inside blood

Rituximab: complementary mechanisms of action

Approximately 200 000 patients have been treated with rituximab, yet the debate over the relative importance of various potential mechanisms of action for this antibody continues. In this issue, Cragg and colleagues (page 1045) report on complement-mediated cytotoxicity induced by various anti-CD20 antibodies. They found that the ability of these antibodies to induce complement-mediated lysis is dependent not only on isotype and antigen binding, but also on the mobility of the resulting antibody-antigen complex in the plasma membrane. The anti-CD20 antibodies that fixed complement most effectively were those that translocated to lipid rafts in the cell membrane following CD20 binding. Lipid rafts are known to play a central role in the transmembrane signaling mediated by a variety of antigens. Thus the finding that anti-CD20 antibodies differ in their ability to segregate antigen-antibody complexes into lipid rafts has implications not only on complement-mediated cytotoxicity but also on apoptosis that can result directly from anti-CD20 binding to antigen.

Further, complement fixation can result in opsonization of the tumor cell, thereby leading to enhanced cellular cytotoxicity. Recent advances, including an understanding of differences between antibodies in their ability to alter membrane trafficking of antigen, will be useful in identifying approaches to selecting new antibodies for development or enhancing the efficacy of currently available antibodies. But one should not expect a rapid and clean conclusion to the debate about the relative clinical importance of transmembrane signaling, antibody-dependent cellular cytotoxicity, and complement-mediated cytotoxicity. In fact, the evidence is mounting that signaling, cellular cytotoxicity, and complement are interactive mechanisms that together are responsible for the antitumor activity of antitumor antibodies. Segregation into lipid rafts is a characteristic of the antigen-antibody complex that could impact on the efficacy of antibody therapy through all 3 major "complementary" antitumor antibody mechanisms of action.

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Antigen receptor signaling in CLL—is the line dead?

B-cell chronic lymphocytic leukemia (CLL) can be segregated into 2 subtypes based upon the nature of the expressed immunoglobulin (Ig) genes. Leukemia cells that use unmutated Ig more often express CD38 and are associated with a higher tendency toward disease progression than are CLL cells that express mutated Ig. Lanham and colleagues (page 1087) presents evidence that CLL cells that have unmutated Ig are more likely than CLL cells with mutated Ig to undergo tyrosine phosphorylation of cytosolic proteins (a mark of signal transduction) upon ligation of the B-cell receptor (BCR) for antigen. These observations are in agreement with those of others (Chen et al, Blood. 2002;100:4609-4614) and suggest that the 2 subtypes of leukemia differ in their capacity to respond to the crosslinking of their surface Ig by antigen. Not unexpectedly, the association between mutational status and signal transduction capacity was not absolute but probably reflects other biologic differences between the 2 leukemia subtypes.

One likely candidate for this is ZAP-70, a protein tyrosine kinase required for receptor signaling in T cells that often is expressed by CLL cells with unmutated Ig, but generally not by CLL with mutated Ig or normal B cells (Rosenwald et al, J Exp Med. 2001;194:1639-1647). The study of Chen et al found that the capacity to signal via the BCR for antigen was associated most closely with the expression of this kinase, even in unusual cases that expressed ZAP-70 but used mutated Ig receptors. Conceivably, the difference in the capacity of the leukemia cells to be stimulated by ligation of their BCR relates to differences in the noted clinical behavior of these 2 subtypes of CLL. If so, then analyses of the receptor signaling capacity might provide for a more reliable prognostic indicator than expression of CD38, Ig mutational status, or other features found differentially expressed by the 2 subtypes of this leukemia.

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