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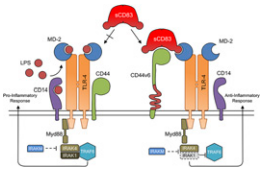
sCD83 Suppression of T Cells via Innate Immune Interactions

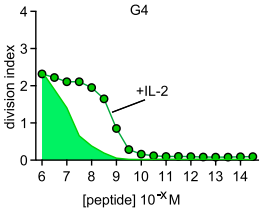


Human CD83 can be expressed as both membrane-bound and soluble forms. The soluble form (sCD83) has been shown to inhibit T cell proliferation in multiple contexts and therefore is being investigated as a potential treatment to combat autoimmunity and enhance transplantation tolerance. Although the extracellular domain of CD83 binds to monocytes and dendritic cells, its ligand on these cells is not known and the mechanism by which sCD83 exerts immunosuppressive effects remains unclear. Horvatinovich et al. (p. 2286) have now identified a ligand for sCD83 on monocytes and have begun to tease apart how sCD83 can suppress T cell activity. sCD83 was found to bind to PBMC-derived $CD14^+$ monocytes via a high affinity interaction with myeloid differentiation factor-2 (MD-2), a cofactor of TLR4 that normally acts to induce TLR4 dimerization to initiate downstream signaling following interaction of MD-2 with LPS. CD14 and CD44 containing the v6 variant in the stem loop region were also involved in sCD83 binding to monocytes but did not directly interact with sCD83. Treatment of monocytes with sCD83 resulted in rapid loss of expression of the IL-1R–associated kinase-1 (IRAK-1), a key early player in signaling through the MD-2/TLR4 complex, but had no effect on expression of other IRAK molecules. Addition of sCD83 to cultures of PBMCs stimulated with anti-CD3 and anti-CD28 impaired proliferation of $CD4^+$ and $CD8^+$ T cells and rendered these T cells unresponsive to secondary stimulation with IL-2. The mechanism of sCD83 suppression appeared to involve induction of PGE_2, IL-10, TNF-α, and IDO in PBMC cultures, and the presence of inhibitory mediators such as IL-10 suppressed the production of T cell effector cytokines. The authors propose that interaction of sCD83 with MD-2/TLR4 on monocytes results in the secretion of suppressive molecules that induce a form of anergy in T cells; this pathway could be targeted for the treatment of autoimmunity and the prevention of graft rejection.

Leaky Gut – Linking Stress and Inflammation

Although studies have shown that exposure to psychological stressors is associated with increased inflammatory responses and changes in the composition of the gut microbiota, how commensal gut microbes contribute to stress-induced inflammatory responses has yet to be elucidated. Using a social disruption (SDR) stress model in which mice undergo repeated social defeat by an intruder mouse in a resident cage, Lafuse et al. (p. 2383) demonstrate that stressed mice have elevated levels of classical monocytes and neutrophils in the spleen when compared with home cage control mice. Splenic monocytes and neutrophils in stressed mice displayed increased levels of IL-1β mRNA and decreased levels of TNF-α mRNA. SDR appeared to induce translocation of specific species of bacteria to the spleen, as mice undergoing SDR demonstrated a significant increase in *Lactobacillus* 16S rRNA, but not that of other gut commensal bacteria, in the spleen but not in other organs. Translocated bacteria primarily localized to splenic monocytes in mice undergoing SDR. Stimulation of purified splenic monocytes and neutrophils from nonstressed mice with live *Lactobacillus animalis* led to increases in not only IL-1β, but also TNF-α, suggesting that SDR may negatively regulate expression of TNF-α induced in response to translocated bacteria. Consistent with these observations, stimulation of isolated monocytes from nonstressed mice with *L. animalis* in the presence of norepinephrine reduced the induction of TNF-α by a β-adrenergic receptor–dependent mechanism. Together, these data demonstrate that during periods of stress, commensal bacteria can translocate from the intestines to the spleen, where they prime innate immune cells for enhanced reactivity to Ag challenge. This study adds to a growing body of evidence of the crucial role played by the immune system in the microbiota–gut–brain axis.

