B cells, CD4+ T-helper cells, and CD8+ cytotoxic T cells, the authors confirm that only CD8+ cell depletion abrogates the drug’s effectiveness, going on to demonstrate that more tumor-specific CTLLs are generated in the combined therapy–exposed mice than in tumor-innoculated untreated mice. They show enhancement of costimulatory B7 molecule expression, CD80 and CD86, on dendritic cells after exposure to the drug in vitro. Memory responses are confirmed in long-surviving mouse splenocyte coculture experiments, with multiple tumor-specific antigen targets responsible. Finally, and perhaps most intriguingly, they find that manipulating the radiotherapy regimen from the more intuitively tumor-toxic single dose to a less toxic fractionated dose regimen in fact enhances the efficacy of combined therapy, impressively leading to the eradication of a less immunogenic cell line in all mice.

Their comprehensive mechanistic approach lends credibility to this model as a future therapeutic strategy. The authors’ assertion that multiple antigenic targets are responsible, on the basis of superior memory T-cell responses to coculture with whole tumor cell versus soluble tumor-specific antigen, may be overstated because the context of antigen presentation in priming (cell-surface, MHC-associated versus soluble) is clearly important in determining the potency of a subsequent immune response. In addition, any convenient “single immune cell compartment” model (in this case CD8+ mediated, not CD4+ or CD20+) is likely an oversimplification based on the use of homogenized inbred mouse strains and inoculated cell lines versus endogenously developing tumors. As always, the murine model awaits first-in-human trials to show that this exciting innovation is not another immunotherapeutic disappointment. However, Dovedi and colleagues have elegantly demonstrated mechanistic and therapeutic efficacy of a logical 2-pronged approach to immunotherapy: enhance immunogenicity of tumor through radiotherapy, enhance systemic immunity through a potent “immune danger” signal, and let the body’s own defenses do the rest.

Conflict-of-interest disclosure: The authors declare no competing financial interests.

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co-option or intussusceptions of pre-existing vessels, or by vasculogenic mimicry by tumor cells, or, finally, through new vessel formation by cancer stem cell. Whatever the mechanisms involved, the development of internal tumor circulation, despite evident morphologic and functional abnormalities, aims unequivocally to guarantee nutrient delivery and waste removal. As a consequence, the study by Rosti et al raises 2 obvious questions: (1) are the JAK2V617F positive endothelial cells the manifestation of genuine tumor angiogenesis, and (2) what are the effects of tumor-derived endothelial cells on the “myeloproliferative” environment? In their study, Rosti et al tested for the presence of JAK2V617F mutation ECs isolated from spleen tissue of 11 patients with primary MF and 7 patients with postpolycythemia or postessential thrombocythemia MF. The authors obtained ECs by laser microdissection (LM) from fixed samples or by cell sorting in fresh samples. Fresh samples were also used to grow endothelial colony-forming cell (ECFC) or EC cultures. Furthermore, in 11 patients, splenic vein samples were evaluated. Overall, among 18 patients, 12 had the detection of at least 1 mutated EC in samples isolated by LM (5 patients), or in EC cultures (4 patients), or in both LM samples and EC cultures (3 patients). One patient had mutated ECs also in the splenic vein sample. Most patients had both wild-type and mutated ECs, suggesting variable combinations of normal and tumor ECs to vessel wall. The authors tried to exclude any potential source of contamination in tested samples: the multifaceted approach used to isolate the ECs and the extensive phenotypic characterization of mutated cells guarantees both the endothelial purity and the true endothelial nature of mutated ECs. Furthermore, ECs often harbored homozygous mutation, and no aneuploidy and/or tetraploidy cells were detected. Indeed, the possibility that ECs could have acquired exogenous DNA carrying the JAK2V617F mutation through cell fusion or phagocytosis was reasonably ruled out. Nevertheless, understanding how mutated ECs and hematopoietic cells interact in the splenic microenvironment is an even more intriguing issue. Environmental components are crucial regulators of normal and malignant stem cell behavior. In particular, within the bone marrow tissue a mosaic of microenvironments provides specified sets of instructions regulating or reinforcing cell fate. Recently, several observations have provided evidence that the vascular niche plays an important role in influencing hematopoietic stem cell (HSC) dormancy, self-renewal, and proliferation. Indeed, functional characterization of JAK2 mutated ECs should be attempted to understand whether tumor angiogenesis promotes splenic myeloproliferation. Our group recently reported that in some patients with Ph-negative chronic myeloproliferative neoplasms (MPNs), circulating ECFCs exhibit some neoplastic signatures such as JAK2V617F mutation, Suppressor of Cyto-kine Signaling (SOCS) gene hypermethylation, or clonal derivation. Importantly, these cells had an exaggerated adhesive affinity toward mononuclear cells and shared an increased expression of m-RNA for various adhesive molecules such as ICAM-1, VCAM1, and E-selectin (L.T. and L.M.L., unpublished data, February 8, 2012). In this regard, it was recently reported that the E-selectin expressed by bone marrow endothelial cells within the vascular niche promotes HSC proliferation at the expense of self-renewal. Overall, data emerging from the study by Rosti and colleagues, together with others, converge toward the attractive assumption that the hemangioblast would be the putative MPN stem cell. Therefore, hemangioblasts should originate both myeloid and endothelial neoplastic progeny. Within this unique tumor model, endothelial cells could serve as a niche component for the hematopoietic cell counterpart, supporting its survival and proliferation (see figure). In this perspective, when considering therapeutic options for MPN patients, we should remember that in the MPN context myeloproliferation and angiogenesis are tightly connected.

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REFERENCES
Blood and endothelial cells: together through thick and thin

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