Th2 and iTreg cells and also have some contribution to 5hmC modification in Th1 and Th17 cells. The importance of 5mC oxidation in promoting cytokine production might be underestimated by Ichiyama et al. in their study. Experiments using Tet2 and Tet3 doubly deficient cells and/or mice might give the answers to these unsolved important questions.

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NF-κB Regulation by NLRs: T Cells Join the Club

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NLRP12 is an innate immune receptor whose regulation of NF-κB signaling in myeloid cells is critical in preventing multiple auto-inflammatory diseases. In this issue of *Immunity*, Lukens et al. (2015) show that a similar NLRP12-mediated mechanism is functionally important in T cells.

Nucleotide-binding domain and leucine-rich repeat containing receptors (NLRs) are a class of intracellular pattern recognition receptors (PRRs) of the innate immune system whose functions appear to be multifaceted. Whereas other classes of PRRs, such as Toll-like receptors (TLRs) and RIG-I-like receptors (RLRs), primarily detect microbial ligands that are indicative of a pathogenic insult, NLRs seem to be involved in a wider variety of cellular functions, including microbial recognition, but also the surveillance of cellular integrity and the regulation of intracellular signaling pathways. Most NLRs with known functions can be grossly categorized into two groups. The first one is capable, upon triggering by a multitude of exogenous and endogenous stimuli, of assembling a multi-protein complex called the inflammasome, which functions to recruit and activate caspase-1, leading to the cleavage and activation of pro-interleukin-1β (IL-1β) and IL-18 into their secreted forms (Henao-Mejia et al., 2014). The second group regulates the canonical and non-canonical arms of NF-κB signaling, a pivotal immune-modulatory intracellular pathway. One prominent member of the latter class of NLRs is NLRP12, originally described in overexpression assays as a negative regulator of NF-κB-induced cytokine production, when NLRP12 was still called PYPAF7 or Monarch-1 (Wang et al., 2002). With the generation of *Nlrp12*$^{-/-}$ mice came the realization that this NLR and its downstream control of NF-κB are critical to prevent a multitude of immune-mediated or -modulated diseases, including allergic contact hypersensitivity (Arthur et al., 2010), colitis, and colorectal cancer (Allen et al., 2012; Zaki et al., 2011).

As diverse as the cellular functions of NLRs are the cell types in which they operate. Originally discovered to be mainly expressed and operational in myeloid cells, the spectrum of tissues and cell types in which NLRs are at play has recently been expanded to other cells of the immune system and eventually even to non-hematopoietic cells (Elinav et al., 2011). In this issue of *Immunity*, Lukens et al. (2015) have shown that this expanded cellular diversity also holds true in regard to NLRP12. Early reports show that NLRP12 plays a prominent role in mononuclear phagocytes, where it regulates NF-κB-induced pro-inflammatory cytokine production to inhibit auto-inflammation (Allen et al., 2012; Arthur et al., 2010; Zaki et al., 2011). Lukens et al. (2015) have now demonstrated that the expression and function of NLRP12 is not limited to the myeloid system. By using a series of expression studies, adoptive transfers, and bone marrow chimera experiments, Lukens et al. (2015) have found a T cell-intrinsic role for NLRP12 in regulating NF-κB signaling and pro-inflammatory cytokine production. Phenotypically, the absence of NLRP12 in T cells manifested in higher expression of activation markers, enhanced cell proliferation, and elevated

