The Journal of Immunology

In This Issue

J Immunol 2011; 186:5017-5018; ;
doi: 10.4049/jimmunol.1190015
http://www.jimmunol.org/content/186/9/5017

Supplementary Material **http://www.jimmunol.org/content/suppl/2011/04/15/186.9.5017.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.

THE JOURNAL OF IMMUNOLOGY

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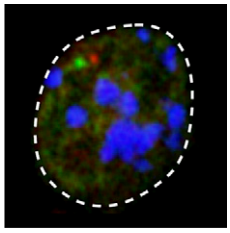
A Role for Sis in *cis*



B cell development includes the sequential rearrangement of *IgH* and *IgL* loci in mice through V(D)J recombination, but little is known about the germline sequences within Vκ genes that influence gene segment usage. An element in the Vκ–Jκ intervening sequence, termed silencer in the intervening sequence (Sis), has been shown to be involved in pericentromeric heterochromatin localization and can act as a recombination silencer. To better understand how Sis functions, Xiang et al. (p. 5356) developed a Sis-specific targeted knockout mouse. Sis deletion did not affect Ig surface expression or the frequency of different B cell populations within the spleen and bone marrow. However, $Sis^{-/-}$ mice had increased proximal and diminished distal Vκ gene usage, skewing the Igκ repertoire, compared with wild-type mice. The alterations in Vκ gene usage in $Sis^{-/-}$ mice were associated with reduced recruitment of the transcription factors IKAROS and CCCTC-binding factor to the Vκ–Jκ intervening sequence, suggesting a *cis*-acting regulatory role for Sis. In pre-B cells, Sis was essential for the pericentromeric heterochromatin positioning of *Igκ* loci in *cis*, as well as *IgH* loci in *trans*, but Sis deletion did not affect allelic exclusion. These results define multiple functions of Sis during recombination and nuclear localization and further our understanding of how Sis affects the generation of Ig diversity.

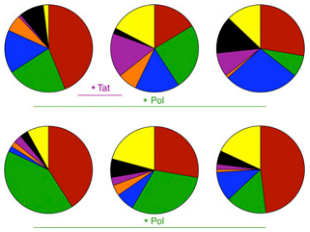
Prodding IFN-α Production

Excessive IFN-α production is a hallmark of systemic lupus erythematosus (SLE) and is usually linked to stimulation of plasmacytoid dendritic cells (pDCs) with nucleic acid-containing immune complexes (ICs). Hagberg et al. (p. 5085) advanced their previous observations that IFN-α production by pDCs is enhanced by NK cells by discerning the mechanisms that contribute to this phenomenon. Coculture of NK cells with pDCs and RNA-containing ICs (RNA-ICs) induced significantly more IFN-α production compared with pDCs stimulated with RNA-ICs alone. $CD56^{dim}$ NK cells were the principal subpopulation responsible for promoting IFN-α production. Costimulation of $CD56^{bright}$ NK cells with IL-12 and IL-18 significantly enhanced their ability to promote IFN-α production from RNA-IC–stimulated pDCs. In particular, secretion of MIP-1β from NK cells and LFA-1–mediated contact between NK cells and pDCs each promoted RNA-IC–stimulated IFN-α production. NK cells from SLE patients showed a reduced capacity to enhance IFN-α production from RNA-IC–stimulated pDCs compared with NK cells from healthy controls, but this difference was eliminated by costimulation with IL-12 and IL-18. These findings affirm that NK cells can enhance pDC-mediated IFN-α production, which could be applied to the development of therapies for SLE and similar autoimmune diseases.

