PI3K, induced by IPI-145 but not idelalisib, in fact lead to more tumor toxicity in vivo? Similarly, might it reduce the effector functions of various immune effectors when used in combination with mAbs? For these answers, we eagerly await the results of the upcoming trials and further in vitro experimentation.

Despite these unresolved questions, this article provides exciting new data and insight into the biology of the PI3K signaling pathway in CLL cells, which will enable the development of more effective drugs for the treatment of this currently incurable disease. Moreover, the more inhibitors we have for the BCR signaling pathway, the more tools we will have to further dissect its critical signaling functions in malignant cells and the more opportunities we will have to explore rational combinations for improved therapeutic efficacy in the future.

Conflict-of-interest disclosure: The author declares no competing financial interests.

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Hox9-Meis1 or Aml1-Eto9a. The choice of models was interesting as both MLL-ENL, KI1 and Hox9-Meis1 are likely to directly activate HIF-1α through MEIS1 expression, whereas Aml1-Eto9a is not known to signal through HIF-1α. They studied the oncogenes in wild-type cells with Hif-1α alleles or where Hif-1α alleles could be conditionally deleted after engraftment. In all 3 models, the results were clear; there was no dependence on HIF-1α for leukemia initiation, propagation, and leukemia-initiating cell self-renewal in transplantation assays. If anything, the onset of leukemia was accelerated in cells deleted for Hif-1α in the Hox9-Meis1 model and when mice were secondarily transplanted with Aml1-Eto9a transduced leukemic cells. One obvious caveat is that compensation by HIF-2α may have obscured a physiologic role for HIF-1α. Although that may be the case, the data do suggest that simply targeting HIF-1α may not be sufficient. Studying AML initiation and propagation in cells with both Hif-1α and Hif-2α conditional alleles would address this question.

So where does this leave the field? Although there are still important mechanistic questions about the role of HIF and adaptation to hypoxia by normal stem/early progenitor cells, the bulk of evidence supports a critical role for HIF function in this area. Clearly, more work needs to be done to define any differential functional effects of HIF-1α and HIF-2α between humans and mice. In AML and other hematologic malignancies, the situation is likely to be more complex. The role of HIF (and specifically HIF-α subunits) may depend on a number of parameters. For example, the nature of oncogenic drivers (genetic and epigenetic) is likely to dictate genome integrity and genome robustness. One could hypothesize that loss of HIF function in some malignancies (and AML in particular) may make tumor initiating and propagating cells more vulnerable to genotoxic stress just like their normal hemopoietic stem/early progenitor counterparts, whereas this may not be true in cells with an altered TP53 function. Oncogenic drivers are also likely to influence self-renewal, the need (or lack of) for quiescence, and optimal metabolism for leukemia initiating and propagating cells. Taken together, this is likely to determine the nature of optimal niches and thus the requirement for HIF function. If these hypotheses are shown to be correct, it would also suggest that HIF requirement will not only vary between patients, but also within a patient at different stages of the disease. Thus, the data from Valasco-Hernandez et al should give pause for more thought and an opportunity to probe more deeply into the interaction between hypoxic adaption and function of cell populations that initiate and propagate AML and other cancers.

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Comment on Iqbal et al, page 3646

New checkpoint of the coagulant phenotype

Janusz Rak

The Research Institute of the McGill University Health Centre

In this issue of Blood, Iqbal et al shed new light on how the procoagulant potential of monocytes/macrophages is controlled by the hitherto unsuspected mechanism modulating the fate of tissue factor (TF) messenger (m)RNA.1

Monocytes, macrophages, and their precursors are cellular mavericks programmed to travel in blood and across tissue barriers to sites of infection, inflammation, injury, and repair.2 This property requires a precise, timely, and localized expression of different functional aptitudes. A startling example of this is the ability of monocytes to enter the circulating blood while effectively “managing” their relationship with the coagulation system.2 Contact with blood can be risky. Monocytes possess the intrinsic potential to activate clotting through expression of TF, the cell surface receptor for the coagulation factor (F)VII/VIIa and potent trigger of the coagulation cascade.3 If monocytes were to express active TF in an unscheduled or exuberant manner, the consequences could be catastrophic, resulting in uncontrolled intravascular activation of clotting processes, as observed in sepsis.4

The remarkable feature of the hemostatic system is its ability to maintain the systemic liquidity of the circulating blood while being able to locally “solidify” blood components to plug up the site of a vascular injury by clots composed of fibrin and platelets. This is accomplished, in part, by the physical separation of latent clotting factors (zymogens) and their potential activators, such as procoagulant surfaces of extracellular matrix and TF expressed by cells outside of the
Targeting HIF function: the debate continues

Paresh Vyas