Effective immune responses to pathogens require the activation and differentiation of both innate and adaptive lymphocytes, such as innate lymphoid cells (ILCs) and T cells, respectively. ILCs consist of distinct helper-like subsets representing innate versions of CD4+ T helper subsets, whereas natural killer cells represent the innate counterpart of CD8+ cytotoxic T cells. By producing effector cytokines, T helper subsets and helper-like ILCs are also involved in the pathogenesis of many inflammatory diseases. Strikingly, the development of ILCs and T cells seems to depend on a shared transcriptional network. For example, GATA3 and Tcf7, which play essential roles during T cell development, are also indispensable for the development of multiple ILC subsets. Bcl11b is another critical component of a T cell lineage fate-specifying transcriptional network. In this issue, Yu et al. and Walker et al. independently describe the role of Bcl11b in specifying ILC2 development.

One would have expected that, similar to GATA3 and Tcf7, Bcl11b would be critical for the development of multiple ILC lineages. However, the two papers in this issue report that Bcl11b appears to be essential for ILC2 development only. Consequently, Bcl11b deficiency leads to impaired immune responses to either papain treatment, influenza virus infection (Yu et al.), or *Nippostrongylus brasiliensis* helminth infection, without affecting the ability of mice to clear bacterial *Citrobacter rodentium* infection (Walker et al.). The authors show that Bcl11b is expressed in mature ILC2s as well as in a subset of Id2+ common helper-like innate lymphoid progenitors (ChILPs); Walker et al. but not Yu et al. also show that a proportion of other mature ILC subsets, such as CCR6+ ILC3s, express Bcl11b. The discrepancy in Bcl11b expression by mature ILC3s between these two studies has not been resolved. Nevertheless, the Bcl11b-expressing ChILPs only give rise to ILC2s but not other ILCs, suggesting that the previously identified ChILPs contain a mixture of distinct committed ILC progenitors. This is consistent with another report in *Nature* suggesting that within the ChILP compartment, the PLZF+ progenitors are largely committed to specific ILC subsets and fail to generate lymphoid tissue inducers, which represent another subset of ChILP-derived ILCs.

Both reports also show that Bcl11b-expressing ILC2 progenitors express high levels of GATA3. However, other studies have reported that GATA3hi progenitors also give rise to other ILCs. In addition, GATA3 is constantly required for the maintenance of ILC2s, whereas inducible deletion of Bcl11b in mature ILC2s does not result in loss of functional ILC2s. Thus, Bcl11b either functions independently of GATA3 or collaborates with GATA3 during ILC2 development, but the detailed mechanism requires further investigation. Moreover, it is not known whether Bcl11b is critical for ILC2 development in humans.

It is intriguing that Bcl11b, which is critical for the development of all T cell subsets, appears to be dispensable for the development of ILC1s and ILC3s. Does this mean that T cells have preferentially adopted the ILC2 transcriptional program during their early development in the thymus? If so, one would predict that T cell progenitors, particularly CD4+ CD8hi thymocytes, might display certain features of ILC2s. This idea is consistent with the notion that T cells carry an endogenous Th2-prone program that makes Th2 lymphocyte differentiation a default cellular fate.

The studies of Yu et al. and Walker et al. not only identify Bcl11b as an ILC2 lineage-specifying factor, they also provide important general insights into the mechanisms of ILC development. Furthermore, this work raises the possibility that dysregulation of Bcl11b in ILC progenitors may contribute to human diseases involving ILC2 function.

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Chao Zhong and Jinfang Zhu; National Institute of Allergy and Infectious Diseases, National Institutes of Health: fjzhu@niaid.nih.gov
Inflammation on the move

Inflammation is a major cause of morbidity, as illustrated by debilitating conditions such as rheumatoid arthritis and inflammatory bowel diseases. IL-1β and TNF are key mediators of inflammation, and agents that neutralize their effects have provided relief for millions of patients, but we may have yet more to discover about inflammation.

In this issue, Kim et al. show that mice with a hypomorphic mutation of Wdr1 (i.e., a mutation that results in underproduction of an otherwise normal product) develop inflammation caused by IL-18.

This is interesting for several reasons. To the cell biologist, Wdr1 is a protein that interacts with filamentous actin. It is the murine homologue of human actin-interacting protein 1 (AIP1). The dynamics of cellular actin is crucial in cell biology and underlies fundamental cellular functions such as cell division, movement, and phagocytosis. Actin oscillates between filamentous actin and soluble actin. Cofilin binds...
filamentous actin and severs the filaments, causing these to dissemble, yielding soluble actin. Wdr1 in mice and AIP1 in humans bind the coflin/filamentous actin complex and energize coflin’s ability to sever the filaments. Null mutations of Wdr1 are embryonic lethal; mice with hypomorphic mutations of Wdr1 are viable but have thrombocytopenia and their neutrophils have crawling defects. These mice also develop autoinflammation.

