left with a conundrum. The functional activation of STAT6 is very common in PMBL, and mutations in the DNA binding region of the gene are frequently found in this disease. However, it remains unclear whether these point mutations in STAT6 have any direct connection to the pathogenesis of this disease. There are many alternative hypotheses by which these mutations may be functionally important in PMBL. They may affect the expression of other important STAT6 target genes, perhaps by modifying the binding specificity of STAT6, or alter interactions with other transcription factors or coregulators. Perhaps the relative loss of function of the mutant forms of STAT6 is necessary to attenuate the enhanced STAT6 function derived from heightened activity of kinases such as Jak2, or loss of negative regulators such as SOCS1. On the other hand, reflecting the immunoglobulin gene rearrangement that normally occurs in B lymphocytes, B-cell lymphomas often display enhanced somatic hypermutation. It is possible that STAT6 is a particular hotspot for such mutations in PMBL with no functional consequence. Thus, rather than STAT6 mutations being “drivers” of PMBL pathogenesis, perhaps they are “passenger” mutations of little consequence. At this point, only further experimentation will illuminate these possibilities.

Nonetheless, these findings highlight 2 key issues. First, the interchange of ideas between the clinic and the lab exemplified in this work will be essential for the advances we need in elucidating the molecular pathogenesis of cancer. Second, regardless of the function of these newly described STAT6 mutations, evidence continues to grow supporting the key role of transcription factors as mediators of oncogenesis and targets for molecular therapy.

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Comment on Kryczek et al, page 1141

Th17 cells in ovarian cancer

David H. Munn  MEDICAL COLLEGE OF GEORGIA

In this issue of Blood, Kryczek and colleagues show that a potent proinflammatory T-cell subset, IL-17–producing Th17 cells, can be found in ovarian cancers, and that their presence correlates with significantly enhanced survival.

Tumors express a variety of antigens, arising from mutations or aberrant processing, which ought to render them detectably “foreign” to the host immune system. Unfortunately, in most cases the patient’s immune system fails to mount a protective response against these tumor-associated antigens. Yet some patients do appear to respond immunologically to their own tumors. When this happens, it is often a favorable prognostic sign.1,2 What are the features of such a beneficial spontaneous antitumor immune response?

It is intuitively logical that a robust CD8+ cytotoxic T cell (CTL) response might predict a favorable outcome since CTLs directly kill tumor cells. Indeed, CD8+ infiltration into tumors has been shown to be associated with favorable prognosis.2 CD4+ T-cell responses may also be critically important in cancer, both in helping to recruit CD8+ CTLs to the tumor and in generating a local inflammatory milieu that supports the function of these CTLs within the tumor. However, the CD4+ arm of the immune system has not been as well characterized in antitumor responses. The situation is made more complex by the variety of CD4+ helper responses—Th1, Th2, and the recently described T-helper 17 (Th17) response—as well as the highly undesirable immunosuppressive regulatory T cell (Treg) response.

In the current study, Kryczek et al analyzed the tumor-infiltrating CD4+ T-cell population from 201 ovarian cancer samples for the presence of Th17 cells.3 Th17 cells play a potent proinflammatory role in certain infections and autoimmune disorders,4 and Th17 cells can display antitumor activity in certain mouse tumor models.4 However, the role of Th17 cells in human tumors has not been well studied. The authors found that some ovarian cancers contained a substantial fraction of tumor-infiltrating CD4+ T cells expressing interleukin-17 (IL-17), indicative of Th17 differentiation. Those patients with a higher number of tumor-infiltrating Th17 cells had significantly better overall survival, irrespective of their tumor stage (panel A in the figure). The presence of Th17 cells was found to be associated with multiple proinflammatory cytokines and chemokines. Th17 cells were also found to be inversely correlated with the number of tumor-infiltrating Foxp3+ Tregs.

