ODN and IL-15 Synergy during B-CLL Growth

B-cell chronic lymphocytic leukemia (B-CLL) is characterized by malignant cell growth within lymphoid tissues, particularly lymph nodes (LN). Although recent studies have demonstrated that the TLR-9 ligand oligodeoxynucleotide (ODN) exhibits synergy with IL-15 to promote B-CLL clonal expansion, the mechanisms driving this relationship are not clear. In this issue, Gupta et al. (p. 1570) demonstrated that IL-15–producing cells are prominent in B-CLL–infiltrated LN. Time course studies using a B-CLL clone known to respond vigorously to ODN+IL-15 stimulation revealed that IL-15 is not critical until at least 24 h after ODN exposure to synergistically promote B-CLL growth. ODN stimulation of B-CLL cells significantly increased surface expression and mRNA levels of two IL-15 receptors, IL-15Rα and IL-2/15Rβ (CD122). Inhibition of NF-κB, which is activated by TLR9 signaling, abolished the ODN-induced rise in both IL-15 receptors at the protein and mRNA levels. Neutralization of IL-15 and CD122 in B-CLL cultures abrogated ODN+IL-15–induced growth when added at the initiation of culture. Interestingly, anti–IL-15 and anti-CD122 also reduced cellular division when added several days after ODN+IL-15 activation, indicating that clonal expansion requires continued IL-15/CD122 signaling. Finally, studies investigating the impact of cell density on ODN+IL-15–induced clonal expansion of B-CLL cells demonstrated that a reduction in cell density compromised ODN+IL-15–induced growth in some B-CLL clones, suggesting that trans IL-15 signaling may be an important factor for the growth of certain clones. Together, these findings demonstrate that NF-κB activation following ODN exposure fosters a rapid expression of IL-15Rα and CD122 to drive ODN+IL-15 clonal expansion of B-CLL cells. Furthermore, this study suggests that blockade of the IL-15/CD122 pathway could be an effective therapeutic target for treating B-CLL.

Modeling T<sub>rm</sub> Dynamics during HSV-2 Infection

Tissue-resident memory CD8<sup>+</sup> T cells (T<sub>rm</sub>) can rapidly eliminate virally infected cells in the mucosa and display spatial heterogeneity within the tissues. Although T<sub>rm</sub> are highly mobile at sites of viral replication, murine studies have demonstrated that T<sub>rm</sub> do not redistribute to adjacent sites to provide wider protection. In this issue, Schiffer et al. (p. 1522) performed mathematical modeling to analyze T<sub>rm</sub>-mediated responses after HSV-2 infection in the human genital tract. Although this model predicted that total T<sub>rm</sub> numbers are stable in the genital tract, their density within distinct spatial regions is highly dynamic, as T<sub>rm</sub> are either lost over time or proliferate in areas of active viral replication. Importantly, the model also demonstrated that interregional diffusion of T<sub>rm</sub> during infection is unlikely. To validate the modeling predictions, the authors performed spatial analysis of T<sub>rm</sub> distribution in paired biopsies from uninfected and infected individuals at 2 and 8 w following healing of lesions. The authors also used the model to predict the impact of therapeutic interventions on spatial T<sub>rm</sub> structure. The model predicted that daily treatment with pritelivir, an HSV-2 helicase inhibitor, would result in a dose-dependent decrease in T<sub>rm</sub> levels and variability across regions, which correlated with a reduction in viral shedding. However, the decline in T<sub>rm</sub> levels and cessation of antiviral therapy after 18 mo predicted viral shedding to a rate higher than pretreatment baseline, suggesting that many years of 100% suppressive therapy may possibly be required to control HSV-2 infection. Finally, the authors simulated the impact of vaccination and determined that a protective vaccine should aim to increase the total number of T<sub>rm</sub> rather than an increase in the density of T<sub>rm</sub> at different regions. In conclusion, this study offers important insights into T<sub>rm</sub> dynamics during active infection and effective vaccine design.

