The Journal of Immunology

In This Issue

J Immunol 2014; 193:5761-5762; ;
doi: 10.4049/jimmunol.1490048
http://www.jimmunol.org/content/193/12/5761

The Journal of Immunology is published twice each month by The American Association of Immunologists, Inc., 9650 Rockville Pike, Bethesda, MD 20814-3994.

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

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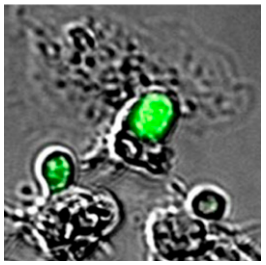
Moving Connections

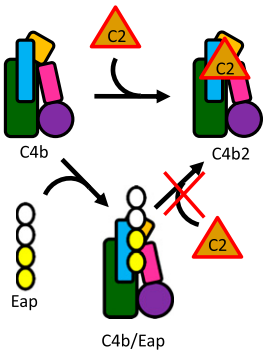


Foxp3$^+$ CD4$^+$ regulatory T cells (Tregs) promote tolerance to self-antigens and commensal microbes through several mechanisms, including downmodulation of costimulatory molecules, such as CD80 on dendritic cells (DCs), and disruption of interactions between DCs and naive CD4$^+$ T cells. Thauland et al. (p. 5894) examined how Treg motility and immunological synapse (IS) formation are influenced by the level of CD80 expression on DCs. Tregs initially formed stable interactions with DCs in coculture, but became highly motile after 24 h and swarmed around DCs. This change in motility was dependent on downregulation of CD80 on DCs mediated by Treg-expressed CTLA-4. Use of supported planar bilayers coated with ICAM-1 and cognate peptide-loaded MHC II to precisely measure Treg motility confirmed that Tregs interacting with the bilayer were motile and had accumulations of pMHC–TCR in the uropod and of LFA-1–ICAM-1 in the lamella. These Tregs formed motile ISs or "kinapses," but the presence of a high concentration of CD80 in the bilayer significantly reduced motility and instead promoted stable IS formation. Interestingly, treatment of Tregs with Fab fragments against CD28, which binds to CD80, resulted in significantly greater Treg motility in bilayers containing pMHC, ICAM-1, and high concentrations of CD80. In contrast, anti–CTLA-4 treatment did not significantly alter motility. Together, these results show that Treg motility and synapse formation are closely linked to CD80 expression.

Teaming Up To Tackle SIV

Despite concerted efforts over the last several decades, no efficacious HIV vaccine is available to date. Using an SIV infection model in rhesus macaques, Gordon et al. (p. 6172) evaluated possible correlates of protection for a preclinical HIV-1 vaccine. All vaccinated animals were vaginally immunized with human papilloma pseudovirus loaded with several SIV genes and then boosted i.m. with gp120 in alum and monophosphoryl lipid A. Half of the animals in the vaccinated group were also primed by i.m. inoculation with ALVAC, a canarypox vector that has been previously tested in HIV vaccines, encoding a subset of SIV genes. Both vaccination strategies elicited monofunctional mucosal T cells and non–neutralizing IgG directed toward the V1/V2 region of gp120. Four weeks after the final immunization, vaccinated and control animals were repeatedly challenged with a low dose of SIV_{mac251}, a pathogenic uncloned challenge strain. Although vaccination did not delay infection or lower set-point viral loads, mucosal viral load was reduced relative to that of control animals. Mucosal SIV load was also found to be inversely correlated with gp120-specific CD4$^+$ T cell proliferation. Only 67% of vaccinated animals, in contrast to 83% of unvaccinated animals, established persistent SIV viremia. Vaccinated animals that were protected from persistent infection had more high avidity anti-V1/V2 Abs. Moreover, animals with higher V1/V2 Ab responses required more viral challenges to establish persistent infection. These results suggest that T cells can team up with functional non–neutralizing Abs to control local SIV infection.