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which have been previously shown to be an adverse prognostic factor in ovarian cancer. It is known that inducible Tregs and Th17 cells share a reciprocal differentiation pathway from uncommitted CD4+ precursors. In the current study, the authors show that macrophages isolated from ovarian tumors biased the in vitro differentiation of uncommitted CD4+ T cells toward Th17 cells. Therefore, the observed inverse correlation between Th17 cells and Tregs in tumors may reflect differing conditions within different tumors, favoring either inflammation (Th17) or suppression (Tregs). Furthermore, the Th17 and Treg lineages have recently been shown to be rather more plastic than previously thought, with several studies suggesting the possibility of interconversion between the 2 lineages. Thus, the inverse relationship between Th17 cells and Tregs observed in ovarian cancers may be more than simply a descriptive association. It may reflect fundamental differences in the nature of the spontaneous antitumor immune response—differences that appear to have significant impact on patient survival.

Finally, the Th17 cells in ovarian cancers were found to simultaneously express high levels of multiple other proinflammatory effector cytokines (IL-2, TNF-α, IFN-γ) in addition to IL-17 (panel B in the figure). In other settings, this so-called polyfunctional pattern of effector cytokine production has been associated with robust CD4+ response to infection and vaccination. Other investigators, including myself, have reported similar polyfunctional cytokine response by Th17-like cells in mouse tumor models as well. Thus, taken together, Kryczek et al have described a functionally important and hitherto unrecognized population of CD4+ T cells in ovarian cancers that favor enhanced inflammatory responses and reduced Treg-mediated suppression. The presence of these polyfunctional Th17 cells was statistically associated with better clinical outcome. This raises the question of whether a similar population could be therapeutically induced or expanded (eg, by vaccines or other active immunotherapy), and if this would likewise result in improved patient outcome.

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PLATELETS & THROMBOPOIESIS

Comment on Greinacher et al, page 1250

Double jeopardy

Richard H. Aster  BLOODCENTER OF WISCONSIN

Patients treated with the widely used “RGD-mimetic” platelet inhibitors sometimes experience severe but self-limited thrombocytopenia after exposure to one of these agents. Since thrombocytopenia occurs within a few hours, it is generally thought that the responsible drug-dependent antibodies affect only circulating platelets.

In this issue of Blood, Greinacher and colleagues describe the case of a 67-year-old man who experienced severe thrombocytopenia and profuse bleeding after a second exposure to the platelet function inhibitor eptifibatide. An eptifibatide-dependent, platelet-reactive antibody specific for the platelet glycoprotein GPIIb/IIIa complex was detected in the patient’s serum, providing a likely explanation for the acute drop in platelet levels. Unlike most patients with eptifibatide-induced immune thrombocytopenia, however, the platelet count remained profoundly low (< 5000/μL) for 4 days. A normal count was not achieved until more than a week later. Four days after the acute episode, the overall numbers of megakaryocytes in the marrow was reduced, and they had a “young” morphology. This suggested that the drug-dependent antibody might have injured mature megakaryocytes in addition to causing destruction of circulating platelets, and provided a likely explanation for the 4- to 6-day delay before platelet levels began to recover. To test this possibility, CD34+ cord blood stem cells were cultured under conditions favoring differentiation into megakaryocytes and were then treated with patient Immunoglobulin G (IgG) in the presence and absence of eptifibatide. Loss of cell viability (trypan blue exclusion) was significantly greater under these conditions than after treatment with drug alone or IgG alone. Cytologic studies showed that drug-dependent cytotoxicity preferentially affected megakaryocytes that had a high surface density of GPIIb/IIIa, presumably a population of relative mature cells. From these findings, the authors conclude that prolonged thrombocytopenia observed in this patient was caused by the cytotoxic effect of a GPIIb/IIIa-specific, drug-dependent antibody on mature megakaryocytes.

The issue of whether platelet-specific antibodies can damage megakaryocytes and impair platelet production has a long and interesting history. Almost a century ago, Frank observed that, in such cases, platelets were destroyed “as fast as they were formed.” Thereafter followed a lively and long controversy over which of these mechanisms was the main
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