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 autoimmune inflammatory diseases. In this issue of Immunity, Lukens et al. (2015) show that a similar NLRP12-mediated function is important in T cells.

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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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 whether such microbial or damage-related recognition is involved in NLPR12-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 (Jérusalem 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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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, F4/80CD11b<sup>+</sup> primitive macrophages and F4/80<sup>int</sup>CD11b<sup>+</sup> 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<sup>int</sup>CD11b<sup>+</sup> macrophages in skin, spleen, pancreas, kidney,