Leptin's Long Reach

Although they are a rare population in the blood, basophils are increasingly being recognized for their effects on multiple immune processes, including allergy, T cell polarization, and memory. A link between allergy and obesity has become more apparent, and clinical studies have shown that obesity is associated with more severe asthma. Suzukawa et al. (p. 5254) have explored this link by examining the effect of leptin on human basophils. Leptin is an adipokine involved in modulating appetite and energy balance and is secreted by adipocytes. Numerous cell types respond to leptin via leptin R (LepR), and this study confirmed that human basophils expressed LepR on the cell surface, and LepR expression could be induced by IL-33 treatment. Leptin was a potent inducer of basophil migration and promoted their survival in vitro. Leptin induced surface expression of CD63, a degranulation marker, which was specifically blocked by anti-LepR treatment. In addition, leptin primed basophil degranulation induced by FcεRI aggregation and promoted production of Th2 cytokines. These results suggest that the level of leptin in the blood, which is related to obesity, may influence inflammation and allergy through its effects on basophils.

Polyfunctional Protection

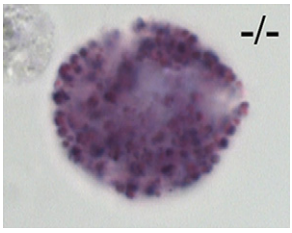


An improved understanding of HIV pathogenesis has come from studies in sooty mangabeys (SM; *Cercocebus atys*), which are natural hosts of SIV. To gain better insight into how SM control infection, Meythaler et al. (p. 5151) analyzed SIV-specific cellular immunity in SM and compared their results with responses in rhesus macaques (RM), for which SIV is pathogenic. The specificity and magnitude of IFN-γ ELISPOT responses against species-adapted SIV primary infection were similar between SM infected with the primary SM isolate SIVsmE041 and RM infected with SIVsmE041 or RM-passaged SIVmac239. These responses correlated with a transient decline in peak plasma viremia. SIVsmE041-infected SM had a greater decline in postpeak plasma viremia and a rapid disappearance of SIV-infected cells from the lymph nodes compared with SIVmac239-infected RM, and these results indicate that SM may develop a more robust early response against species-adapted SIV compared with RM. SM had a greater frequency of granzyme B-positive $CD8^+$ T cells before and during SIV infection relative to RM. SIVsmE041-infected SM also had a greater frequency of Gag-specific polyfunctional $CD8^+$ T cells in comparison to RM

www.jimmunol.org/cgi/doi/10.4049/jimmunol.1190015

infected with SIVmac239. Thus, early $CD8^+$ T cell responses may be key to the immunologic mechanism by which SM control SIV infection and avoid the immunopathology observed in RM.

Muting Mast Cells



Mast cell degranulation is tightly controlled through positive and negative regulation of intracellular signals via adapter proteins. In this issue, Ulivieri et al (p. 5095) define a role for the Shc adapter family protein p66Shc during FcεRI-dependent signaling in mast cells. Previous studies have shown that p66Shc could inhibit TCR-driven activation of Ras/MAPK signaling. Mice lacking p66Shc had spontaneous lymphocyte activation as well as lupus-like symptoms, including areas of alopecic skin with activated mast cell infiltration. In this study, p66Shc was found to be constitutively expressed in murine mast cells. Deletion of p66Shc did not affect mast cell differentiation, but FcεRI-mediated Ag stimulation induced enhanced responses in $p66Shc^{-/-}$ mast cells compared with wild-type controls. Transfection experiments confirmed that p66Shc specifically modulates FcεRI-mediated mast cell activation by driving recruitment of the negative regulator SHIP1 to the transmembrane adapter linker for activation of T cells. These data identify a novel role for p66Shc in negatively regulating mast cell activation and provide insight into mechanisms that could be exploited to calm overexuberant mast cell responses.

