The Journal of Immunology

In This Issue

J Immunol 2014; 192:4467-4468; ;
doi: 10.4049/jimmunol.1490016
http://www.jimmunol.org/content/192/10/4467

Supplementary Material **http://www.jimmunol.org/content/suppl/2014/05/02/192.10.4467.DC1**

The Journal of Immunology is published twice each month by
The American Association of Immunologists, Inc.,
1451 Rockville Pike, Suite 650, Rockville, MD 20852

Print ISSN: 0022-1767 Online ISSN: 1550-6606.

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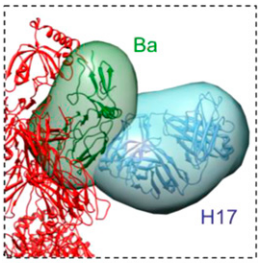
Clamping onto Complement



Ba/H17 CLASH

Complement activation is homeostatically maintained at a low level, and dysregulation of complement can result in dangerous pathology. Severe dysregulation of the alternative pathway of complement activation in diseases such as dense deposit disease is associated with autoantibodies known as C3 nephritic factors (C3NeF) that stabilize the C3 convertase. The mAb 3E7 and its humanized counterpart H17 have been found to prevent the binding of both the stimulatory factor B (fB) and the inhibitory factor H to activated C3, and thus may exert opposing effects on the C3 convertase. Paixão-Cavalcante et al. (p. 4844) sought to clarify the mechanism by which these mAbs affect alternative pathway activation to determine whether they could have therapeutic potential. The mAbs were found to bind with high affinity to both free C3b and C3b as part of the C3 convertase, and their binding to C3b interfered with fB binding and subsequent formation of the C3bB proenzyme. Treatment of C3 convertase with the mAbs prevented convertase activity, even if the convertase was stabilized in its active form by C3NeF. Structural analysis using electron microscopy revealed that H17 bound a region of C3b that overlapped with the binding site for the Ba domain of fB, suggesting a mechanism for the mAb-mediated inhibition. The ability of these mAbs to inhibit the activity of C3NeF-stabilized convertases suggests their possible use in treating dense deposit disease, which is in need of effective treatment options.

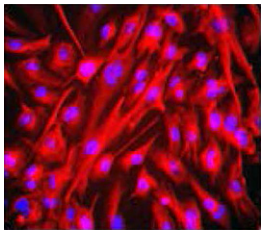
MDSCs Modulate TB

Infection with *Mycobacterium tuberculosis* is accompanied by an accumulation of $Gr1^+$ cells in the lungs of infected mice. Although depletion with anti-Gr1 Abs has been shown to ameliorate tuberculosis (TB) disease pathology, Gr1-expressing neutrophils may play a protective role in TB by phagocytizing mycobacteria and promoting T cell immune responses. Previous studies by the authors in F2 hybrid mice from TB-resistant A/Sn and TB-susceptible I/St mice demonstrated that mice succumbing to TB showed a rapid accumulation of $Gr1^+Ly6G^+$ cells in the lungs. However, unlike conventional neutrophils, which are $Gr1^{high}$, the accumulated cells were $Gr1^{dim}/Ly6G^{dim}$. In this study, Tsiganov et al. (p. 4718) provide evidence that the accumulated $Gr1^{dim}$ cells are not neutrophils, but myeloid-derived suppressor cells (MDSCs), a population of immature immunosuppressive $Gr1^+CD11b^+$ cells. Intratracheal challenge of I/St mice with *M. tuberculosis* led to the accumulation of $Gr1^{dim}CD11b^+$ cells in the lungs by day 24 postchallenge, and this accumulation was accompanied by a decrease in $Gr1^{high}CD11b^+$ cells. Phenotypic and morphological comparison between $Gr1^{high}$ and $Gr1^{dim}$ cells indicated that $Gr1^{dim}$ cells were an immature heterogeneous population. $Gr1^{dim}CD11b^+$ cells isolated from the bone marrow of uninfected and *M. tuberculosis*–infected mice on day 17 or 24 postchallenge suppressed $CD4^+$ and $CD8^+$ T cell responses to *M. tuberculosis*–specific Ags and T cell IFN-γ production in a contact- and NO-dependent manner. This study characterizes a population of MDSCs that could potentially play an important role in driving TB progression.

