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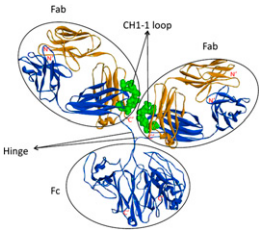
Flexing Abs



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.

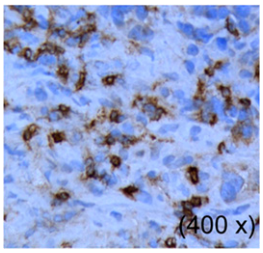
Saved from Sepsis by IL-7

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

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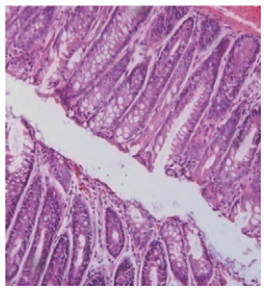
γδ T cells was a more significant marker of poor clinical outcome. These data indicate that the authors have found a novel clinical predictor of breast cancer severity and identified a potential target for immunotherapy.

Bcl6 Bias against Th2



Bcl6 is a transcriptional repressor that has been shown recently to regulate Th cell differentiation. Previous studies have also shown that $Bcl6^{-/-}$ mice spontaneously develop Th2-mediated inflammation. Sawant et al. (p. 4759) explored the role of Bcl6 in regulatory T cells (Tregs) and how this influences T cell polarization. They found a similar percentage of $CD4^+CD25^+Foxp3^+$ Tregs in $Bcl6^{-/-}$ mice relative to wild-type (WT) controls. $Bcl6^{-/-}$ Tregs could suppress T cell proliferation in vitro, and adoptive transfer of $Bcl6^{-/-}$ Tregs could curb the development of colitis in vivo. However, adoptively transferred $Bcl6^{-/-}$ Tregs could not suppress Th2-mediated allergic airway inflammation, and transfer was associated with more intense Th2 responses in the lung. Mixed bone marrow chimera experiments revealed that $Bcl6^{-/-}$ Tregs had a specific defect in controlling Th2 responses; no apparent defect was observed in modulation of Th1 or Th17 responses. Gene expression analysis showed significant upregulation of Th2- and Treg-related genes in $Bcl6^{-/-}$ Tregs relative to WT Tregs, especially that encoding the Th2 transcription factor Gata3. Further investigation showed that Bcl6 could directly repress Gata3-driven transcription of Th2 genes. These results provide mechanistic insight into how Bcl6 deficiency causes Th2-mediated inflammation and also reveals a role for Bcl6 in Tregs.

Biosensor B Cells

To be effective, the ideal HIV vaccine will need to elicit a broadly neutralizing Ab (bNAb) response. The trick, of course, is how to achieve this. Ota et al. (p. 4816) addressed this challenge with the production of B cell lines that expressed bNAbs and germline-reverted broadly neutralizing Abs (gl-bNAbs) as BCRs. They used these BCRs to test how well bNAb-expressing cells would be able to recognize both HIV pseudovirions and potential vaccine proteins. Using the induction of rapid intracellular calcium levels as a marker of activation and hence recognition, they found that infectious virions expressing HIV Env protein were poorly recognized. Poor or delayed BCR recognition of the Env protein, due to the low density of Env spikes on the surface of the virion, was proposed as the reason for this observation. However, soluble gp140 trimers and a multimerized, scaffolded epitope protein that is an Env mimic stimulated a strong response. Neither the virions nor the bNAb stimulatory proteins generated a response from gl-bNAb BCRs. These data point the way to a novel approach to identify HIV vaccine candidates and provide support for the inclusion of soluble Env trimers or Env-mimicking multimerized scaffolded epitopes in any vaccine formulation. The authors also conclude that further investigation is necessary to generate epitope formulations that can stimulate the production of an anti-HIV response from naive gl-bNAb producing B cells, thus mounting a quicker protective response to infection.