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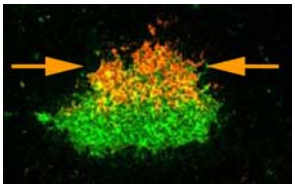
# In This Issue

## Antigen Independence!



Follicular dendritic cells (FDCs) are the workhorses of the germinal center (GC), persisting for long periods of time presenting Ags and providing costimulation. FDCs also arrange membrane-bound immune complexes (ICs) of T-dependent Ags at regular 200- to 500-Å intervals on their surface. Building on this, El Shikh et al. (p. 3482) investigated whether T cell-independent (TI) responses were produced by BCR cross-linking by the IC: T-dependent Ag on the FDC surface. They found that FDCs bearing OVA:IC produced a specific IgM response in anti-Thy1-pretreated nude mice within 48 h. Human and murine B cells cultured in vitro with the FDCs bearing OVA:IC had the same response. Importantly, when nude mice were immunized with OVA:IC they developed GL-$7^+$ GCs 48 h after immunization that contained Blimp-$1^+$ plasmablasts and FDC reticula with ICs. By comparison, FDCs that had unbound OVA showed no induction of GCs, IgM, or plasmablasts. The ability of FDC:ICs to produce TI IgM responses was inhibited by blocking FDC-FcγRIIB or by neutralizing the FDC-associated costimulatory molecules C4BP and BAFF. Thus, the authors provide the first report of how FDCs can produce T cell-independent responses to T cell-dependent Ags.

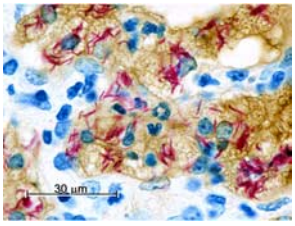
## It's All in How You Present It

The challenge in creating an effective immunotherapy against tumors is to direct a strong immune response specifically to tumor-associated Ags. However, a method to achieve this response is still undiscovered. Charni et al. (p. 3398) used the ability of NK cells, which play an important role in antitumor immunity by selectively killing some cancerous cells, to develop a new way of directing an antitumor response. Stable expression of a small hairpin RNA for ERK5 (shERK5) in human and murine leukemic cells decreased ERK5 levels and led to killing of leukemic cells in vivo. As shERK5 reduced ERK5 expression and thus MHC-I expression, the tumor cells became targets for the NK cells. As would be expected, activation of the ERK5 pathway caused induction of MHC-I expression. Coinjection of wild-type tumor cells with shERK5-expressing cells into the peritoneum reduced the survival of the wild-type cells. Prior injection of shERK5-expressing cells into mice diminished the ability of wild-type leukemic cells to develop in vivo. Taken together, these data demonstrate that shERK5 in leukemia cells can reduce the ability of these cells to express MHC-I, making them more effective targets for NK cell killing and potentially becoming a candidate for antitumor vaccines.

## Toll Signaling: Next Stop, Arachidonic Acid

Macrophages regulate many of their innate immune responses through the activation of TLRs. How cytokines are produced through TLR signaling has been well studied; however, the role of TLRs in arachidonic acid (AA) mobilization and eicosanoid production remains somewhat of a mystery. Building on their previous work, Ruipérez et al. (p. 3877) used multiple TLR agonists to determine how various phospholipase $A_2$ ($PLA_2$) isoforms cause macrophages to release AA. They found that TLR1/2, TLR2, TLR3, TLR4, TLR6/2, and TLR7 were able to mobilize AA by activating both cytosolic group $PLA_2$ ($cPLA_2$) and soluble $PLA_2$ ($sPLA_2$). Calcium-independent $PLA_2$ was not involved in this pathway. Blocking $sPLA_2$ group V through the use of inhibitors or RNA interference attenuated the AA mobilization activated through TLR1/2, TLR2, TLR3, and TLR4. This was accompanied by a corresponding reduction in ERK1/2 and $cPLA_2$ phosphorylation. Taken together, the data demonstrate that macrophages mobilize AA via TLR activation through a $cPLA_2$- and ERK1/2-dependent mechanism.

## Susceptible Genetics for Tuberculosis




Resistance to tuberculosis is exceptionally complex. However, in DBA/2J and C57BL/6J mice, four tuberculosis resistance loci (*Trl1-4*) are responsible for influencing susceptibility. Marquis et al. (p. 3757) created congenic mice, D2.B6/Chr7 and D2.B6/Chr19, which have the B6 resistant portions of chromosome 7 and 19 on the DBA/2J background. The *Trl3* locus and *Trl4* locus are on the portions used of chromosomes 7 and 19, respectively. D2.B6/Chr7 mice, which contain B6-derived *Trl3*, were more resistant to tuberculosis infection than wild-type D2 mice. Resistance was measured by the reduced presence of tuberculosis replication and by host survival. Transfer of the B6-derived Chr.19 *Trl4* portion did not confer resistance, nor did it improve or affect the resistance acquired by mice that carried B6-derived *Trl3*. Importantly, the resistance conferred by *Trl3* was not due to an increase in T cell effector responses but was caused by an increase in the ability of macrophages to kill mycobacteria. This bacterial control was independent of NO synthase 2. Gene expression analysis identified a number of differentially regulated genes that correlated with *Mycobacterium tuberculosis* infection and are found in the *Trl3* interval. Thus, the authors have identified a potential starting point for the investigation of specific candidate genes within the *Trl3* locus that could lead to tuberculosis resistance.