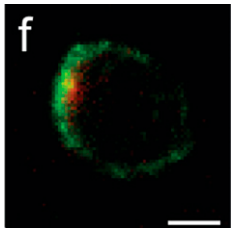
A Confederation of Kinases

The PI3K pathway regulates multiple inflammatory cytokine responses, and Wang et al. (p. 5217) have observed that this regulation is due in part to the convergence of the mammalian target of rapamycin complex 1 (mTORC1) and glycogen synthase kinase 3 (GSK3)-β signaling pathways. Inhibition of mTORC1 by rapamycin treatment of LPS-stimulated monocytes decreased phosphorylation-mediated inactivation of GSK3-β and caused a significant increase in IL-12 and decrease in IL-10 production compared with controls. GSK3-β inhibition had the opposite effect on IL-12 and IL-10 levels, indicating that GSK3-β blockade interfered with the effects of rapamycin treatment on LPS-stimulated monocytes. GSK3-β was phosphorylated by the p85S6K isoform of S6K1, a kinase downstream of mTORC1. S6K1 inhibition of LPS-stimulated monocytes prevented GSK3-β phosphorylation and had an effect on cytokine production similar to that of rapamycin treatment, but the ability of S6K1 to influence cytokine production was blocked by GSK3-β inhibition. GSK3-β has been shown previously to alter cytokine responses through its effects on the transcription factors CREB and NF-κB p65. Here, rapamycin treatment of LPS-stimulated monocytes significantly inhibited binding of the transcription factor CREB to nuclear DNA and caused an increased association of NF-κB p65 with the coactivator of transcription CBP. Moreover, NF-κB p65 inhibition dampened the effects of rapamycin treatment on cytokine production. These results provide insight into the mechanism by which mTORC1 signaling affects the functions of GSK3-β and downstream cytokine responses.

Stromal Synergy

The thymic stromal environment instructs developing thymocytes to discern self from non-self Ags. Stromal medullary thymic epithelial cells (mTECs) support this process by expressing a variety of tissue-restricted Ags (TRA). Mice deficient in different individual TNFR superfamily members have reduced TRA gene expression, and transplantation of these thymi into normal mice induces autoimmune responses. Mouri et al. (p. 5047) define a link between TNFR superfamily members lymphotoxin β R (LTβR) and receptor activator for NF-κB (RANK) during mTEC differentiation. Mice deficient in both LTβR and RANK ligand had defects in thymic organization and mTEC differentiation compared with mice singly deficient in either of these molecules. Treatment of fetal thymic organ cultures with agonistic anti-LTβR induced RANK expression in mTECs and promoted their differentiation. Similarly, RANK expression was reduced in embryonic thymi from mice deficient in LTβR compared with control littermates. This RANK-specific trend was not seen for CD40. Thus, these results indicate that LTβR and RANK signaling cooperate to promote optimal mTEC differentiation. This knowledge of TNFR family interactions helps to clarify mechanisms influencing the fine balance between tolerance and autoimmunity.

Negating Negative Regulation



Numerous signaling mechanisms regulate T cell responses, including cAMP-mediated activation of type I protein kinase A (PKA). Type I PKA is targeted to the TCR by a scaffold complex containing ezrin and downregulates T cell signaling by activating C-terminal Src kinase. The RI anchoring disruptor (RIAD) peptide has been shown to bind to type I PKA and disrupt its binding to ezrin, which prevents negative regulation of T cell activation. Mosenden et al. (p. 5119) examined the effect of disrupting the type I PKA–TCR interaction on T cell activation using transgenic mice engineered to express RIAD in a T cell-specific manner. T cells from RIAD-transgenic mice showed increased TCR-proximal signaling and greater IL-2 production compared with wild-type (WT) controls. RIAD-transgenic T cells were also less sensitive to T cell inhibition mediated by cAMP or PGE_2 treatment relative to WT mice. Defective T cell responses that are associated with murine AIDS (MAIDS) and HIV have been linked to overactivation of cAMP-type I PKA signaling. In this study, RIAD-transgenic mice infected with a mixture of murine leukemia viruses better controlled viral replication and resisted progression to MAIDS compared with WT mice. These observations provide further evidence that cAMP-type I PKA signaling is critical to modulating T cell activation and combating infections that cause acquired immunodeficiency.

Summaries written by Christiana N. Fogg, Ph.D.