Seeking Specific Functions for SARM

Toll/IL-1R (TIR) domain–containing adaptor proteins are key participants in TLR signaling during innate immune responses. Although the *Caenorhabditis elegans* ortholog of the highly evolutionarily conserved TIR protein sterile α and HEAT/Armadillo motif–containing protein (SARM) regulates antimicrobial peptide induction in worms, SARM has mainly been found to have neuronal functions in mice. To determine whether mouse SARM can also modulate peripheral innate immune responses, Gürtler et al. (p. 4821) analyzed cytokine production in SARM-deficient macrophages. Relative to wild-type macrophages, SARM-deficient macrophages showed significant impairments in the production of CCL5, but not of any other cytokines or chemokines tested, following TLR4 or TLR7 stimulation. Surprisingly, SARM deficiency did not affect TLR-induced activation of NF-κB, IFN regulatory factor 1 (IRF1), or IRF3, although these are the main transcription factors implicated in *Ccl5* expression. SARM deficiency also did not alter TLR-induced MAPK signaling or *Ccl5* mRNA stability or splicing. Instead, SARM controlled the assembly of p65, IRF1, and IRF3 at the *Ccl5* promoter and the recruitment of RNA polymerase II in response to TLR signaling. SARM was also required for CCL5 expression following stimulation of cytosolic pattern recognition receptors. Thus, SARM acts in a manner distinct from other TIR-containing adaptors to selectively control pattern recognition receptor–induced CCL5 expression in macrophages.

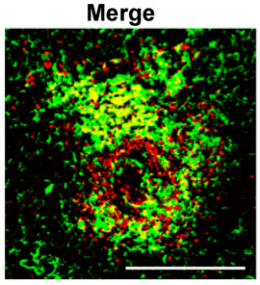
Joining Forces To Fight Asthma



Mesenchymal stem cells (MSCs) are connective tissue progenitor cells that participate in tissue repair and remodeling and can modulate immune responses. The migration of MSCs to the airways following allergen sensitization and challenge together with the observed ability of MSCs to suppress lung inflammation have suggested that these cells may be important in the pathogenesis of asthma. In this issue, Gao et al. (p. 4560)

addressed the potential role of TGF-β1, which can act as a mediator of airway remodeling, in the migration of MSCs to the lung during allergic airway inflammation. Challenge with cockroach allergen (CRE) in a mouse model of asthma increased numbers of MSCs in the lung and levels of TGF-β1 in broncoalveolar lavage fluid and peripheral blood. Allergen also induced the activation of TGF-β1 signaling in MSCs in vitro. An anti–TGF-β1 neutralizing Ab impaired MSC migration, both in vitro toward medium from CRE-challenged human airway epithelial cell cultures and to the mouse lung following CRE challenge in vivo. TGF-β1 Ab treatment also increased airway inflammation in CRE-treated mice. MSCs were found to dramatically inhibit CRE-stimulated cytokine secretion from $CD4^+$ T cells, leading the authors to suggest that TGF-β1 may control allergic inflammation by recruiting MSCs to the airways. This insight into MSC function in asthma and its relationship to TGF-β1 provides a basis for future work addressing the possibility of exploiting this pathway to control allergic airway inflammation.