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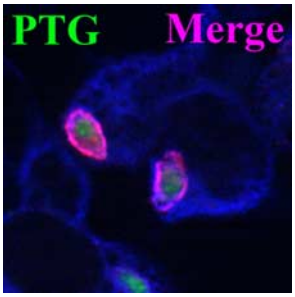
## Parasite Evasion




The parasite *Toxoplasma gondii* is an obligate intracellular parasite that is infectious and causes disease in a number of mammalian species. Although most healthy individuals remain asymptomatic, immunocompromised hosts such as HIV-positive individuals and pregnant women can develop severe, even fatal, disease. In the infected macrophage, *T. gondii* parasites must maintain the intracellular vacuole in which they reside and evade killing by antimicrobial molecules such as NO produced by inducible nitric oxide synthase (iNOS). Zhao et al. (p. 3775) have shown that both iNOS and the immunity-related GTPase (IRG) family member Irgm3 are necessary for in vivo primed macrophages to control *T. gondii* replication and disrupt the parasites' intracellular vacuole. Virulent type I *T. gondii* can evade the effects of IRG-mediated vacuolar disruption, but replication of this strain can still be controlled by iNOS. The mechanism of virulent parasite evasion is related to the differential association of the IRG proteins Irga6 and Irgb6 to the membrane of the vacuole. A previously identified virulence determinant from type I *T. gondii* was expressed in an avirulent strain of the parasite but did not confer the same ability to evade vacuolar destruction. Thus, the authors have determined a new mechanism by which virulent *T. gondii* controls its survival in the host.

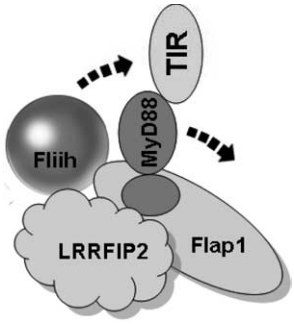
## Size Matters

Chitin, the second most abundant natural polysaccharide, is an important component of fungi and parasitic nematodes as well as other organisms. Thus, understanding how the immune system responds to this ubiquitous molecule is of great interest. Da Silva et al. (p. 3573) hypothesized that chitin regulated innate immunity by the function of the molecule's size. To test this hypothesis, the authors tested the effects of variously sized chitins on murine macrophages isolated from the peritoneum or bronchoalveolar tissue. Large pieces of chitin (70–100 $\mu$m) did not elicit a TNF response from these macrophages and were deemed to be inert in this context. By comparison, intermediately sized chitin (IC; 40–70 $\mu$m) and small chitin (SC; $<$40 $\mu$m) stimulated a TNF response in macrophages, and SC caused IL-10 protein secretion. The IC and SC used somewhat different receptor pathways to induce their signaling effects. IC involved the TLR 2 and dectin-1 to mediate NF-$\kappa$B signaling. However, the effects of SC were mediated by TLR2-dependent and -independent pathways, as well as dectin-1. The mannose receptor and Syk kinase were also involved in the signaling events stimulated by SC. Thus, this ubiquitous polysaccharide influences cell cytokine production through a variety of receptors and molecules, with the size of the chitin determining which pathway is used.

## Granulomas Need Costimulation Too

Despite the interest in B7 costimulation molecules, little investigation has been done to determine their role in *Mycobacterium tuberculosis* infection and developing antimycobacterial Th1 effector cells. Immunotherapies directed against autoimmune diseases and chronic inflammation are now being developed based on the interaction of B7 and CD28, making understanding the role of costimulation in combating infectious disease more important. Bhatt et al. (p. 3793) addressed this question by infecting mice deficient in B7.1 and B7.2 (B7DKO) with *M. tuberculosis* Erdman by aerosol delivery. B7DKO mice were able to initially control infection, but during chronic infection they were more susceptible to the pathogen when compared with wild-type mice. B7KDO mice also had impaired Th1 responses to infection, and their granuloma formation was slower. Upon examination, the lung granulomas of the B7-deficient mice had reduced lymphocytic infiltrate compared with wild-type infection mice. Without the proper granuloma architecture, the mycobacterial lesions spread to encompass a greater area in the lungs of B7KDO mice and eventually led to necrosis. Thus, while B7/CD28 costimulation was not necessary for the early control of *M. tuberculosis* in mice, it was critical for the long-term control of the pathogen within lung granulomas. Without B7, the bacterium cannot be contained within the relative protection of granuloma architecture, a relevant point for anyone considering immunotherapies based on the modulation of B7/CD28 costimulation activity.

## The Nitty Fliih-ty of TLR4 Signaling




The exact mechanism by which TLRs signal is still in the process of being elucidated. Dai et al. (p. 3450) have identified two leucine-rich repeat (LRR) binding proteins, LRRFIP2 and Flap-1, which interact with the MyD88 adaptor and positively regulate NF-$\kappa$B activity. Previous work from this laboratory identified Fliih, a LRR protein that is a negative regulator of NF-$\kappa$B. When macrophages were stimulated with LPS, the newly identified LRRFIP2 positively regulated cytokine expression. This indicated that LRRFIP2 plays a role in TLR-4-mediated responses. LRRFIP2 and Flap-1 competed with Fliih to bind to MyD88 and mediated signaling after LPS stimulation. Kinetic analysis demonstrated that LRRFIP2, Flap-1, and Fliih followed a sequential order in their interaction with the MyD88 adaptor to affect NF-$\kappa$B signaling initiation through eventual repression. Taken together, the authors have presented data that describe the mechanism responsible for the NF-$\kappa$B signaling events following LPS stimulation of TLR-4 in macrophages.

**Summaries written by Kira R. Gantt, Ph.D.**