



## COVID-19 Research Tools

Defeat the SARS-CoV-2 Variants

InvivoGen



### In This Issue

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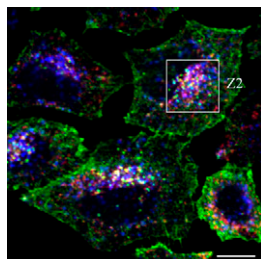
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## Unlocking IgM's Mysteries

**T**OSO, which is selectively overexpressed in chronic lymphocytic leukemia (CLL) cells, was recently identified as the long-elusive receptor for IgM: Fc $\mu$ R. In this issue, Vire et al. (p. 4040) further characterized this receptor and assessed its subcellular localization and trafficking. Fc $\mu$ R was found to be O-glycosylated, but not N-glycosylated, and the degree of glycosylation differed between normal B cells and CLL cells. Although Fc $\mu$ R was expected to be a cell surface receptor, the majority of this molecule was localized intracellularly, especially in the *trans*-Golgi network, and glycosylation was required for its trafficking to the cell surface. Upon binding IgM on the cell surface, the Fc $\mu$ R–IgM complexes were immediately internalized and then traveled through the endocytic pathway to be degraded in the lysosomes. The authors identified domains of the Fc $\mu$ R intracellular tail responsible for cell surface expression and internalization and then addressed the modulation of Fc $\mu$ R expression. Whereas BCR activation has been shown to upregulate Fc $\mu$ R, stimulation of the intracellular receptors TLR7 or TLR9 dramatically downregulated its expression in CLL cells. This characterization of Fc $\mu$ R begins to define its role in normal immune surveillance and identifies it as a potential target for the development of therapies for CLL.



## Worming Out of Immunity

**C**hronic helminth infections induce immune suppression that can impair responses to vaccines or secondary infections. To identify mechanisms by which parasite infections may interfere with vaccination, Hartmann et al. (p. 4088) analyzed the effect of natural infection with *Litomosoides sigmodontis* on humoral immunity to third-party Ags. *L. sigmodontis* infection inhibited Ab responses to a T-dependent, but not a T-independent, Ag, suggesting that Th cells, rather than B cells, were the direct targets of parasite-induced suppression. This hypothesis was supported by adoptive transfer experiments that revealed suppression of OVA-specific Th cell proliferation by *L. sigmodontis* infection, which led to inhibition of OVA-specific IgG production. T cells exposed to the parasite upregulated Th2 cytokines, such as IL-10, and the numbers of regulatory T cells (Tregs) were increased in transferred, but not resident, T cells. Although host Tregs did not mediate the parasite-induced inhibition of T cell proliferation, host-derived IL-10 was critical for Foxp3 induction and the suppression of proliferation in transferred T cells. These data provide insight into the impaired vaccine efficiency observed in individuals hosting

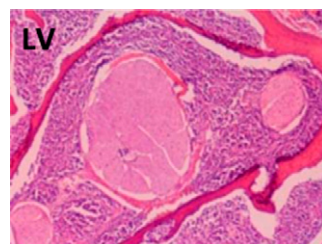
nematodes and may be applicable to future vaccine strategies for the estimated 1 billion people currently infected with helminths.

