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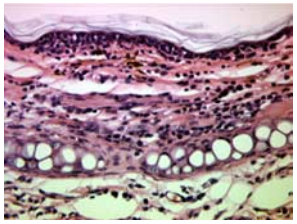
THE JOURNAL OF IMMUNOLOGY

In This Issue

A Reversal of Tolerance



The decision between autoimmunity and tolerance is a complex process that is not yet fully understood. To clarify mechanisms responsible for the induction of peripheral tolerance, Miyagawa et al. (p. 1109) used transgenic mouse strains expressing either high or low levels of OVA (mOVA) as a self-Ag under the control of a skin-specific promoter (K14). OVA-specific (OT-1) $CD8^+$ T cells adoptively transferred into K14-$mOVA^{high}$ mice were activated, and the mice developed a graft-vs-host disease-like inflammatory skin disease. In contrast, OT-1 cells transferred into K14-$mOVA^{low}$ mice did not induce disease. In these mice, the transferred cells proliferated but were not fully activated and did not acquire effector functions. Treatment of K14-$mOVA^{low}$ mice with IL-15 after adoptive transfer of OT-1 cells reversed tolerance and led to disease development as well as OT-1 T cell activation and effector activity. IL-15, but not IL-7, could directly induce full activation of tolerized OT-1 cells isolated from K14-$mOVA^{low}$ mice. In support of these data, treatment of K14-$mOVA^{high}$ mice with anti-IL-15 Abs after adoptive transfer blocked the development of skin disease, and K14-$mOVA^{high}$ mice deficient in either IL-15 or IL-15Rα also developed little or no disease. Taken together, these data suggest that IL-15 is a critical regulator of autoreactive $CD8^+$ T cells and may serve as an attractive target for immunotherapeutics aimed at modulating tolerance.

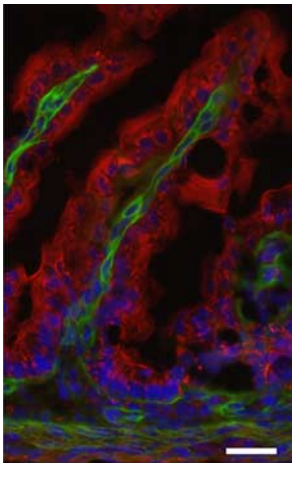
CD27 Lends a Helping Hand

Although $CD4^+$ T cell help is not necessary for initiation of a $CD8^+$ T cell response, help during the primary response is required for optimal development of $CD8^+$ T cell memory. CD27:CD70 interactions have been shown to be important for memory $CD8^+$ T cell differentiation, leading Xiao et al. (p. 1071) to address the more complicated question of whether CD27 is involved in $CD4^+$ T cell help of $CD8^+$ T cell responses. CD27 expression on $CD4^+$ T cells promoted their accumulation at both priming and effector sites in an OVA-specific adoptive transfer model. Transfer of either wild-type or $CD27^{-/-}$ $CD4^+$ T cells into $CD27^{-/-}$ recipients demonstrated that CD27 on $CD4^+$ T cells promoted the expansion of memory $CD8^+$ T cells and their accumulation at the effector site following restimulation. Microarray analysis followed by ex vivo detection of cytokine production indicated that CD27 induced a Th1 phenotype in $CD4^+$ T cells and markedly increased expression of the CD20-like molecule MS4A4B (also known as Chandra). Interestingly, further microarray analysis also identified MS4A4B as a specific marker for memory $CD8^+$ T cells that had received help from CD27-sufficient $CD4^+$ T cells. These data add important details to our understanding of the mechanisms involved in the development of an effective $CD8^+$ memory T cell response.

