (*IL4I1*; see below), CCR6 acts as a specific marker of the T_H17 cell lineage and its expression is also *RORC* dependent. One of the peculiar features of T_H17 cells in comparison with T_H1 and T_H2 cells is

their rarity at sites of inflammation. The first reason for this rarity is the existence of self-regulatory mechanisms that limit their expansion. There are at least 2 different self-regulatory mechanisms that limit human T_H17 cell expansion: (1) the poor ability to produce IL-2 in response to T-cell receptor signaling⁷⁰ and (2) the reduced capacity to enter into the cell cycle.⁷¹ Both these events are related to the *RORC*-dependent abnormally high expression in T_H17 cells of *IL4I1*.^{70,71} The other important reason for explaining the rarity of T_H17 cells in the inflammatory sites is their high plasticity, which allows these cells to produce IFN- γ and then rapidly shift to the T_H1 phenotype. The first demonstration of T_H17 cells shifting to T_H1 cells was provided by the demonstration that T cells derived from the inflamed mucosa of patients with Crohn disease contained remarkable proportions of $CD4^+$ T cells producing both IL-17 and IFN- γ , which were named T_H17/T_H1 cells.⁷ Of note, T_H17/T_H1 cells were found to originate from T_H17 cells on their culturing *in vitro* in the presence of IL-12⁷ or even TNF.⁷² We have recently defined T_H17 -derived T_H1 cells as nonclassic to distinguish them from classic T_H1 cells, and we have also identified the main differences between the 2 cell types.⁷³

CD8⁺ T_C17 cells

The existence of $CD8^+$ T_C17 cells was first described in mice with combined deficiency of the *T-bet* and *Eomes* genes. Under these conditions, mice showed extended neutrophil infiltration and exhibited the presence of a number of antigen-specific T cells

that produced IL-17A, IL-21, and IL-22 and expressed ROR γ t.⁷⁴ In a subsequent study it was found that in wild-type mice virtually all T_C17 cells showed the ability to produce IFN- γ in addition to IL-17, exhibited a dramatic ROR γ t upregulation and a slight decrease in T-bet expression, and also lacked cytolytic activity because of significantly decreased levels of both perforin and granzyme B in comparison with that seen in T_C1 cells. STAT3 activation was required for T_C17 polarization. Finally, T_C17 cells displayed a surface phenotype distinct from T_C1 cells with regard to the expression of the IL-18 receptor, CD45RB, CD38, CD103, and CCR6, but these differences did not allow any true discrimination between the 2 subsets. A strong plasticity of T_C17 to T_C1 cells was also observed.⁷⁵ The frequency of human PB T_C17 cells was found to be even smaller than that of T_H17 cells. Human T_C17 cells were CD27⁺CD28⁺CD45RA⁻ or CD27⁻CD28⁺CD45RA⁻. About 70% of these cells produced IFN- γ in addition to IL-17. They expressed CCR6 but differed from human T_H17 cells because of the high expression of CCR5 but not CCR4. Human T_C17 cells were found to originate *in vitro* from naive CD8⁺ T cells after stimulation with anti-CD3/anti-CD28 antibody in the presence of a cocktail of cytokines, such as IL-1 β , IL-6, IL-23, and TGF- β .⁸ Of note, however, even human T_C17 cells were found to originate from CD161⁺CD8⁺ precursors,⁷⁶ and CD161⁺ T_C17 cells appeared to be pathogenic in patients with MS.⁷⁷

Group 3 ILCs

Group 3 ILCs or ILC3s are characterized by the expression of the transcription factor ROR γ t, which is critical for their development and function.^{9,78} In addition, they express IL-7R, IL-17, and IL-22 and a number of TNF family members, such as LT α 1 β 2.⁹ ROR γ t⁺ ILC3s appearing during embryogenesis correspond to the previously described lymphoid tissue inducer cells and are strictly required for the prenatal development of lymph nodes and Peyer patches.^{9,78} ROR γ t⁺ ILC3s are also present in small percentages after birth in human subjects and mice mainly at mucosal surfaces (Fig 1)^{9,25,26} and can be dissected into CCR6⁺ ILC3s (preferentially expressing CD4, IL-17, and IL-22) and CCR6⁻ ILC3s, which mainly produce IL-22.²⁵ Among CCR6⁻ ILC3s, a particular subset expresses the natural cytotoxicity receptor NKp46 and produces not only IL-22 but also some IFN- γ .^{9,25} In addition to their expression and dependence on ROR γ t, CCR6⁻ ILC3s also express and require the transcription factor T-bet, which is important for the differentiation toward NKp46⁺ ILC3s.²⁵ Similar to their mouse counterpart, human ILC3s are characterized by expression of ROR γ t, IL-7R, LT α 1 β 2, and IL-22 (and to a lower extent IL-17). Human ILC3s are present both during fetal development and after birth in small percentages not only in the gut lamina propria but also in the tonsils, from where they have been best characterized.^{9,26,33-35}

