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

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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 γt$^+$ 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*

Abbreviations used

APC: Antigen-presenting cell
CRTH2: Chemoattractant receptor-homologous molecule expressed on T_H2 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

In 1986, Mosmann et al[1] 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, 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

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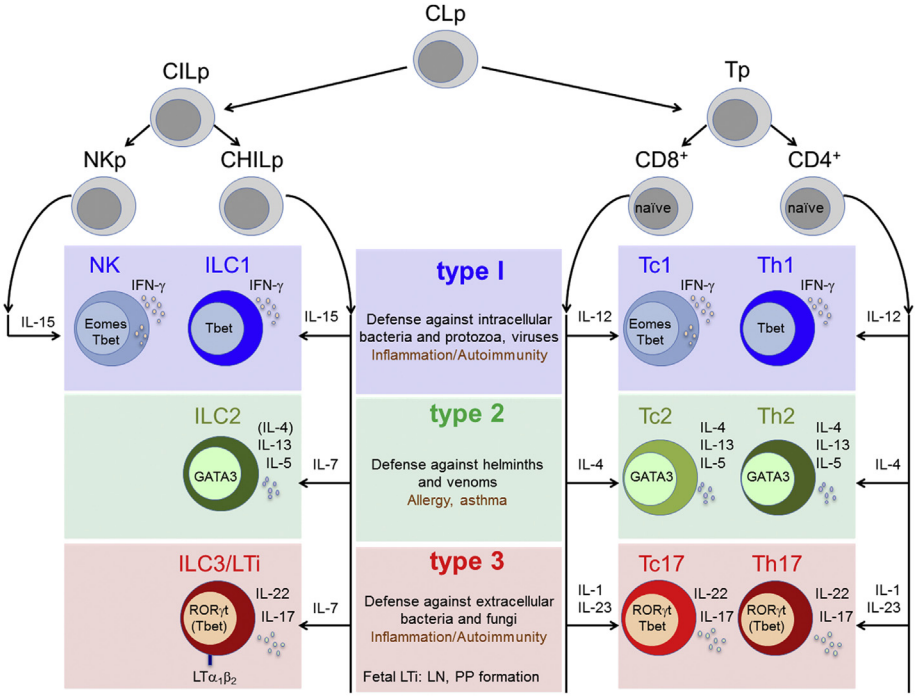

FIG 1. The 3 major types of innate and adaptive cell-mediated effector immunity. Type 1 immunity is composed of T-bet$^+$ IFN-γ–producing CD4$^+$ T_H1 cells and ILC1s and T-bet$^+$Eomes$^+$CD8$^+$ T_C1 and NK cells. Type 2 immunity is composed of GATA-3$^+$CD4$^+$ T_H2 cells, CD8$^+$ T_C2 cells, and ILC2s, which produce IL-4, IL-5, and IL-13. Type 3 immunity is composed of RORγt *(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 mice[1] 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]