Helping B Cells in the Tonsil

Follicular helper T (Tfh) cells, a specialized subset of CD4<sup>+</sup> T cells, promote B cell maturation, but the subset of tonsillar CD4<sup>+</sup> T cells that promotes maturation of memory B cells into Ab-forming cells remains to be characterized. In this issue, Kim et al. (p. 1359) characterized a novel human tonsillar CD4<sup>+</sup> T cell subset that promotes humoral recall responses. CD4<sup>+</sup> T cells expressing high levels of P-selectin glycoprotein ligand-1 (PSGL-1) resided only in the T cell zone of human tonsil sections and were not found within the follicular mantle and germinal centers. PSGL-1<sup>hi</sup> PD-1<sup>hi</sup> CXCR5<sup>hi</sup> CD4<sup>+</sup> T cells were similar to Tfh cells in terms of expression of cell surface markers, including CD40L. However, gene expression profiling revealed that PSGL-1<sup>hi</sup> PD-1<sup>hi</sup> CXCR5<sup>hi</sup> T cells and Tfh cells were transcriptionally distinct. Compared with cocultures including Tfh cells, memory B cells produced more IgG when cocultured with PSGL-1<sup>hi</sup> PD-1<sup>hi</sup> CXCR5<sup>hi</sup> T cells. IL-10 was produced exclusively by PSGL-1<sup>hi</sup> PD-1<sup>hi</sup> CXCR5<sup>hi</sup> T cells. In the presence of anti–IL-10 Ab, Ig production in PSGL-1<sup>hi</sup> PD-1<sup>hi</sup> CXCR5<sup>hi</sup> T cell and memory
B cell cocultures was reduced. Ab-mediated blockade of both IL-10 and IL-21 further inhibited Ig production in cocultures, indicating that the two cytokines work independently to promote Ig production by B cells. Furthermore, PSGL-1hi PD-1hi CXCR5hi T cells upregulated CD40L upon stimulation. Together, these data identify a population of extrafollicular CD4+ T cells in human tonsils that promote memory B cells to produce Abs via CD40L, IL-10, and IL-21.

Membrane-Associated Proteinase 3 Inhibits T Cell Proliferation

Polymorphonuclear neutrophil (PMN)-derived serine proteases, such as proteinase 3 (P3), regulate the tumor microenvironment and inflammation. However, the effects of PMN-derived P3 on T cell proliferation are unknown. Thus, Yang et al. (p. 1389) examined the effects of membrane P3 (mP3)-expressing PMN and acute myeloid leukemia (AML) blasts on T cell proliferation. Coculture of healthy donor PMN and autologous PBMCs stimulated with anti-CD3/CD8 mAbs inhibited both CD4+ and CD8+ T cell proliferation in a PMN dose-dependent manner. PMN-mediated inhibition of T cell proliferation was largely abrogated when the cells were separated in a Transwell system, indicating that contact is required for maximal T cell inhibition by PMN. Addition of anti-P3 Ab to PMN–PBMC cocultures restored T cell proliferation. Moreover, the enzymatic function of P3 was required for the inhibition of T cell proliferation: addition of serine protease inhibitors reduced PMN-mediated inhibition of T cell proliferation. When PMN lacked mP3, inhibition of T cell proliferation was reduced. Proliferation of CD8+ and CD4+ T cells was significantly inhibited when cocultured with AML cells expressing high levels of mP3, whereas proliferation of T cells cocultured with AML expressing low levels of mP3 was comparable to PBMCs stimulated with anti-CD3/CD28 mAbs. Addition of anti-P3 Ab significantly restored T cells’ capacity to proliferate in the presence of mP3-expressing AML blasts. These data indicate that mP3 expression by PMN and AML cells inhibits T cell proliferation and suggest that targeting of P3 may be an effective immunotherapy for the treatment of AML and autoimmune diseases.