K-Eap-ing Complement at Bay



The complement system can cause opsonization of invading bacteria to label them for phagocytosis and can be activated via the classical, alternative, or lectin pathways (CP, AP, or LP, respectively), which all converge on activation of the C3 component. *Staphylococcus aureus* has been shown to evade complement attack via numerous C3 convertase inhibitors that act on the AP. To investigate whether *S. aureus* also expresses inhibitors of the CP and/or LP, Woehl et al. (p. 6161) screened a library of secreted staphylococcal proteins and identified the extracellular adherence protein (Eap) as a potent inhibitor of both of these pathways, but not of the AP. Soluble Eap, but not the structurally related proteins EapH1 and EapH2, inhibited C3b deposition on the bacterial surface and subsequent phagocytosis by neutrophils. Eap was found to form a 1:1 complex with complement component C4b, binding with nanomolar affinity and thereby blocking binding of C2 to C4b. This Eap–C4b binding inhibited formation of the CP/LP C3 proconvertase, C4b2, and downstream formation of the C3 convertase, C4b2a. The Eap binding site on C4b was shared with other factors important for CP and LP activity and regulation, suggesting that this site is a functional hotspot for these pathways. Thus, *S. aureus* can evade complement activation via all three pathways, and this Eap-mediated mechanism of CP/LP inhibition may be applicable to future therapeutic modulation of complement activation.

Borrelia Blues with *Bbaa1*

Different mouse strains display varying levels of arthritis symptoms following *Borrelia burgdorferi* infection, and gene expression analysis has linked differences in the type I IFN pathway to greater disease severity in C3H mice relative to C57BL/6 (B6) mice. Forward genetic analysis

www.jimmunol.org/cgi/doi/10.4049/jimmunol.1490048

identified a quantitative trait locus on chromosome 4, called *Bbaa1*, as a region associated with Lyme arthritis severity that included several type I IFN genes. Ma et al. (p. 6050) assessed the role of *Bbaa1* in Lyme arthritis and rheumatoid arthritis (RA) using reciprocal interval-specific congenic lines in which the C3H *Bbaa 1* was introgressed on the B6 background (B6.C3-*Bbaa1*), and the B6 *Bbaa 1* was introgressed on the C3H background (C3.B6-*Bbaa1*). B6.C3-*Bbaa1* mice showed more severe Lyme arthritis symptoms following *B. burgdorferi* infection relative to control B6 mice, but the symptoms were less severe than in C3H mice. Treatment with a type I IFNR-blocking mAb prior to infection significantly reduced arthritis in B6.C3-*Bbaa1* mice. In a model of RA, B6.C3-*Bbaa1* mice treated with serum from arthritic K/BxN mice developed more severe arthritis than the parental B6 strain, and symptoms were attenuated by treatment with the type I IFNR-blocking mAb. These results suggest that *Bbaa1* influenced RA as well. Transcript analysis of bone marrow–derived macrophages (BMDMs) confirmed that the *Bbaa1* locus regulated induction of type I IFN and IFN-inducible genes and also influenced the functional phenotypes of the BMDMs. Together, these findings link the *Bbaa1* locus to type I IFN expression and show its impact on Lyme arthritis and RA severity.

Rictor Goes Rogue

The serine/threonine kinase mammalian target of rapamycin (mTOR) exerts a variety of regulatory effects in many different cell types, acting as part of the mTORC1 and mTORC2 signaling complexes, which also include the proteins raptor or rictor, respectively. Although mTOR is activated following mast cell stimulation, it is not known how mTORCs might affect mast cell function in response to FcεR1 stimulation. Because mTORC2 expression has been shown to be downregulated in resting mature mast cells, relative to immature or transformed cells, Smrz et al. (p. 5924) assessed the role of mTORC2 components in mast cell degranulation following FcεR1 aggregation. Using the transformed human mast cell line LAD2, the authors found that FcεR1 aggregation stimulated phosphorylation of mTOR and rictor, but that neither inhibition of mTORC1/mTORC2 nor short hairpin RNA (shRNA)-mediated knock-down of mTOR affected mast cell degranulation. In contrast, downregulation of rictor via shRNA resulted in an increase in mast cell degranulation following FcεR1 aggregation, but not C3a or thapsigargin stimulation. Mechanistic analysis using rictor knockdown revealed that rictor negatively regulated calcium signaling and F-actin reorganization in these mast cells and impaired early signaling events, including phosphorylation of Akt(Thr308), downstream of FcεR1 aggregation. Modest overexpression of rictor in LAD2 cells confirmed these data, resulting in reduced degranulation and Akt(Thr308) phosphorylation following FcεR1 aggregation. Taken together, these results identify mTOR-independent roles for rictor in controlling mast cell activation.