Comment on Chopra et al, page 437

TWEAKing for a fight with GVHD

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In this issue of Blood, Chopra et al provide convincing evidence that tumor necrosis factor (TNF)-like weak inducer of apoptosis (TWEAK) ligand acting through its receptor, fibroblast growth factor-inducible 14 (Fn14), is crucial to the intestinal apoptosis seen in graft–versus-host disease (GVHD) and associated mortality.

Clinically, GVHD is difficult to manage, particularly in leukemia or lymphoma patients who have undergone hematopoietic stem cell transplantation (HSCT). This is in part due to limitations of the understanding of GVHD disease mechanisms, or associated inflammatory cell damage of a patient’s systemic tissues from the transplanted cells, including immune–reactive apoptotic damage of the gastrointestinal (GI) wall. Attempts to control this damage center around thwarting systemic proinflammatory cytokine actions, which results in a greater propensity for patient side effects. Treatment is with a range of anti-inflammatory drugs to suppress the patient’s immune system, just when it is needed the most. Chronic proinflammatory damage can often be as dangerous to the patient as the original blood cancer he or she is being treated for, with significant morbidity and mortality. Clearly, there is an unmet clinical need for more targeted therapies to counter side effects from HSCT therapy. Understanding proinflammatory processes that damage the GI wall from such therapies would lead to a better understanding of apoptotic damage processes underway in HSCT patients but may also provide critical clues in the fight against other inflammatory bowel disorders and conditions.

Understanding a disease and its damaging mechanisms is one thing. Being able to pharmacologically counter that disease or any therapy–inducing side effects is quite another. Nonspecific anti-inflammatory agents and steroids are the only real alternatives at present. In recent decades, advances in disease understanding have far outstripped the pharmaceutical and biotechnological industries’ capability to oppose these diseases in the clinic. One bright light for the triumph of pharmacology over disease is therapies developed to affect chronic inflammatory conditions that involve the pleiotropic cytokine TNF. Since the introduction of infliximab and adalimumab humanized monoclonal antibodies and etanercept TNF-receptor fusion protein, the treatments of chronic inflammatory conditions, including rheumatoid arthritis, Crohn disease, and ulcerative colitis, have been markedly improved by the clinical instigation of these TNF-blocking agents. The breathtaking success of these agents has caused the industry to focus its attention onto other members of the TNF-receptor superfamily. Results with a variety of TNF-receptor superfamily blocking agents have shown mixed success thus far. Taking a more long-term view of the clinical successes of these agents suggests certain TNF-receptor family modulating agents will indeed be introduced into the clinic, but the disease-specificity of the TNF receptor and the context-specificity of these therapies still need to be worked out. A more tissue-specific method may be necessary. Also, a more personalized medicine approach may be fundamental to improving the patient’s clinical score and associated toxic side effects.

TWEAK is a good example of the TNF-receptor superfamily that may be useful in certain clinical contexts, but its potential remains relatively unknown. TWEAK is itself a multifunctional cytokine with many potential cellular activities including proliferation, inflammation, migration, angiogenesis, and apoptosis. TWEAK (also known as TNFSF12/APO3L/CD255) was discovered and termed a TNF-like pro-apoptotic agent in human HT-29 colon carcinoma cells. The receptor for TWEAK was assumed to be a member of the TNF-receptor superfamily, and after some initial assumptions around death receptor-3, the receptor for TWEAK was found to be Fn14, an unusual small-cell surface receptor. (B) Use of an anti-Fn14 IgG blocking antibody (αFn14) prevents TWEAK-induced cellular damage, particularly in progenitor GI cells, which overexpress Fn14 receptor.
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.

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
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