## TL Takes Control

**I**ntestinal epithelial cells (IECs) physically isolate the intestinal lumen from the rest of the body and play an active part in modulating intestinal immune responses. Expression of the nonclassical MHC class I molecule thymus leukemia Ag (TL) is mainly restricted to IECs, where it interacts with CD8 $\alpha\alpha$  homodimers on intraepithelial lymphocytes. To better define the involvement of TL in the control of intestinal CD4<sup>+</sup> T cell responses, Olivares-Villagómez et al. (p. 4051) employed an adoptive transfer model of colitis. In this model, TL expression promoted colitis development and IL-17 production by donor-derived cells. Mice deficient in TL had a reduced IL-17-producing population but an increased population of regulatory T cells, relative to TL-sufficient mice. When Th17 cells were transferred into TL<sup>+/+</sup>RAG-2<sup>-/-</sup> or TL<sup>-/-</sup>RAG-2<sup>-/-</sup> mice, the TL-deficient mice developed significantly less colitis; however, no such difference was observed with transferred Th1 cells. In coculture experiments, TL expression on IECs led to enhanced IL-17 production and reduced IFN- $\gamma$  production by activated Th17 cells but did not affect Th1 cell cytokine expression. Finally, TL expression was found to be important for an effective Th17 response to intestinal *Citrobacter rodentium* infection. Taken together, these data suggest that TL on IECs interacts with CD8 $\alpha\alpha$  on CD4<sup>+</sup> T cells to support Th17 differentiation and mucosal inflammation.

## Myeloma Marksmen

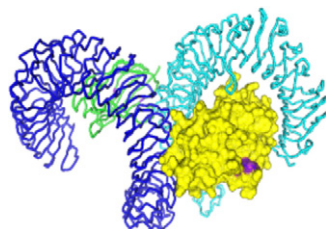
**I**n multiple myeloma (MM) treatment, donor alloreactive T cells can exert a graft-versus-myeloma (GVM) effect with significant clinical efficacy. To determine the cells responsible for this effect and their mechanism of action, Freeman et al. (p. 3987) studied myeloma-bearing, CD122<sup>+</sup> cell-depleted NOD/SCID mice that recapitulated many of the clinical features of MM. Human naive T cells were adoptively transferred into these mice, leading to myeloma suppression and extended survival. Analysis of the mechanism responsible for these clinical improvements revealed that T cells in myeloma-infiltrated bones lysed resident myeloma cells. Interestingly, these T cells did not kill myeloma cells from mice that had not received adoptively transferred T cells. Two T cell populations were observed to expand within the myeloma-infiltrated bones: single-positive CD8<sup>+</sup> T cells and unconventional double-positive CD8<sup>+</sup>CD4<sup>+</sup> T cells,



both of which bore CD8 $\alpha\alpha$  homodimers. These cells were able to degranulate and express cytotoxic mediators, and their expansion was MHC class I-dependent and required contact with the myeloma cells. This model of MM suggests a role for double-positive cytotoxic T cells in the GVM effect and may be useful in the development of future treatments for this disease.

## MD-2 Makes Its Move

Innate immune activation in response to bacterial LPS is tightly regulated and is triggered by a receptor complex consisting of TLR4 and the secreted glycoprotein myeloid differentiation-2 (MD-2). Signaling through TLR4 involves numerous tyrosine phosphorylation events. Gray et al. (p. 4331) have now found that MD-2 is also phosphorylated in response to LPS stimulation. This phosphorylation could be inhibited by a tyrosine kinase inhibitor or by cytochalasin-D, suggesting that MD-2 phosphorylation occurred during intracellular trafficking rather than on the cell surface. Two tyrosine residues located outside the TLR4–MD-2–LPS dimerization interface, Tyr<sup>22</sup> and Tyr<sup>131</sup>, were identified as the likely sites of phosphorylation. The Src kinase Lyn, which has been proposed to be involved in TLR4 phosphorylation, directly interacted with MD-2, and the two proteins appeared to colocalize in the endoplasmic reticulum. The relevance of this kinase to LPS signaling was demonstrated by a Lyn-specific inhibitor, which blocked MD-2 phosphorylation in response to LPS and prevented LPS-induced NF- $\kappa$ B activation and IL-8 production. Tyrosine phosphorylation of MD-2 is therefore likely to be an important step in TLR4 signaling and stimulation of innate immunity.



