chain amyloidosis. This can occur without a rise in the size of the monoclonal protein, and the monitoring physician must be aware of the development of diarrhea, edema, or lower extremity paresthesias. Others have suggested that measurement of the NT-proBNP become part of the evaluation of patients with monoclonal gammopathy of undetermined significance who are being observed to detect early amyloid cardiomyopathy.

Amyloidosis is rare, and because no specific diagnostic test exists, lacking a high index of suspicion, it can easily be overlooked. The responses to chemotherapy reported in this manuscript clearly benefit our patient population even with advanced cardiac disease. The development of new agents for the treatment of amyloidosis include pomalidomide and the potential for carfilzomib, MLN-9708, and the exciting development of amyloid-specific monoclonal antibodies offers great hope for the future of our patients.

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REFERENCES


THROMBOSIS & HEMOSTASIS

Comment on Sorvillo et al, page 3502

Presenting ADAMTS13 on a TTP-associated MHC

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In this issue of Blood, Sorvillo et al investigate possible molecular triggers leading to idiopathic, autoimmune thrombotic thrombocytopenic purpura (TTP) by identifying naturally processed A Disintegrin And Metalloprotease with ThromboSpondin type 1 motif 13 (ADAMTS13)-derived peptides presented on human dendritic cells.1

TTP is a rare but serious pathological disorder in which the ultra large form of von Willebrand factor (ULVWF) released by activated endothelium into the circulation cross-links platelets, causing intravascular agglutination under high shear stress, ie, primarily in the microvasculature.2 Most patients with idiopathic TTP have acquired autoantibodies to ADAMTS13, a large circulating metalloprotease that cleaves ULVWF at a specific site, generating VWF multimers that are significantly less adhesive than ULVWF.3,4 Anti-ADAMTS13 antibodies in plasma from TTP patients consist primarily of IgG4 and IgG3 subclasses, indicating the involvement of effector T cells in the etiology of this disease,5 and the major histocompatibility complex (MHC) allele HLA-DRB1*11 has recently been identified as a risk factor for the development of TTP. The study by Sorvillo et al presented in this issue1 systematically investigated the HLA restriction of ADAMTS13 peptide presentation on human MHC Class II by isolating and expanding dendritic cells from 17 healthy blood donors in culture, “feeding” them different concentrations of recombinant ADAMTS13 protein, and then recovering the peptides presented on their surface and identifying them using mass spectrometry. Interestingly, dendritic cells exposed to ADAMTS13, but not control cells treated with phosphate-buffered saline alone, presented peptides derived from several ADAMTS13 domains, and peptides derived from its C-terminal CUB2 domain were presented with the highest efficiency. Dendritic cells from donors with an HLA-DRB1*11 allele exposed to a higher ADAMTS13 concentration presented only differentially processed versions of the same CUB2 peptide, which contains the predicted DRB1*11-binding sequence FINVAPHAR. The binding of naturally processed ADAMTS13 peptides to MHC Class II on human dendritic cells indicates that these peptides may contain clinically relevant T-cell epitopes, although future experiments showing stimulation of human effector T cells by similar peptides will be required to confirm this hypothesis.

Autoimmune TTP is caused by antibodies that bind to ADAMTS13 and neutralize its proteolytic activity. Most acquired TTP patients circulate antibodies that bind to the spacer domain of ADAMTS13, although antibodies with specificity for other regions, including the CUB domains, have also been identified in subsets of TTP patients.6,8 Although T-cell and B-cell epitopes often occur in close proximity or even overlap, they can also be derived from spatially distant regions of a protein antigen. This is because the presentation of T-cell and B-cell epitopes to the immune system is fundamentally different. CD4 T-cell epitopes consist of peptides at least 9 to 16 residues in length derived from antigens such as ADAMTS13, which bind to the MHC Class II binding groove on antigen-presenting cells. The MHC Class II-peptide complex is presented to T-cell receptors on, presumably in the case of TTP, autoreactive T cells that escaped thymic deletion and subsequently became..
stimulated by ADAMTS13. B-cell epitopes are 3-dimensional surfaces, eg, of properly folded protein antigens, recognized by antibodies and by receptors on the surface of memory B cells. Unlike T-cell epitopes, they are often comprised of noncontiguous amino acid sequences in the protein antigen.

A major contribution of this study is that it identifies ADAMTS13 peptides that have been naturally processed in the MHC compartment of human dendritic cells and then presented on their surface, which is required for subsequent effector T-cell stimulation leading to antibody formation. Both epitope prediction algorithms and studies of synthetic peptides binding to HLA proteins, although extremely useful in many immunologic investigations, tend to overpredict T-cell epitopes. The elution of a predominant ADAMTS13 core peptide from dendritic cells isolated from donors with the risk-associated allele HLA-DRB1*11 points the way to additional future studies that will determine whether this is indeed an immunodominant epitope involved in the etiology of autoimmune/idiopathic TTP. Clearly, the vast majority of individuals with an HLA-DRB1*11 allele will never develop the rare autoimmune disorder TTP. The identification of T-cell epitopes involved in the development and progression of TTP, however, will lead to the isolation and characterization of T cells responsible for the production of neutralizing anti-ADAMTS13 antibodies. In addition to the immediate clinical relevance of such studies, this will present an opportunity to study the processes by which T cells that evaded thymic deletion become autoreactive and thus pathogenic. For example, approximately two-thirds of TTP cases occur in women, and pregnancy can be the initiating event.9 Idiopathic TTP has also been associated with HIV, various drugs, bone marrow transplantation, malignancies, infections, and inflammatory disorders.10 The common factors among these precipitating events and conditions are poorly understood. The identification of specific epitopes in ADAMTS13 will facilitate studies in which the relevant pathogenic T cells may be isolated from peripheral blood donated by human subjects with TTP and will also better define HLA-associated risk factors for TTP. Finally, many autoimmune responses, eg, rheumatoid arthritis, are provoked by epitopes in multiple, often poorly-defined, antigens. The developing mechanistic story of human autoimmune responses to a single well-defined protein antigen, ADAMTS13, will likely be of significant interest to researchers carrying out both basic and clinical studies of other autoimmune disorders.

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REFERENCES


Comment on Leonhardt et al, page 3307

Targeting neovascularization in GVHD

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In this issue of Blood, Leonhardt et al1 report that neovascularization during graft-versus-host disease (GVHD) is regulated by α6 integrins and the micro RNA miR-100.

Judah Folkman, the visionary physician-scientist who ultimately convinced doubting colleagues that neovascularization was critical to the development and metastasis of human cancers, often repeated the mantra, “Science goes where you imagine it.”2 Despite the often imaginative research of scientists who have devoted their lives to the study of mechanisms of GVHD following allogeneic hematopoietic stem cell transplantation (HSCT), meaningful therapeutic advances have so far been sparse, and the primary strategies used to prevent and treat GVHD in most centers have evolved little from the approaches advanced by Thomas, Storb, and colleagues more than a quarter century ago.3 The current study suggests that targeting of neovascularization might yield a new class of therapies aimed not only at effector T cells, the primary targets of therapies advanced to date. As elegantly reviewed in Blood,4 studies of the role of vascular proliferation in GVHD were conducted surprisingly early in the course of the development of experimental and clinical HSCT. Indeed, pioneering transplant immunologists Brent and Medawar5 described in 1966 the “bright and scarlet reaction” of inflammation in GVHD that was clearly dependent on local microvascular changes. By the mid-1970s, Siliky and Auerbach6 quite clearly described a phenomenon that they termed “lymphocyte-induced angiogenesis” that occurred in the context of graft-versus-host reactions, demonstrating a direct correlation

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