The inflammasome is to immunologists what actin is to cell biologists. Intracellular sensors, such as the NOD-like receptors (NLRs) and the absent in melanoma 2 (AIM2)–like receptors (ALRs), sense damage or danger signals and recruit ASC (apoptosis-associated speck-like protein containing a caspase recruitment domain). In this complex, ASC generates caspase-1 by proteolytic cleavage of procaspase-1. Caspase-1 in turn cleaves pro–IL-1β and pro–IL-18, generating the potent proinflammatory cytokines IL-1β and IL-18 that are secreted from the cell.

Kim et al. report on a significant amount of work involving a comprehensive analysis of this novel mouse model. They show that myeloid cells from hypomorphic Wdr1 mutants have more filamentous actin than wild-type mice with spontaneous activation of ASC and caspase-1; the cells generate huge amounts of IL-1β and IL-18 as expected. This points to a critical role for actin dynamics in controlling the inflammasome. Surprisingly, the mice suffer inflammation of cartilage tissue rather than a generalized inflammation, and the inflammation is caused not by the elevated IL-1β but by IL-18. Furthermore, monocytes and not macrophages, neutrophils, or dendritic cells are responsible for the production of IL-18. The authors observed massive infiltration of neutrophils, but it was monocytes that migrated to the tissue, produced IL-18 locally, and initiated the inflammation.

This study provides a cellular framework for understanding the role of IL-18 in inflammation. This is a novel and intriguing paper that implicates the actin-depolymerizing cofactor Wdr1 in the regulation of the pyrin inflammasome and IL-18 production by monocytes. These results add to the growing literature on the role of actin polymerization in inflammation and may have translational implications for the therapy of patients with autoinflammatory conditions.


Niels Borregaard, University of Copenhagen: borregaard@rh.dk

Augmenting NF-κB in poor-risk CLL: A general paradigm for other cancers?

Chronic lymphocytic leukemia (CLL) is a chronic lymphoproliferative disorder of B lymphocytes. It has an extremely variable clinical course. Some patients have a rather indolent course, whereas others are known to have a rapidly progressive disease. Most patients die from causes related to CLL that can be due to bone marrow failure, infection, or transformation to a high-grade lymphoma. Clinical stratification of CLL has revealed that a subset of patients with poor prognosis harbor cytogenetic alterations and lack mutations at the immunoglobulin locus. Therefore, the development of additional molecular biomarkers for patients at high risk for early lethality from CLL could help direct their care toward enrollment in clinical trials of promising experimental approaches such as inhibitors of BCL2 or BCR signaling or CD19 chimeric antigen receptor T cells (which have been shown to eradicate CLL in patients who have failed other approaches). In this issue, Mansouri et al. report that somatic mutations in the NFKBIE gene occur in 7% of poor prognosis patients, and this may be a common mechanism contributing to disease progression by sustaining the survival of malignant CLL cells.
The NF-κB pathway is ubiquitously activated in CLL cells by cell surface receptor signaling cascades through the B cell receptor and Toll-like receptors, so this identification of additional mutational events that reinforce NF-κB signaling appeared biochemically redundant. *NFKBIE* encodes the IκBε protein, a potent and seemingly stoichiometric inhibitor of the IκB kinase (IKK) in CLL cells as demonstrated by Mansouri et al. Surprisingly, even partial depletion of *NFKBIE* with RNA interference in cell culture was sufficient to activate IKK and promote NF-κB transcriptional activation, consistent with the findings that the *NFKBIE* mutations are heterozygous in CLL samples and that these samples had modest increases in NF-κB signaling. Whether the most recurrent *NFKBIE* mutation identified in this work (a 4-bp deletion in exon 1 that resulted in a frame shift and potentially expressed truncated protein) has neomorphic oncogenic functions besides the inability to inhibit IKK remains unknown.

More broadly, the finding of heterozygous *NFKBIE* mutations as a marker of poor prognosis raises the possibility that similar mutations or heterozygous loss of *NFKBIE* caused by genetic deletion or epigenetic silencing may also further sculpt NF-κB signaling and thereby promote the progression of more common malignancies. Unfortunately, most of the publicly available tumor genomes include a significant amount of contaminating normal cells, and therefore haploid loss of *NFKBIE* may not be appreciated. Single nuclei sequencing of neoplastic cells isolated freshly from tumors will address this and other issues of potential haploidy in cancer by unambiguously determining the cancer genome and concurrent genetic events. For CLL patients, the finding of the *NFKBIE* mutations in high-risk patients refocuses our attention on developing NF-κB inhibitors to use in tandem with other approaches and for considering experimental clinical trials for such patients.


David Tuveson, Cancer Center at Cold Spring Harbor Laboratory: dtuveson@cshl.edu
Kanti R. Rai; Feinstein Institute for Medical Research, North Shore-LIJ Health System: krai@nshs.edu