Mutations without AICDA

Activation-induced cytidine deaminase (AICDA) is required for somatic hypermutation of Ig genes during a germinal center reaction. To characterize the mutations that may occur in the absence of AICDA and investigate the relationship between AICDA and the error-prone polymerase POL η, Longo et al. (p. 1299) analyzed a large number of H and L chain rearrangements from three patients lacking AICDA. Although the frequency of mutations was significantly reduced in the absence of AICDA, hypermutation still occurred. Sequence analysis of Ig genes in these patients showed significantly fewer mutations in both AICDA target motifs and POL η target motifs compared with normal B cells, suggesting that AICDA activity may be required for POL η activity. Unlike in AICDA-competent individuals, the mutations were not targeted to CDRs and not associated with any discernable target motif, suggesting that hypermutation in AICDA-deficient B cells was randomly localized. This process did, however, appear to preferentially occur at G:C base pairs and to be biased toward transitions rather than transversions, indicating that AICDA may also regulate uracil DNA-glycosylase (UNG) activity. These data begin to elucidate the relationship between AICDA and other factors in the affinity maturation process and lend support to the idea that an AICDA-independent mechanism can cause some degree of somatic hypermutation.

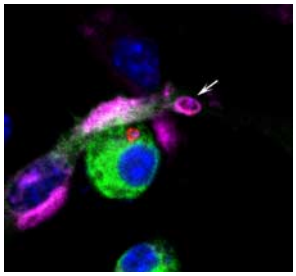
Intestinal Maintenance



Transforming growth factor β-activated kinase 1 (TAK1) is an indispensable mediator of many inflammatory signaling pathways. Kajino-Sakamoto et al. (p. 1143) hypothesized that TAK1 might modulate TNF activity and thereby control intestinal epithelial homeostasis. To test this idea, they created conditionally targeted mice with TAK1 specifically deleted in intestinal enterocytes (villin-$CreTAK1^{FL/FL}$). These mice displayed massive intestinal bleeding and died within 1 day of birth yet had normal intestines as late as embryonic day 17.5. Deletion of TAK1 did not cause a defect in intestinal epithelial differentiation but did increase apoptosis and inflammation in the gut around embryonic day 18. To examine the effects of enterocyte-specific TAK1 deletion in adult mice, the authors developed an inducible TAK1 knockout. These mice developed severe intestinal inflammation accompanied by an increase in apoptotic cells

and proinflammatory mediators within 2 days of the initiation of gene deletion. To determine whether TNF activity induced this intense inflammation, a double knockout mouse strain lacking both TNFR1 and TAK1 was generated. The intestinal damage in villin-CreTAK1$^{FL/FL}$ neonatal mice was completely rescued in these mice, but ileitis and severe colitis developed when they were 2–3 wk old. These results suggest that TAK1 is critically important for the maintenance of intestinal epithelial integrity by preventing both TNF-dependent and independent inflammation.

CpG Cure All



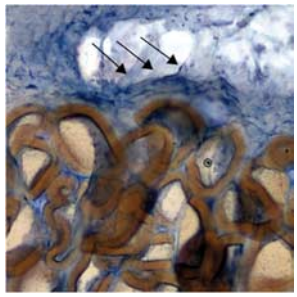
Unmethylated CpG motifs derived from bacteria, viruses, and parasites stimulate multiple types of immune cells via TLR9. In this issue, two articles analyze the activities of CpG-oligonucleotide type B (CpG-B) with potential implications for the treatment of infectious disease. In the first article, Malaspina et al. (p. 1199) addressed the effects of CpG-B on human B cells from HIV-infected individuals at different stages of disease. B cells in HIV-infected individuals are impaired in effector function and mount particularly poor memory responses; however, CpG-B treatment was able to restore defective BCR-mediated proliferation of CD27$^+$ memory/activated B cells from HIV-viremic individuals. Naive B cells from HIV-viremic, HIV-aviremic, or HIV-negative individuals all proliferated robustly and showed enhanced survival in response to CpG-B despite the defects that have been observed in naive B cells of HIV-infected individuals. CpG-B could also augment cytokine production of BCR-stimulated B cells and could act alone to stimulate Ig secretion by CD27$^+$ B cells in the context of HIV infection. These results suggest that CpG-B treatment could potentially overcome many of the defects observed in B cells of HIV-infected individuals, and the inclusion of CpG oligonucleotides in vaccine formulations could prove useful in enhancing immunity to HIV.

