had weak or absent ADAMTS13 inhibitor activity, and inhibitor levels often did not correlate well with disease activity. Therefore, a significant subset of patients with nonfamilial TTP was left without a clear cause of ADAMTS13 deficiency. From a treatment standpoint, the inability to reliably identify an autoimmune etiology in a sizable fraction of patients made clinical trials of immunomodulation therapy difficult to design.

The mystery of the missing cause of ADAMTS13 deficiency in nonfamilial TTP may soon be clarified. In this issue, Scheiflinger and colleagues (page 3241) report the discovery of noninhibitory anti-ADAMTS13 antibodies in a patient with nonfamilial TTP. The patient had severely decreased ADAMTS13 activity, but no detectable ADAMTS13-inhibiting antibodies. Using a novel enzyme-linked immunosorbent assay (ELISA) with recombinant human ADAMTS13 as an antibody-binding substrate, they discovered both immunoglobulin G (IgG) and IgM anti-ADAMTS13 antibodies in the patient's plasma in concentrations markedly higher than normal plasma.

Although preliminary, this observation may help fill the current gap in pathogenic models of nonfamilial TTP. It appears that ADAMTS13 deficiency may be caused by different kinds of autoantibodies, not all of which are detected by inhibitor studies. It may be that patients with TTP can develop antibodies with varying degrees of functional inhibition and protein clearance effects, and such variability could account for the sometimes-perplexing results of inhibitor studies. Future studies to determine if ADAMTS13-binding antibodies are prevalent in nonfamilial TTP, and whether levels correlate with disease course, will be of great interest.

An assay that detects a broad range of ADAMTS13-binding antibodies may prove to be the critical tool needed to identify patients and monitor treatment response in ADAMTS13-deficient, nonfamilial TTP. With such a new resource, the promise of significant advances in immune modulation treatment in TTP may be close at hand.

—Thomas J. Raife
University of Iowa

Fighting HIV: a little help from *Toxoplasma*?

In their everyday fight for survival, germs must face not only the sophisticated immunologic weaponry developed by their natural hosts, but also the potential interfering effects of other microorganisms. As illustrated by a growing number of examples, such interference cannot be simply ascribed to competition for space or vital substrates (including receptor molecules), but it is often mediated by the microbial manipulation of the host immune system, in particular of soluble mediators such as cytokines and chemokines.[1] Golding and colleagues (page 3280) provide a new paradigm of this concept by showing that a protein encoded by the parasite *Toxoplasma gondii*, the cyclophilin C-18, blocks the infectivity and fusogenic activity of HIV. This study is a natural extension of the observation reported in May of this year by some of the same authors[2] who identified C-18 as the principal parasite component that mediates the immunomodulatory effects of *Toxoplasma*, demonstrating that this cyclophilin directly binds and activates CCR5, a chemokine receptor that represents a critical entry gateway for HIV on the surface of human cells. At this stage, the potential clinical implications of this observation remain uncertain. On one side, it is conceivable that *Toxoplasma* infection, while representing one of the most threatening complications of AIDS, might paradoxically induce a temporary abatement of HIV replication, as seen for example during acute measles[3]; on the other side, however, there are no clinical data, at present, to support this concept. In fact, the in vivo interactive network is likely to be more complex, as suggested by experiments in mice bearing a full-length HIV-1 transgene, in which infection with *Toxoplasma* was shown to induce a significant increase in proviral transcription.[4]

While interference with HIV presumably represents a purely accidental side-effect for *Toxoplasma*, the question arises as to how the parasite might benefit from activation of CCR5. In this respect, it is noteworthy that diverse microbial pathogens have evolved strategies to modulate chemokine functions.[1] Some viruses, such as human herpesvirus 6 (HHV-6) and human T-cell lymphotropic virus I (HTLV-I) or HTLV-II, are potent inducers of host chemokines, while others, including various herpesviruses and poxviruses, encode functional chemokine agonists that were ancestrally hijacked from the host genome.[5] Even though the mechanism selected by *Toxoplasma* (a cyclophilin with no sequence homology to cellular chemokines) may be unique, this emerging pattern suggests that control of the chemokine system may provide a key to survival for invading microorganisms.

An interesting perspective stemming from the present findings is the possibility of exploiting *Toxoplasma* C-18 for developing novel CCR5-targeted HIV entry inhibitors. Several such inhibitors have been identified in recent years, with a few already under clinical evaluation. Why then consider an additional lead molecule, particularly one derived from a pathogenic parasite? One good reason could be that none of the compounds currently under scrutiny has yet attained a proven record of safety and clinical effectiveness. But another argument that is difficult to refute is that "natura artis magistra" ("nature is the master of art"). Since CCR5 is a member of the 7-transmembrane-domain receptor family, obtaining atomic-level structural information remains a challenging task. However, we can learn about the structure of a receptor by observing it from the ligand perspective. Naturally selected CCR5-binding molecules, including *Toxoplasma* C-18 and chemokines, may teach us a precious lesson, courtesy of aeons of evolution, on how to effectively block one of the essential gateways of HIV.