Mouse and human ILC3s differ in some characteristics. In human subjects tonsil ILC3s homogeneously express CCR6 and lack CD4. Tonsil ILC3s can be dissected according to the expression of NKp44 and CD56, which are not present in the mouse.³³⁻³⁵ Moreover, although mouse IL-22 is preferentially expressed by NKp46⁻ ILC3s,²⁵ human IL-22 expression is strictly confined to NKp44⁺ ILC3 subsets (especially CD56⁺), which basically coexpress NKp46.^{26,35} Finally, in contrast to the NKp46⁺ ROR γ t⁺ mouse ILC3 subset, T-bet is not expressed *ex vivo* by tonsil-derived ILC3s, although plasticity of ILC3s has

been reported both in mice and human subjects.^{25,26} In addition to the cytokines mentioned, human tonsil ILC3s have also been shown to express IL-26, GM-CSF, TNF, CCL20, and IL-2. Cytokine production by mouse and human ILC3s can be mainly elicited by stimulation through IL-1, IL-23, and IL-7 and in human subjects also by engagement of the activating receptor NKp44.^{9,26,33-35} Markers of murine and human group 3 ILC subsets are shown in Table I.

Type 3 cell-mediated effector immunity in protection and immunopathology

The main protective role of type 17 immunity is against extracellular bacteria and fungi because of the ability of IL-17 to promote neutrophil and MP recruitment in tissues and to induce antimicrobial peptide production by epithelial cells.⁷⁹ In animal models of infection, IL-17-deficient mice have been shown to be highly susceptible to bacteria and fungi, including *Klebsiella pneumoniae*, *Staphylococcus aureus*, and *Candida albicans*.⁵⁸ Definitive proof for the protective activity of type 17 immunity against extracellular bacteria and fungi comes from the following observations: (1) patients with autosomal dominant hyper-IgE syndrome who are highly susceptible to staphylococcal and fungal infections have STAT3 mutations and impaired T_H17 cell development⁶⁹; (2) IL-17 receptor deficiency was linked to *Candida* species infection⁶⁹; (3) autosomal recessive mutation of caspase recruitment domain family, member 9 (CARD9), an adaptor molecule that drives IL-17 immunity, confers susceptibility to *Candida* species infection⁶⁹; (4) gain-of-function mutations in STAT1, which strongly inhibit the development of IL-17-producing cells, were found in patients with chronic mucocutaneous candidiasis⁶⁹; and (5) in cases of chronic mucocutaneous candidiasis associated with autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy syndrome, IL-17-producing cells were competent, but the patients generated neutralizing antibodies to IL-17.⁶⁹

On the other hand, compelling experimental evidence has initially demonstrated that type 3 immunity plays a key role in the initiation and maintenance of several autoimmune diseases, such as RA, MS, insulin-dependent diabetes mellitus, uveitis, psoriasis, and IBD, suggesting that the role of type 1 immunity, which had been previously considered exclusively pathogenic, could even be protective in these disorders. However, subsequent studies have shown both overlapping and differential roles of T_H1- and T_H17-mediated immunity in tissue inflammation, which suggests the existence of a more complex relationship between them than has hitherto been suspected.

It is clear that there is both antagonism and cooperation between type 1 and type 3 immunity because the lack of type 1 cytokines appears to promote a response dominated by type 3 cytokines and *vice versa*.⁸⁰ More importantly, the early and persistent shifting of T_H17 (and also of T_C17) cells to the production of IFN- γ , a shift from type 3 to type 1 immunity, begs the question of the real nature of T_H1 (and T_C1) cells at inflammatory sites. ILC3s might also participate in the complex regulation of autoimmune diseases, in particular psoriasis and IBD. IL-22 and IL-17 from ILC3s are sufficient to induce psoriasis in mouse models, whereas T cells are necessary to maintain the inflammation.⁸¹ Moreover, because of their ability to modulate epithelial cell functions and restrain commensal bacteria and pathogens, ILC3s display a dual role in the pathogenesis of IBD. Although

innate IL-22 plays a protective role in IBD models,⁵⁹ expression of IL-17 and IFN- γ from ILC3s has been implied to drive inflammation in innate IBD models, such as anti-CD40 or *Helicobacter hepaticus*-induced colitis.²⁵ Along this line, IL-17 expression by ILC3s was also found to be increased in the guts of patients with Crohn disease.⁸²

CONCLUDING REMARKS

The immune system has evolved a series of different mechanisms of response to protect the host against a great variety of potentially offending pathogens. However, with regard to the role of innate and adaptive cell-mediated immunity, 3 major types can be identified, which we propose to define as type 1, type 2, and type 3 immunity. The observation that within each type of response the T_H/T_C cells and ILCs share transcription factor and effector cytokine expression suggests that these 3 types of immunologic programs are indispensable and optimized to cope with different types of pathogen challenges. However, the distinct activation signals, tissue location, action timing, and polarizing signals during an immune response imply that T cells and ILCs do not play completely redundant roles. In the next years, it will be challenging to elucidate the precise contribution of the innate versus adaptive arms of cell-mediated effector immunity in protection against distinct pathogens and pathogenesis of inflammatory diseases.

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