## Defining Graft Personalities

A mismatch of minor histocompatibility Ags (mH-Ags) can cause CTL expansion and graft rejection of MHC-matched allografts. Different mH-Ags can be immunodominant in distinct transplant situations, leading Kwun et al. (p. 3997) to examine mH-Ag immunodominance in H2<sup>b</sup>-matched heart and skin transplantation. In heart transplantation, the H60 Ag was immunodominant in generating a CD8<sup>+</sup> T cell response, whereas the H4 Ag was immunodominant in skin transplants. Surprisingly, neither differences in mH-Ag abundance in the heart versus skin nor differences in stimulation by tissue-resident dendritic cells were responsible for the observed immunodominance hierarchy. Next, the possible influence of vascularization was addressed, as heart transplants are highly vascularized but skin transplants are not. Reversing the vascularization pattern by using nonvascularized cardiac allografts and vascularized skin grafts resulted in a corresponding reversal in mH-Ag immunodominance, such that H4 became dominant in the heart and H60 in the skin. Depletion of donor T cells also induced H4 immunodominance in vascularized heart allografts, sug-

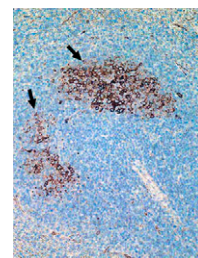
gesting that these T cells, which could transmigrate via primary graft vascularization, were responsible for the H60 immunodominance. These data contribute to our understanding of immunodominance and may support the development of strategies for transplantation success.

## Th1 Tinkering with Allergy

Allergies to the major birch pollen Ag Bet v 1 are very common and often lead to hypersensitivity responses when Bet v 1-specific T cells and IgE molecules cross-react to Ags in food allergens. In this issue, Neunkirchner et al. (p. 4077) analyzed a TCR specific for the immunodominant epitope Bet v 1<sub>142–153</sub> and assessed the potential of transgenic T cells expressing this TCR to modulate Th2 responses. The TCR was cloned from a CD4<sup>+</sup> T cell clone isolated from a birch pollen-allergic individual and was retrovirally transduced into Jurkat T cells. These T cells maintained the Ag specificity of the original T cell clone and cross-reacted similarly with Bet v 1-related food and pollen allergens. The TCR was next transduced into human peripheral blood T cells from allergic and nonallergic individuals. These T cells, which also maintained specificity for the Bet v 1<sub>142–153</sub> epitope, were successfully polarized to a Th1 phenotype. Interestingly, these TCR transgenic Th1 cells, from both allergic and nonallergic individuals, could strongly inhibit cytokine production by syngeneic TCR transgenic Th2-polarized cells. Thus, it may be possible to develop immunomodulatory therapies through the strategic manipulation of allergen-specific T cells.

## B Cell Backer

Active in most, if not all, cell types, NF- $\kappa$ B transcription factors control many facets of immunity and are regulated by a complex network of inhibitory proteins. One of these inhibitors, I $\kappa$ BNS, is a nuclear protein with a more restricted expression pattern than many I $\kappa$ B family members. In this issue, Touma et al. (p. 3942) examined B cell development and function in I $\kappa$ BNS knockout mice, which have already been shown to have dysregulated cytokine production in T cells, macrophages, and dendritic cells. Analysis of these mice revealed impairments in the development of marginal zone B cells, B1 B cells, and plasma cells, relative to wild-type (WT) mice. Following stimulation, B cell proliferation and class switching to the IgG3 isotype were reduced in I $\kappa$ BN<sup>-/-</sup> versus WT cells. The knockout B cells also expressed lower levels of secreted IgM but augmented levels of cell surface IgM. Impairment in plasma cell differentiation in the I $\kappa$ BN<sup>-/-</sup> mice was demonstrated by a reduction in Ab-secreting cells and deficient production of Ag-specific IgG Abs both in vitro and following influenza infection in vivo, compared with WT mice. Induction of the transcriptional program responsible for plasma cell differentiation was also deficient in the knockout mice. The pleiotropic impairments in B cell differentiation observed in I $\kappa$ BN<sup>-/-</sup> mice suggest that this member of the NF- $\kappa$ B machinery is vital to the proper development of B cell responses.



Summaries written by Jennifer Hartt Meyers, Ph.D.