—Paolo Lusso
San Raffaele Scientific Institute and
University of Cagliari

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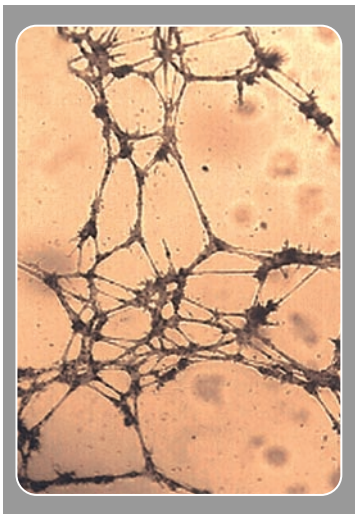
Exciting times for myeloma research

The importance of the interaction of myeloma cells with bone marrow microenvironment has recently been recognized. Myeloma cells were found to interact with bone marrow stromal cells, osteoblasts, osteoclast precursors, and osteoclasts to trigger disease progression, and



this knowledge is likely to be transferred into novel and, one hopes, more effective treatment strategies. Another important interaction of myeloma cells concerns bone marrow endothelial cells.

Folkman introduced the concept of angiogenesis in solid tumors 3 decades ago.[1] Vacca et al were the first to show that bone marrow angiogenesis is increased in active compared with nonactive multiple myeloma.[2] Recently, angiogenesis has been shown to be increased in a large variety of hematologic malignancies. Among them, myeloma was the first malignancy in which increased bone marrow angiogenesis was shown to be an independent prognostic factor for survival by Rajkumar et al[3] and our group.[4] This research field was also inspired by the work of Barlogie's group showing that thalidomide induces remissions in refractory myeloma patients, which was an important milestone in the treatment of multiple myeloma, even though this drug also has other properties besides its antiangiogenic action.[5]

In this issue of *Blood*, Vacca and colleagues (page 3340) provide new insights into the role of endothelial cells in multiple myeloma. The authors studied a variety of biologic features of endothelial cells extracted from bone marrow of patients with active multiple myeloma (MMECs) and compared these results with biologic features of human umbilical vein endothelial cells (HUVECs) as a model of normal quiescent endothelial cells. Genetic, phenotypic, functional, and ultrastructural features of endothelial cells are described. Vacca et al show that MMECs exist in subsets, secrete growth and invasive factors for myeloma cells, and can be inhibited by thalidomide. These results expand our understanding of the biology of MMECs and of the possible paracrine and cell-to-cell interactions of endothelial and myeloma cells.

Where do we go from here? Myeloma cells secrete a variety of angiogenic cytokines and activate multiple pathways to induce angiogenesis. Furthermore, different subsets of MMECs were found in the present study by Vacca et al. These results are consistent with the suggestion that the inhibition of a single signaling pathway in this complex system may be overcome by the activation of alternative pathways, and an appropriate combination of inhibitors may be necessary to achieve the desired goals in the treatment of multiple myeloma.

—Orhan Sezer
Universitätsklinikum Charité

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"Full length, midi, or mini": a fashion statement for transplants in myeloma

High-dose therapy (HDT) with autologous hematopoietic stem cell transplantation (AHSCT) is the standard of care for patients with newly diagnosed multiple myeloma.[1] This results in an event-free survival and overall survival (OS) of approximately 30 and 60 months, respectively. Unfortunately, there is no plateau in survival curves. It is highly controversial whether the outcomes of single HDT with planned tandem AHSCT improves survival.[2] The final analysis of the Intergroupe Francais Du Myélome 94 (IFM94) trial is the only one of 5 randomized trials (none yet published) to show a survival benefit (although one could argue that the other trials do not have long enough follow-up). Even with tandem AHSCT, plateaus in survival curves are not observed.

The etiology of disease relapse has been hypothesized as due to (1) infusion of contaminating tumor cells in the autograft, and/or (2) inability to eradicate minimal residual disease. Allogeneic transplantation (AlloTx) may overcome both of these obstacles by infusing tumor-free grafts and eradication of minimal residual disease through a graft-versus-myeloma (GVM) effect. There are indications that a plateau may be present following AlloTx. In patients who relapse following AlloTx, a GVM effect has been demonstrated by donor lymphocyte infusions.

Conventional ("full length") AlloTx's have excessively high mortality rates: the transplant-related mortality (TRM) has ranged from 20% to 57% within the first year. Thus, in the setting of 5-year median survivals with AHSCT, conventional AlloTx's have been terminated by the "fashion police" as too toxic. Is there a "kinder and gentler" approach for patients with myeloma that may lead to a cure? Trials using reduced dose–intensity regimens have been explored in myeloma. The initial trials included