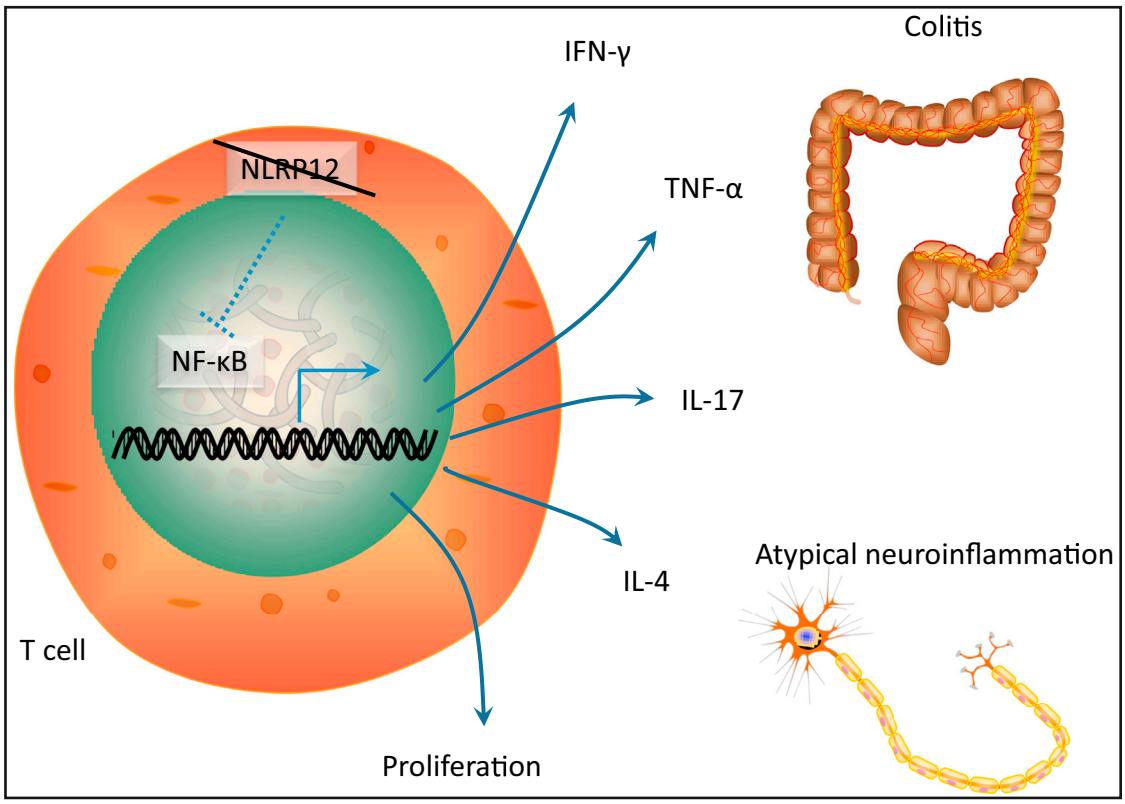

Figure 1. NLRP12 Regulates NF-κB and Cytokine Responses in T Cells
Lukens et al. (2015) demonstrate that absence of NLRP12 leads to enhanced NF-κB signaling, hyperproliferation, and elevated cytokine secretion in T cells. This results in the manifestation of auto-inflammatory disorders, including colitis, and in atypical experimental autoimmune encephalomyelitis (EAE).

secretion of cytokines involved in type I immunity (e.g., IFN-γ), type II immunity (IL-4), and type III immunity (IL-17). As a consequence, mice adoptively transferred with NLRP12-deficient T cells developed enhanced inflammatory symptoms in disease models classically associated with pro-inflammatory T cells, including colitis and atopic dermatitis. Surprisingly, in another prototypically T cell-driven disease model, experimental autoimmune encephalomyelitis (EAE, the mouse model for multiple sclerosis), NLRP12 deficiency led to ameliorated, rather than enhanced, disease severity. Interestingly, Lukens et al. (2015) noted increased ataxia and loss of balance in *Nlrp12*$^{-/-}$ mice in this model, indicative of the development of atypical EAE. This NLPR12-dependent switch from classical to atypical EAE was mediated by IL-4, and when Lukens et al. (2015) blocked IL-4 in *Nlrp12*$^{-/-}$ mice, autoimmunity persisted but the neurological phenotype was reverted back to a more classical pathology (Figure 1).

The discovery of a T cell-intrinsic role of a PRR is not without precedent. Despite the fact that T cells are not classically considered to be pathogen-sensing cells, they express a variety of PRRs that are functionally involved in the regulation of immune responses. For instance, T cell-intrinsic expression of TLR2 maintains intestinal homeostasis by integrating signals derived from the intestinal microbiota (Round et al., 2011). Like other PRRs, NLRP12 might be potentially involved in T cell sensing of endogenous or exogenous signals. Of note, in myeloid cells, NLRP12 has been implicated in the sensing of the intracellular pathogen *Yersinia pestis*, the causative agent of plague (Vladimer et al., 2012). Whether T cells are able to sense these or other ligands through NLRP12, and whether such microbial or damage-related recognition is involved in NLRP12-mediated regulation of NF-κB and with initiation and propagation of inflammatory responses, remains to be unraveled in future studies.

