was specific for thrombin generation and fibrin formation.

Perhaps more interesting, Zhu et al showed that polyphosphate played a role in more than just thrombin generation through feedback activation of factor XI. Polyphosphate directly interacted with fibrin in a way that made the thrombus less susceptible to lysis by fibrinolytic agents. Blocking polyphosphate reduced thrombus stability and increased lysis of the fibrin clot. All of this suggests that polyphosphate is an intriguing target for antithrombotic agents. Such an antithrombotic would not only reduce thrombin generation but also alter fibrin structure to promote lysis of any thrombus that does form.

One of the holy grails of antithrombotic therapy is to have agents that are effective without increasing the risk of bleeding. Zhu et al discuss the data suggesting that the contribution of the contact pathway to hemostasis is to augment the existing platelet-driven thrombin generation. In this study, Zhu et al significantly advance our understanding of possible contributions of the contact pathway to thrombus formation. If, as this study suggests, factor XI and polyphosphate have a greater contribution to thrombus formation than hemostasis in human blood, then those molecules make appealing targets for novel antithrombotic agents.

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Comment on Wikstrom et al, page 1503

Does GVHD make amateurs out of professional APCs?

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In this issue of *Blood*, Wikstrom and colleagues highlight antigen-presenting cell (APC) dysfunction as a potential cause of impaired antiviral immunity in graft-versus-host disease (GVHD).[1]

Along with malignant relapse and GVHD, posttransplant immunodeficiency and infections represent major barriers to successful allogeneic hematopoietic transplantation. Cytomegalovirus (CMV) infection in particular is a frequent cause of morbidity posttransplant, especially for recipients of T-cell–depleted and umbilical cord blood allografts as well as patients with GVHD.[2,3] GVHD is often viewed as a central problem because it necessitates treatment with corticosteroids and can also lead to thymic damage, both of which compromise immune recovery and may increase the risks of infection and relapse.[4-6]

Although impaired antimicrobial T-cell immunity posttransplant is frequently attributed to reduced T-cell recovery, competent adaptive immune responses require several steps, including T-cell activation by APCs such as dendritic cells (DCs). Moreover, there is a growing awareness that other immune cells besides αβ T cells contribute to anti-CMV immunity posttransplant, and the pathophysiology of CMV reactivation involves more than just T-cell deficiency.[7] Furthermore, in addition to impaired T-cell immune reconstitution, patients at risk for CMV infection due to GVHD have also been found to demonstrate reduced DC reconstitution, and CMV infection itself can impair DC function.[8,9]

To evaluate the function of DCs during viral infection posttransplant, Wikstrom and colleagues turned to experimental mouse models of bone marrow transplantation (BMT), which have proven to be tremendously valuable to the field of hematopoietic transplantation since its inception. First, the authors discovered that allogeneic BMT recipients with GVHD were profoundly more susceptible to infection with murine CMV (MCMV) posttransplant than syngeneic BMT recipients, and MCMV-infected mice with GVHD demonstrated more severe hepatic necrosis than uninfected mice with GVHD or infected mice without GVHD. The authors also found that there was reduced expansion of MCMV-reactive CD8 T cells in syngeneic transplant recipients after DC depletion, demonstrating the importance of DCs for generating an anti-MCMV immune response post-BMT.

Evaluating MCMV-reactive T cells after allogeneic BMT, the authors found that GVHD appeared to have an effect similar to DC depletion after syngeneic BMT. There was reduced expansion of MCMV-reactive CD8 T cells in allogeneic transplant recipients with GVHD. There were also fewer splenic $CD8\alpha^+$ and $CD11b^+$ DCs in infected mice with GVHD, the splenic DCs that were present in mice with GVHD were less likely to be infected with MCMV, and these DCs demonstrated reduced expression of the costimulatory molecules CD40 and CD86. These defects could be overcome by transfer of MCMV-specific transgenic T cells or by transfer of polyclonal T cells from donor mice that had been exposed to MCMV.

The findings of the authors highlight the importance of DC function for mounting effective antiviral T-cell responses posttransplant. Interestingly, although MCMV-specific transgenic T cells appeared to expand less in mice with GVHD, they remained effective in controlling the virus. These were naive T cells, suggesting that APC-related defects posttransplant can be overcome if there is an adequate MCMV-reactive T-cell pool. However, this APC

independence of naive MCMV-specific T cells may be specific to immune responses with transgenic T cells, as polyclonal T cells from donor mice previously exposed to MCMV were more effective at controlling MCMV infection than polyclonal T cells from unexposed donors. Another possibility is that GVHD may elicit T-cell–intrinsic defects that can be overcome by MCMV-specific transgenic T cells or by MCMV-specific memory T cells.

Further studies addressing T-cell vs APC defects in GVHD (and after corticosteroids) are warranted, as well as studies incorporating the role of natural killer cells. Differences between naive and memory antiviral T cells in relation to APC dysfunction posttransplant are of particular interest given the recent clinical demonstration that allografts depleted of naive T cells may be associated with less-severe acute GVHD and reduced incidence of chronic GVHD.[10] CMV-specific T cells could be detected posttransplant in that study, although their effectiveness in controlling CMV infection remains to be determined. Regardless, it is clear that henceforth both T-cell and DC defects should be considered in designing experimental and clinical studies related to antiviral immunity in transplant recipients with GVHD.

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