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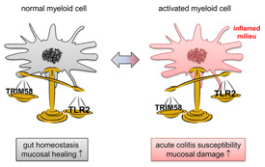
Trim58 Trims TLR2 in Colitis

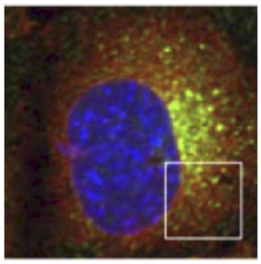


Inflammatory bowel disease has been associated with aberrant TLR signaling. In order to discover proteins that may mediate TLR signaling, Eyking et al. (p. 1636) performed yeast two-hybrid screens and identified a novel interaction between TRIM58 and TLR2. The researchers demonstrated that TRIM58 overexpression resulted in a dose-dependent decrease in TLR2 expression and that the RING domain of TRIM58 is necessary for proteolytic degradation of TLR2. Following dextran sulfate sodium (DSS)-induced colitis, TRIM58-deficient mice (*Trim58*$^{-/-}$) showed an increase in TLR2 expression, IL-1β, and enhanced colitis scores. The increase in IL-1β production was abolished by deletion of *Tlr2* in *Trim58*$^{-/-}$ cells. To test the role of TRIM58 in myeloid cells, conditional knockout mice (*Trim58*$^{MC-/-}$) were created and showed rapid mucosal damage in response to DSS. However, these mice did not display delayed healing as seen in *Trim58*$^{-/-}$ mice, suggesting that Trim58-deficient myeloid cells contribute to early inflammation in the DSS-colitis model. Finally, TRIM58 mRNA levels in mucosal tissue samples from patients with ulcerative colitis were significantly reduced when compared with normal patient tissues, in which TRIM57 protein was consistently present. Thus, TRIM58 is important in maintaining control over aberrant TLR2 signaling in myeloid cells, and may represent a novel therapeutic target in inflammatory disorders.

Distinct Development of Fetal and Adult Vγ9Vδ2 T Cells

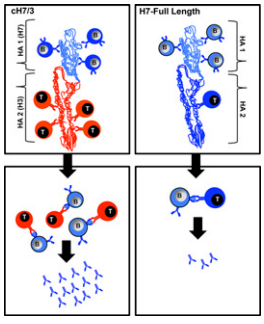
Phosphoantigen-reactive Vγ9Vδ2 T cells are the dominant population of γδ T cells in the circulation of human adults. Although it has been hypothesized that Vγ9Vδ2 T cells originate in the fetus and persist through adulthood via clonal expansion, scenarios involving postthymic output as a source of these cells have not been excluded. To track the lineage relationship of this cell subset, Papadopoulou et al. (p. 1468) analyzed the CDR3 repertoire of blood and thymus postnatal (birth until adult) and fetal Vγ9Vδ2 T cells. The adult blood Vγ9Vδ2 TCR repertoire had key features that were present in the postnatal, but not the fetal, thymus, including key features encoding for phosphoantigen reactivity. Additionally, expansion of fetal blood Vγ9Vδ2 T cells with a microbial-derived phosphoantigen did not result in an adult-like CDR3 repertoire, indicating that adult blood Vγ9Vδ2 T cells are not derived from fetal blood Vγ9Vδ2 T cells. Consistent with these observations, phosphoantigen reactivity was found to be present in the postnatal thymus and was further enhanced in vitro by the microbial phosphoantigen (E)-4-hydroxy-3-methyl-but-2-enyl phrophosphate (HMBPP). Finally, the authors demonstrated that the generation of fetal or adult Vγ9Vδ2 CDR3 repertoire was determined by the fetal and postnatal nature of the hematopoietic stem and precursor cells. Therefore, these data indicate that fetal blood Vγ9Vδ2 T cells originate in the fetal thymus, whereas adult blood T cells are generated independently after birth and are further selected in the periphery by microbial phosphoantigen exposure.

Recruiting STING to the ER



The endoplasmic reticulum (ER)-resident adaptor protein stimulator of IFN genes (STING) plays a central role in sensing cytoplasmic DNA. Once activated, STING translocates from the ER via the Golgi apparatus to perinuclear microsomes, where it facilitates induction of IFNs and proinflammatory cytokines. In this issue, Ran et al. (p. 1560) sought to elucidate mechanisms regulating this trafficking process. The authors identified YIPF5, an ER–Golgi transport protein, as a positive regulator of cyclic GMP-AMP synthase–STING-mediated type I IFN production. Specifically, the C-terminal transmembrane domain of YIPF5 was found to directly bind to STING, suggesting that membrane localization is important for this interaction. Additionally, YIPF5 was found to colocalize with SEC31A in the outer layer of the COPII coat of the ER membrane, thereby facilitating STING trafficking from the ER to the Golgi. Consistent with these observations, knockdown of COPII components, including SEC31A, inhibited induction of type I IFN in the presence of cytoplasmic dsDNA. Therefore, this study demonstrates that YIPF5 is essential for innate immunity to DNA viruses and facilitates COPII-dependent STING trafficking, observations that may be useful for developing strategies to modulate STING-related diseases.

Helping CD4 Memory in Avian Flu Vaccination



Historically, vaccination against avian influenza has not produced robust immunity. Because previous work suggested that poor Ab responses to avian influenza vaccines result from inadequate CD4$^+$ T cell help, DiPiazza et al. (p. 1502) devised a vaccine strategy to enhance CD4$^+$ T cell help using chimeric hemagglutinin (HA) proteins. Mice were primed with one of two commercially available seasonal

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flu vaccines to establish H3 HA-specific (i.e., seasonal immunity) $CD4^+$ T cell memory. Mice were then vaccinated with either a full length H7, avian influenza HA, or a chimeric HA protein (cH7/3) consisting of the H7 globular head and the H3-stem domain. H7-specific Ab titers were significantly increased in mice that had been primed with a seasonal vaccination and boosted with a cH7/3 vaccine. Consistent with these observations, the number of H7-specific germinal center B cells also increased in the animals primed with the seasonal vaccine, followed by the cH7/3 vaccine. Together, these data demonstrate that chimeric proteins can harness established $CD4^+$ T cell memory to enhance Ab responses to neoantigens. This vaccine strategy may be particularly useful during a pandemic, when time and resources are limited.

IL-33 during Early B Cell Development

Although IL-33 has been exclusively studied as an extracellular cytokine that binds the ST2 receptor on target cells, its N-terminal domain may also mediate nuclear localization and chromatin binding, suggesting an intracellular role as a transcriptional regulator. In this issue, Stier et al. (p. 1457) demonstrated exclusive expression of IL-33 in the nucleus of bone marrow (BM) resident progenitor B (pro-B) and large precursor B (LPB) cells. ST2 expression, however, was not detected at either the transcript or protein level in these populations. RNA sequencing analysis of pro-B and LPB cell populations within IL-33–deficient (*Il33*$^{-/-}$) mice revealed a unique IL-33–dependent transcriptional profile. When compared with wild-type populations, IL-33–deficient pro-B and LBP cells had an increase in targets of E2F transcription factors and genes involved in cellular proliferation, but a decrease in the p53-dependent pathways. These data suggest that IL-33 may attenuate fitness during early B cell development by decreasing proliferation or cell survival. Mixed BM chimeric mice showed that IL-33 deficiency increased the frequency of developing B cells via a cell-intrinsic mechanism starting at the pro-B cell stage. Finally, IL-33 was detected during early B cell development in human samples, and *Il33* mRNA expression was decreased in patients with B cell chronic lymphocytic leukemia. Together, these data demonstrate an important, cell-intrinsic role for IL-33 during early B cell development.