Comment on Kusakabe et al, page 1374

c-Maf rules the island

Paul A. Ney  NEW YORK BLOOD CENTER

In this issue of Blood, Kusakabe et al make a compelling case that the transcription factor c-Maf is critical for erythroblastic island formation and fetal erythropoiesis. The cell adhesion molecule VCAM-1 is a potential mediator of c-Maf activity.

The erythroblastic island was ultrastructurally identified as a common organizational unit of bone marrow more than 50 years ago. Erythroblastic islands are composed of erythroblasts, at various stages of maturation, and a central macrophage. The central macrophage supports erythroid cell survival and proliferation through intercellular signaling, and facilitates enucleation. Along this line, several molecules have been identified that mediate intercellular attachments and macrophage-erythroblast interactions within the island. Still, despite these advances the role of the central macrophage in erythroid development remains somewhat obscure. Kusakabe et al now show that the basic region-leucine zipper transcription factor c-Maf is critical for erythroblastic island formation. The macrophage is the site of c-Maf activity, and c-Maf deficiency is associated with severe embryonic anemia and lethality. This study opens a new avenue into the investigation of erythroblastic islands.

Establishing the cell type responsible for a phenotypic effect is challenging and critical in any study of heterotypic intercellular interactions. Kusakabe et al performed mixing experiments with c-Maf–deficient erythroblasts and macrophages that convincingly show that defects in erythroblastic island formation, caused by the loss of c-Maf, reside with the macrophage. However, can the same be said of the embryonic anemia and lethality, or does c-Maf deficiency also have an erythroid cell autonomous effect on development? One approach to address this question is to examine the effect of c-Maf deficiency on erythropoiesis, when it is induced specifically in the macrophage and erythroid lineages; however, this requires a conditional Maf-mutant mouse strain. In lieu of this, 2 other lines of evidence suggest that c-Maf function in macrophages and erythroid island formation are required for efficient erythropoiesis. First, c-Maf is expressed in macrophages but not erythroblasts in the fetal liver, which suggests that macrophages are the primary site of c-Maf activity. Second, adult mice transplanted with c-Maf–deficient fetal liver cells do not develop anemia. This experiment shows that there is no cell autonomous requirement for c-Maf in erythroid development, and further implies that erythroblastic island function is most important during fetal development. Alternatively, there may be a fetal-specific requirement for c-Maf in erythroblastic island formation. Finally, consistent with the proposed role of the central macrophage, Kusakabe et al show that survival of mature c-Maf–deficient erythroblasts is defective in vivo. Thus, c-Maf deficiency causes defective macrophage development and impairs erythroid cell survival and development through its effect on the erythroblastic island.

Given that c-Maf is the first transcription factor identified that is important for erythroblastic island function, it raises the question of the relevant targets of c-Maf in macrophages. Here, Kusakabe et al provide evidence that VCAM-1 is one such target. VCAM-1 has a proven role in erythroid island formation, which makes it an excellent candidate for a mediator of c-Maf activity; however, because VCAM-1 is not essential for erythropoiesis, there are likely to be other relevant c-Maf targets. Known regulators of erythroblastic island formation, such as retinoblastoma and erythroblast-macrophage protein, have been excluded; thus, additional targets of c-Maf are likely to be novel and their identification an important future objective. Beyond the role of macrophages in erythroid development, erythroblastic islands also serve as a paradigm for interactions between hematopoietic cells and their microenvironment. In this regard, the present identification of a transcriptional regulator of erythroblastic island formation may lead to broader insights into the regulation of hematopoiesis.

REFERENCES

6. Soni S, Bala S, Gwynn B, Sahr KE, Peters LL, Hanspal M. Absence of erythroblast macrophage protein...
CMV: when bad viruses turn good

A. John Barrett  NHLBI

Cytomegalovirus (CMV) has had a reputation for causing morbidity and mortality after allogeneic stem cell transplantation (SCT). In this issue of Blood, Elmaagacli et al find an unexpected favorable association of a low rate of leukemic relapse in acute myeloid leukemia patients who reactivate CMV in the first few weeks of SCT.1

E very now and then retrospective analyses of SCT data bring up unexpected and counterintuitive findings. This is the case in the article by Elmaagacli and colleagues from the SCT group in Essen, Germany. Analyzing 266 consecutive patients with acute myeloblastic leukemia (AML) who received SCT from HLA-identical relatives or unrelated donors between 1997 and 2009, they found an unusual association between early CMV reactivation and transplantation outcome. Seventy-seven patients developing their first CMV pp65 antigenemia at a median of 6 weeks after transplantation were found to have a remarkably low risk of leukemic relapse (9% at 10 years after SCT) compared with a 42% risk in 189 patients not reactivating CMV. Furthermore, they found that, far from being a risk for increased transplantation-related mortality, the occurrence of CMV reactivation was not deleterious for survival. In support of a specific effect of CMV they found that positive CMV serology in donor or patient was itself protective against relapse while reactivation of other viruses had no impact.

Historically, CMV disease has been a major complication of allogeneic SCT.2 In the days before high-sensitivity monitoring of CMV antigenemia by PCR for pp65 protein and preemptive treatment of CMV disease with ganciclovir or foscarnet, CMV pneumonitis accounted for up to 20% mortality after transplantation for leukemia.3 Even today, when death from CMV pneumonitis is rare, we regard viral reactivation as bad, leading to CMV disease if not controlled by antivirals, which in their turn cause cytopenia and renal damage. CMV reactivation implies immunodeficiency, loss of control of a resident DNA virus, and breakdown of immunosurveillance against residual leukemia. The detection of the virus early after transplantation might be expected to be associated with an increased risk of relapse. Indeed, an earlier study from the National Institutes of Health demonstrated that persisting pp65 antigenemia in the first 3 months after SCT was associated with defective T-cell replication against CMV peptides, an increased risk of leukemic relapse from the 3-month landmark, and a higher transplantation-related mortality.4

The findings from Elmaagacli et al therefore fly in the face of established perceptions. Unexpected findings merit special scrutiny if they are to be validated, and in this article the authors have gone to extensive lengths to support their conclusions. An obvious confounding factor is that CMV reactivation is closely linked to the occurrence of acute graft-versus-host disease (GVHD), which in turn implies a graft-versus-leukemia effect; indeed, it has been suggested that CMV reactivation is a trigger for GVHD development.5 In this series, grade II-IV acute GVHD doubled the risk of CMV reactivation and preceded pp65 antigenemia in 90% of cases. However, within the group of 187 individuals with grade II-IV acute GVHD, CMV reactivation still had an independent impact on relapse: in 77 reactivators the relapse rate was only 9% compared with a 38% relapse rate in 189 nonreactivators. The same benefit for CMV reactivation held true for chronic GVHD, considered to be an important long-term control of residual leukemia. In careful multivariate analysis CMV reactivation remained an independent variable alongside established risk factors for relapse.
c-Maf rules the island

Paul A. Ney