These remaining questions notwithstanding, the study by Lukens et al. (2015) represents an important step toward better mechanistic understanding of T cell-driven auto-inflammatory disease. Missense mutations in NLRP12 cause hereditary periodic fever syndromes in humans (Jéru et al., 2008), and the finding by Lukens et al. (2015) now calls for the systematic investigation of whether dysregulation of T cell cytokine signaling is causally involved in the development of inflammatory symptoms in patients with mutated NLRP12. Furthermore, the study represents an exciting starting point for further mechanistic elucidation of conceptually important questions related to the roles of NLRs in cell-intrinsic innate instruction of adoptive immunity. For instance, which subsets of T cells express NLRP12? Is the cytokine dysregulation specific to a particular set of T helper (Th) cells? Is subset-specific NLRP12 activity in Th1, Th2, and Th17 cell lineages differentially regulated in different disease settings? Answering these questions will be instrumental to understanding the pathogenesis of NLRP12-mediated inflammatory disorders. Overall, the versatile functions of NLRs and their often unexpected cellular

distributions do not cease to surprise the scientific community, and it is plausible that more cell types and functions are soon to be joining the club.

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tEMPting Fate MaYBe the Solution

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In the present issue of *Immunity*, Hoeffel et al. (2015) reconcile a controversy by demonstrating that a distinct wave of yolk-sac-derived erythro-myeloid progenitors (EMPs) differentiate to fetal monocytes in the liver and further to adult macrophages in the majority of tissues.

Macrophages are evolutionarily ancient innate immune cells that are found in most tissues and organs and whose functions are highly specialized to their specific environments. It has been generally accepted that the majority of tissue-resident macrophage subsets originate during fetal hematopoiesis and are thereafter maintained by local self-renewal with minimal contribution of bone marrow (BM)-derived progenitors. However, the hemogenic site of origin within the embryo has remained a matter of intense debate, with controversial experimental evidence supporting both fetal liver-derived and yolk-sac (YS)-derived progenitors. In this issue of *Immunity*, Hoeffel et al. (2015) show that the majority of hematopoietic stem cell (HSC)-independent tissue-resident macrophages originate from fetal monocytes, which arise from a transient wave of YS-derived erythro-myeloid progenitors (EMPs) that colonize the fetal liver.

For the past 4 decades, it has been widely accepted that blood monocytes derived from BM hematopoietic stem cells (HSCs) differentiate to macrophages upon tissue entry. However, over the past 4 years, a torrent of reports has overturned this dogma. These reports have unequivocally demonstrated an embryonic origin for the vast majority of tissue-resident macrophages, which thereafter are maintained largely independently of adult HSC-dependent hematopoiesis. Exceptions include intestinal and dermal macrophages that are mainly BM monocyte derived (Ginhoux and Jung, 2014). Fetal hematopoiesis occurs in distinct "waves," but their differential contributions to embryonic and adult macrophage populations and the identity of precursors has remained poorly characterized. In the last trimester before the emergence of mature tissue macrophages, fetal organs contain two potential myeloid progenitor populations, F4/80^{hi}CD11b^{lo} primitive macrophages and F4/80^{int} CD11b^{hi} fetal monocytes, which are proposed to arise from the YS and fetal liver, respectively (Schulz et al., 2012). Opinions differ on the question of which of the two are the precursors of the mature tissue resident macrophages. Using fate-mapping, recent reports conclude that tissue macrophages are predominantly of fetal monocyte origin (Epelman et al., 2014; Hoeffel et al., 2012), with the exception of microglia that derive from early brain-seeding YS-derived primitive macrophages (Ginhoux et al., 2010). Consistently, adoptive cell transfer studies reveal a bona fide alveolar macrophage progenitor potential of fetal monocytes (Guilliams et al., 2013; Schneider et al., 2014). However, Geissmann and colleagues have provided a strong argument that tissue macrophages are derived from primitive YS-derived macrophages, based on the presence of F4/80^{hi}CD11b^{lo} macrophages in skin, spleen, pancreas, kidney,