IL-2 Tweaks the Triggering Threshold in $CD8^+$ T Cells



A full understanding of how individual T cells integrate signals from their TCRs with those received via cytokine receptors to proliferate in response to Ag has remained elusive. To address this issue, Au-Yeung et al. (p. 2445) used mice bearing a Nur77-eGFP reporter, which is responsive to signals from the TCR but not from cytokine receptors. Stimulation of OTI TCR transgenic $CD8^+$ T cells expressing this reporter with high-, medium-, and low-affinity OVA-derived ligands both in vitro and in vivo revealed that these cells had a high minimum threshold of activation that was not modulated by peptide affinity or dose. However, treatment of these cells with IL-2 reduced the TCR stimulation threshold necessary to induce cell division, and this reduction was most evident when cells were treated with low doses of peptide or with low affinity peptides. IL-15, which, like IL-2, signals through JAK1/3, could also reduce the threshold for T cell proliferation, and this effect could be reversed with a JAK3 inhibitor. In contrast to its effects in $CD8^+$ T cells, IL-2 did not affect the threshold of stimulation necessary to trigger proliferation of $CD4^+$ T cells.

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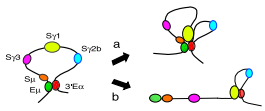
To identify a mechanism for the different effects seen following IL-2 treatment of $CD4^+$ versus $CD8^+$ T cells, the authors analyzed the responsiveness of these cells to IL-2 and found that, although both cell types were unresponsive to IL-2 in the naive state, activated $CD8^+$ T cells were much more sensitive than activated $CD4^+$ T cells to low doses of IL-2. Expression of the cell cycle regulator c-Myc was found to be upregulated and sustained when $CD8^+$ T cells were stimulated with both Ag and IL-2, and this molecule was therefore proposed to be responsible for the reduced threshold for $CD8^+$ T cell proliferation in the presence of IL-2. These data suggest that the presence of IL-2 can elicit a response from $CD8^+$ T cells in conditions of limiting TCR stimulation and indicate that $CD8^+$ T cells may be more sensitive than $CD4^+$ T cells to environmental cues such as IL-2.

53BP1 Controls Chromatin during Class Switch



During class switch recombination (CSR), DNA double-strand breaks (DSBs) are formed in switch (S) regions of the *Igh* locus through a process initiated by activation-induced cytidine deaminase (AID). The DNA damage-associated protein 53BP1 is a component of repair foci that accumulate at DSBs and is required for long-range CSR. In this issue, Feldman et al. (p. 2434) hypothesized that 53BP1 may support deletional CSR by playing a structural role in chromatin looping, in addition to its known role in DSB repair. Analysis of the C region of the *Igh* locus in activated B cells revealed that the 3′Eα in the 3′ regulatory region (3′RR) preferentially interacts with Eμ. In addition, this analysis more thoroughly defined the chromatin architecture attained by the 3′RR, which the authors propose mediates looping interactions with Eμ and the elements controlling germline transcription of the locus. Chromatin conformation capture assays in B cells lacking 53BP1 and/or AID demonstrated that 53BP1 and AID acted additively to mediate both the Eμ:3′Eα looping, which was particularly dependent on 53BP1, and intra-3′RR looping, which was dependent on both of these molecules. In contrast, looping involving 3′Eα and germline transcript promoters appeared to be independent of 53BP1. 53BP1 was found to interact with chromatin at multiple sites in resting B cells, and its distribution changed dramatically upon B cell activation. Binding of 53BP1 to chromatin appeared to be influenced by, but not completely dependent on, AID and could be dynamically redistributed over the Sμ–Cμ region of the *Igh* locus in activated B cells via chromatin spreading. 53BP1 *Igh* chromatin binding in resting B cells was associated with H4K20me2 epigenetic marks, and the authors went on to characterize the distinct chromatin marks present in the *Igh* locus in resting versus activated B cells. Taken together, these data reveal insights into the chromatin topology of the mouse *Igh* locus and suggest that 53BP1 may play an architectural role during CSR in chromatin looping independent of the DNA damage response.