receptor with lower sequence similarity to TNF receptors, but nonetheless a receptor containing a signature TNF–receptor–associating factor domain. FN14 was found to be highly expressed in many cells of nonlymphoid lineage and was particularly well expressed in epithelial and mesenchymal progenitor cells. FN14 expression is upregulated in tissue damage settings in response to a variety of insults including hypoxia, oxidative stress, and chemical/mechanical injury. Given FN14’s original identification from a fibroblast growth factor–induced screen, its enhanced expression in cancer tissue (including hepatoma, glioma, and non–small-cell lung cancer) is not entirely surprising. The TWEAK–FN14 system has a pivotal role in inflammatory bowel disease (IBD) models and intestinal epithelial cell death induced by irradiation and IL-13, both key early events in IBD pathogenesis, as well as mucosal epithelial barrier breakdown necessary for pathogen–induced immune cell molecular patterning. FN14’s more limited tissue distribution than TNF receptors and its enhanced expression in progenitor cells make it an intriguing receptor that could prove very useful in combatting specific tissue damage and certain cancer types.

Similar to the pharmacologic targeting of TNF and its receptors, a variety of recombinant soluble TWEAK variants and TWEAK– or FN14–specific antibodies have been generated, with some currently under evaluation in clinical trials. Time will tell about the eventual success of these TWEAK–FN14 modulating agents, but their future looks hopeful. Here, Chopra et al eloquently use such TWEAK–FN14 regulating agents in a mouse model of GVHD to much success. Using lethally irradiated mice receiving allogeneic HSCT as a model of GVHD and graft-versus-leukemia/lymphoma (GVL) effect, they found that an FN14–blocking antibody–dependent cellular cytotoxicity–deficient human immunoglobulin G1 significantly reduced severity of GVHD GI damage without any negative effects on the required GVL activity (see figure). Importantly, FN14–blocking antibodies can prevent allogeneic HSCT-induced GVHD damage without inhibiting the desired GVL responses. In HSCT, cotreatments need to inhibit proinflammatory effects from the transplanted cells while maintaining desirable disease-reversing responses from those same cells. Currently, general anti-inflammatory co-treatments serve to inhibit both GVHD and GVL. FN14–blocking antibodies (1) improved the GI apoptotic scoring of the mice as a mark of acute GVHD severity, (2) maintained the anti-lymphoma responses, and (3) significantly improved the disease score and overall survival rates of the model animals.

TNF receptors play many key roles in healthy tissues and can be key in pathological responses observed in a range of chronic immune diseases. Not only does TWEAK/FN14–specific blockade highlight the specific nature of some members of the TNF–receptor superfamily in certain human conditions, but it heralds that this ligand and receptor could be rather useful in controlling GVHD damage without impinging on the positive effects of the HSCT treatment itself. Furthermore, agents that control the TWEAK/FN14 system may also prove to be clinically useful in other chronic inflammatory disorders, particularly those involving the GI tract.

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Comment on Warkentin et al, page 486

The wacky hypercoagulable state of malignancy

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In this issue of Blood, Warkentin et al describe a novel clinical syndrome of warfarin–associated severe venous limb ischemia occurring in a series of 10 patients with malignancy after initiating treatment of deep venous thrombosis. Patients in this series also demonstrated a decline in platelet counts after stopping heparin, warfarin–associated supratherapeutic international normalized ratios (INRs), and evidence of persistent thrombin generation despite anticoagulation. 1

The hypercoagulable state of malignancy has been documented for more than a century, yet it seems we continue to find new manifestations. Indeed, omnicoagulable may be a better term for a clinical state that involves both the venous and arterial vasculature in nearly every part of the human body, from the well-known saddle pulmonary embolus to
Cancer-associated thrombosis

Deep Vein Thrombosis and Pulmonary Embolism

Disseminated intravascular coagulation

Arterial thromboembolism

Warfarin-induced limb gangrene

Myriad manifestations of cancer-associated thrombosis.

distal calf vein thrombi, from cerebral sinus thrombosis in children with acute leukemias to incidentally discovered portal and superior mesenteric vein thrombi in adults with pancreatic cancers, and from strokes to peripheral arterial emboli\(^2\)\(^4\) (see figure). To this lengthy list, the authors suggest a new syndrome be added.

The complications associated with warfarin therapy have also been known for a long time. Although warfarin is most notoriously associated with skin necrosis, the occurrence of venous limb gangrene has been reported previously both in patients with heparin-induced thrombocytopenia (HIT) and in patients with malignancy.\(^5\) The current report, however, provides a much larger case series than previously published, created in part by a comprehensive retrospective analysis of the records of 2 hospitals over a 10-year period. The initial database accessed by the investigators included patients who tested negative for heparin-platelet factor 4 antibodies, cross-referenced against diagnoses of malignancy. The authors then undertook an exhaustive chart review and additional comprehensive hematologic testing in available plasma specimens, the latter a particular strength of this report. Taken together, the clinical picture and testing provide a narrative of a disturbed procoagulant-anticoagulant balance leading to venous gangrene, a condition not altogether dissimilar from the pathogenesis of HIT-associated gangrene that the authors have previously reported. It is noteworthy that all patients with histologic evidence of malignancy had adenocarcinoma, which may be of particular relevance to the pathophysiology of the hypercoagulable state of malignancy.\(^6\)

The process by which patients were identified, however, creates inherent weaknesses in this descriptive series: if only those patients who are being worked up for HIT (the entry point for study inclusion) are sought out, then necessarily the “syndrome” will include only those patients with an “HIT-like” presentation. This process would exclude patients, for instance, with venous gangrene but without thrombocytopenia. Further, because only patients with malignancy were included, it is unclear whether a similar picture exists in patients without malignancy, as has been reported, for example, with warfarin-induced skin necrosis. The series could be further confounded by the presence of patients with false-negative results for HIT or by patients with malignancy-associated disseminated intravascular coagulation.

Regardless of whether this is truly a clinically distinct syndrome or not, the lethal complication of warfarin-associated venous gangrene is a grave complication of which clinicians should be aware. This report provides yet another argument against the use of warfarin for treatment of cancer-associated thrombosis (defensible in this series because many patients were only subsequently diagnosed with malignancy). Unfortunately, warfarin remains commonly used more than a decade after a seminal randomized study demonstrated its inferiority to low-molecular-weight heparins.\(^7\) Of course, clinicians should always be aware of the highly consequential albeit simpler diagnoses of pulmonary embolism and deep venous thrombosis that complicate the lives of tens of thousands of cancer patients worldwide. Much work remains to be done to better prevent and treat the myriad manifestations of cancer-associated thrombosis.

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The wacky hypercoagulable state of malignancy

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