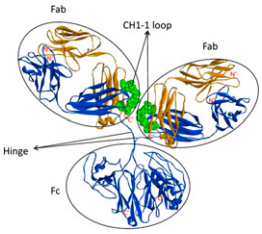
THE JOURNAL OF IMMUNOLOGY

In This Issue

Flexing Abs



Ab structure is known to change during Ag binding, but structural shifts attributed to specific Ag interactions versus those which are due to intrinsic properties of the Ab have not been clearly discerned. Sela-Culang et al. (p. 4890) undertook an exhaustive analysis of the existing structures of 49 Abs in both free and Ag-bound states to better define these structural changes. The majority of Abs analyzed showed a consistent and significant conformational change during Ag binding at a site distal from the Ag-binding site in a loop within the H chain constant domain, which has been associated previously with interactions between L and H chains. In addition, a conformational change within the binding site in the CDR-H3 was observed consistently during Ag binding in about one third of Abs analyzed. Ag size influenced the relative orientation of H and L chains within Abs such that large protein Ags were associated with a greater change in orientation when compared with the binding of peptide Ags. This in-depth analysis of free and bound Ab structures better characterizes regions within Abs that consistently change during Ag binding, which may provide insight into novel aspects of Ab function.

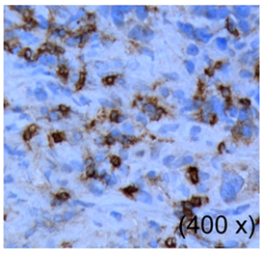
Saved from Sepsis by IL-7

Septic shock is associated with many irregularities in the immune response, including lymphopenia and a decrease in T cell proliferation. Therapeutic interventions are sought to boost appropriate immune responses during sepsis, and Venet et al. (p. 5073) now assess the ability of recombinant IL-7 to restore immune function in septic patients. Relative to healthy controls, plasma concentrations of IL-7 in septic patients were slightly elevated. Expression of CD127, the IL-7R α-chain, on $CD4^+$ and $CD8^+$ T cells was not significantly affected by sepsis, and together these observations suggested that sepsis did not cause any major defects in the IL-7 signaling pathway. Ex vivo treatment of PBMCs from septic patients with recombinant human IL-7 (rhIL-7) restored $CD4^+$ and $CD8^+$ T cell proliferation, as well as IFN-γ production by $CD8^+$ T cells, to levels similar to those observed in healthy controls. rhIL-7 treatment of PBMCs from septic patients also induced BCL2 expression and STAT5 phosphorylation, both critical components of the IL-7 intracellular signaling pathway. Overall these results indicate that IL-7 treatment of lymphocytes from septic patients restores multiple immune parameters, and support future investigation of IL-7 as a therapeutic intervention during sepsis.

Alternative Anaphylatoxin

The complement cascade, with its myriad immune-activating components, is the source of the anaphylatoxins C3a, C5a, and $C5a^{desArg}$. These critical players induce inflammation and recruit polymorphonuclear cells through the ligation of their respective G-protein-coupled receptors, C3aR and C5aR. The affinity of $C5a^{desArg}$ for C5aR was thought to be lower than that of C5a, and $C5a^{desArg}$ is formed through rapid carboxypeptidase-mediated removal of C-terminal arginine in the serum. These observations suggested that $C5a^{desArg}$ may be a less active form of anaphylatoxin. Reis et al (p. 4797) dispelled this hypothesis with a novel label-free assay that demonstrated that at physiological levels $C5a^{desArg}$ was more efficient at stimulating cell activation than C5a. This increase in cell activation was seen in both a transfected cell line and in primary human polymorphonuclear cells. Activation was mediated solely through C5aR as was shown through the use of the C5aR antagonist PMX-53. Interestingly, C5a and $C5a^{desArg}$ stimulated different Gα proteins despite their shared use of C5aR. Analysis by mass spectroscopy of post-translational modifications to both C5a and $C5a^{desArg}$ showed partial cysteinylation at Cys^{27} and glycosylation at Asn^{64}. These data indicate that $C5a^{desArg}$ plays as vital a role in promoting local inflammation, immune surveillance, and immune homeostasis as its brethren anaphylatoxins.

γδ T Cells as a Clinical Predictor



The great variety of tumor-infiltrating lymphocytes (TILs) vastly complicates the field of cancer immunopathogenesis. Ma et al. (p. 5029) shed some light onto this intricate area with an elegant study looking at the incidence of γδ T cells in primary breast cancer tissue. Previous studies from this group indicated that there are high levels of γδ regulatory T cells in breast cancer tissue and that these TILs have suppressive effects. Using retrospective multivariate analyses on patient samples spanning six years, the authors found in this study that most breast cancer patients had an accumulation of γδ T cells. These specific TILs correlated with HER2 expression, lymph node metastasis, and advanced tumor stages. An inverse correlation was observed between the presence of γδ T cells and both relapse-free survival and overall survival of the patients. Comparison of intratumoral γδ T cells with other prognostic variables by multivariate and univariate analyses indicated that the presence of intratumoral γδ T cells was the most significant prognostic factor for determining breast cancer severity. Whereas the presence of intratumoral γδ T cells and $FoxP3^+$ cells were found to correlate with each other in tissue samples, the presence of intratumoral

www.jimmunol.org/cgi/doi/10.4049/jimmunol.1290070