In the second article, Bartholomeu et al. (p. 1333) identified CpG motifs present in the genomic DNA of *Trypanosoma cruzi* and examined how these motifs might induce inflammatory responses. Although TLR9 was previously shown to be important for defense against intracellular parasites, the sequence(s) of *T. cruzi* recognized by TLR9 and the mechanism by which the parasite DNA and TLR might meet were unknown. The authors screened the *T. cruzi* genome and identified many mouse- and human-like CpG motifs, mainly of the CpG-B and CpG-C classes. Synthetic oligodeoxynucleotides (ODN) containing these motifs stimulated inflammatory cytokine production from murine dendritic cells, murine macrophages, and human PBMCs and skewed cellular and humoral immune responses toward a Th1 phenotype. Synthetic ODN or live *T. cruzi* parasites were then found to induce TLR9 signaling in vitro. Infection of dendritic cells with *T. cruzi* parasites led to their co-localization with TLR9 in the late endosomal compartment, and delivery of *T. cruzi* genomic DNA to these endo-lysosomes induced TLR9 signaling and proinflammatory cytokine production. These two demonstrations of the utility of CpG motifs in protection against infection indicate the potential of these motifs as adjuvants in a wide variety of therapeutic applications.

TNF Signaling Gets More Complex

Signaling induced by TNF is vital to the inflammatory response. TNFR1, the primary TNF receptor, associates with several nonenzymatic adaptor proteins, but signaling through these molecules does not lead to the tyrosine phosphorylation reactions that are important for TNF function. To identify the proximal steps involved in TNF-induced tyrosine phosphorylation, Pincheira et al. (p. 1288) asked whether TNFR1 complexed with nonreceptor tyrosine kinases. Indeed, immunoprecipitation experiments demonstrated that TNFR1 was constitutively associated with Jak2, c-Src, and PI3K and that stimulation with TNF could induce additional recruitment of these kinases into the TNFR1 complex. Jak2 and c-Src were shown to be constitutively active when associated with TNFR1, and the activity of both kinases was required for activation of Akt. Jak2 was also important for the activation of p38 MAPK and JNK, and Jak2 and c-Src did not modulate one another's activity. Additionally, Jak2 specifically activated STAT3 while c-Src specifically activated NF-κB, and the activity of both kinases led to the expression of TNF-induced gene products. This demonstration that TNFR1 signaling requires association with molecules other than death domain-containing molecules such as TRADD greatly enhances our understanding of the diverse effects mediated via this important receptor and links the Jak pathway to TNF-mediated effector functions.

Allergic Side Effects



Inhibition of the serine protease dipeptidyl-peptidase IV (DPPIV) in type 2 diabetes treatment prevents its activation of insulin-releasing peptide hormones. However, DPPIV also cleaves many other molecules, including chemokines, suggesting that inhibition of this enzyme could have undesired side effects. Forssmann et al. (p. 1120) analyzed the regulation of the chemokine eotaxin (CCL11) by DPPIV to address the potential effects of DPPIV inhibition on allergic inflammation. In vitro studies demonstrated that both membrane-bound and soluble DPPIV inhibited CCL11 activity. In vivo, CCL11-induced eosinophil mobilization into the blood and recruitment to inflammatory sites were augmented in DPPIV$^{-/-}$ rats compared with DPPIV$^{+/+}$ rats. In addition, inhibition of DPPIV or injection of a DPPIV-resistant chemokine analog increased CCL11-mediated eosinophil recruitment into the skin in DPPIV$^{+/+}$ animals. Intradermal injection of CCL11 indirectly induced local DPPIV expression and led to the recruitment of cells expressing surface-bound DPPIV. Finally, the authors found that DPPIV-cleaved CCL11 showed a surprising lack of feedback inhibition of DPPIV activity. This advance in the understanding of DPPIV-mediated regulation of allergic inflammation has important implications for patients treated with DPPIV inhibitors.

Summaries written by Jennifer Hartt Meyers, Ph.D.