Egging on Pathology with CD209a



Clinical disease severity in *Schistosoma mansoni* infections shows significant heterogeneity, from mild gastrointestinal disease to life-threatening schistosomiasis, characterized by granulomatous inflammation and fibrosis surrounding deposited parasite eggs. Similarly, murine models of disease show variations in severity. CBA/J (CBA) mice develop severe pathology mediated by T cell induction of IL-17 triggered by Ag-stimulated dendritic cell (DC) production of IL-1β and IL-23, whereas C57BL/6 (B6) mice only develop mild disease. To better understand the variations in egg-induced immunopathology, Ponichtera et al. (p. 4655) used microarray analysis to focus on CD209a, a murine C-type lectin receptor homolog of human dendritic cell–specific ICAM-3–grabbing nonintegrin (DC-SIGN) known to bind to schistosome egg glycans. CD209a expression is 18-fold higher in CBA bone marrow–derived DCs (BMDCs) compared with B6 BMDCs. Flow cytometric and immunohistochemical analyses showed both an increase in CD209a expression by various APC subpopulations and a higher frequency of $CD209a^+$ cells in CBA compared with B6 granulomas and lymphoid tissue. Coculture of CBA splenocytes with naive $CD4^+$ T cells in the presence and absence of eggs identified $CD11c^+$ cells as the inducers of T cell IL-17. Short hairpin RNA inhibition of CD209a in these cocultures decreased DC-derived IL-1β and IL-23 production and led to a resulting decrease in IL-17 production by $CD4^+$ T cells that was associated with SRC, RAF-1, and ERK1/2 MAPK activation. Alternatively, overexpression of CD209a in B6 BMDCs led to increased IL-1β and IL-23 expression followed by IL-17 production by cocultured $CD4^+$ T cells. Collectively, these data describe an IL-17–dependent mechanism that regulates the development of severe immunopathology in helminthic disease.

Triggering T Cells in Trachoma

Current antibiotic treatment protocols aimed at controlling *Chlamydia trachomatis*, a bacterial pathogen that causes trachoma, a leading cause of preventable blindness, have had limited efficacy. In evaluating the success of vaccination strategies, the authors previously described a plasmid-deficient live-attenuated trachoma vaccine (LATV) which either solidly protected (SP) or partially protected (PP) immunized macaques from a challenge with virulent *C. trachomatis*. Olivares-Zavaleta et al. (p. 4648) sought to define the role of T cells in trachoma vaccine–mediated immunity by ocularly and i.m. boosting LATV-vaccinated SP and PP macaques after a 2-y resting period, which led to an increase in $CD4^+$ and $CD8^+$ T cells in the peripheral blood of both SP and PP macaques. Despite challenge with virulent trachoma organisms, SP and PP macaques retained their original immune status and SP macaques experienced only transient ocular infections, which resolved after 21 d. Peripheral blood $CD8^+$, but not $CD4^+$, T cells from SP and PP macaques proliferated in vitro in response to *C. trachomatis* soluble Ag extract, with greater proliferation by cells from SP donors. Inflammatory cytokines measured in the tears were increased in SP, but not PP, macaques on day 7 postchallenge. In vivo $CD8^+$ T cell depletion of *C. trachomatis*–challenged SP macaques abrogated protective immunity against ocular infection. Taken together, these findings demonstrate a crucial role for $CD8^+$ T cells in LATV-mediated protective immunity and further our understanding of adaptive T cell immunity in response to *C. trachomatis* infection.

Memory Stem Cells Succumb to SIV

Although the mechanisms by which clinically relevant immunodeficiency develops in HIV-infected humans and SIV-infected rhesus macaques (RM) are not fully understood, important roles are played by chronic immune activation and the infection of $CD4^+$ central memory T cells. In addition, a recently identified subset of $CD8^+$ memory T cells with stem cell–like properties, T memory stem cells (T_{SCM}), has been implicated in the long-term maintenance of anti-SIV $CD8^+$ T cell responses. To determine whether $CD4^+$ T_{SCM} are also involved in SIV pathogenesis, Cartwright et al. (p. 4666) examined the fate of these cells in SIV-infected RM and in sooty mangabeys (SM), a natural host for SIV in which the virus replicates but generally does not cause pathology. Uninfected RM had significantly higher percentages of $CD4^+$ T_{SCM} than uninfected SM, and a higher percentage of these cells expressed the SIV coreceptor CCR5. Pathogenic SIV infection did not alter the total numbers of $CD4^+$ T_{SCM} in RM; however, numbers of $CCR5^+CD4^+$ T_{SCM} were significantly depleted and the proliferation rate of $CD4^+$ T_{SCM} was increased relative to uninfected controls. In contrast, no reduction in $CCR5^+CD4^+$ T_{SCM} or changes in proliferation were observed in SIV-infected SM. SIV DNA was undetectable in $CD4^+$ T_{SCM} in 8 of 10 SIV-infected SM but robust infection of $CCR5^+CD4^+$ T_{SCM} was found in RM. These data suggest that $CD4^+$ T_{SCM}, as cells that are infected by SIV and maintained following infection, are important both for disease progression and for long-term persistence of SIV in RM.