expression by antisense or small interfering RNA approaches strongly reduced the growth of BCR-ABL–expressing cell lines or primary cells in mouse models in vivo. Their studies suggested that Lcn2 contributes to leukemogenesis via dual mechanisms of induction of apoptosis in normal hematopoietic cells and enhancement of tissue invasion by leukemia cells. These results in a CML model are consistent with those of the current study in MPN, and suggest that Lcn2 expression could represent a conserved mechanism that promotes progression of myeloid malignancies. Additional studies evaluating the effect of Lcn2 deletion using genetic mouse models on leukemic and normal hematopoiesis are required to more definitively determine its contribution to leukeme progression.

The studies of Kagoya et al also have implications for the evolution of MPN to AML, suggesting a possible contribution of Lcn2-induced ROS and DNA damage to acquisition of mutations in both JAK2V617F+ and JAK2V617F− cells. It is recognized that AML arising from JAK2V617F+ MPN is often JAK2V617F−. This has been explained by existence of JAK2V617F− preleukemic populations that may bear mutations in other genes, such as TET2, which could confer clonal preservation or expansion.5 The current studies showing that JAK2V617F− normal clones accumulated DNA damage to the same extent as JAK2V617F+ clones in the MPN mouse model are intriguing, but further evaluation is needed to determine whether Lcn2-induced induction of ROS and DNA damage indeed contributes to leukemia evolution in MPN models. Confirmation of such a role may offer additional strategies to alter the progression of MPN and enhance response to treatment.

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were seen in wild-type BRAF tumors, of which mutations in MAP2K1 (which encodes MEK1 protein) were the most common (7/21). This is the first time that non-BRAFV600E mutations have been reported in more than one patient with LCH. The authors also identified mutations in the ARAF and ERBB3 genes in individual tumors (see figure). Of note, 23 other somatic mutations were identified but did not include genes that either were members of the MAPK pathway or could affect that pathway (such as members of the PI3K/akt/mTOR pathway).

The manuscript by Emile et al focuses on ECD and provides findings that have important similarities and differences from those observed in LCH.2 This group did not use WES but searched for mutations in specific genes using pyrosequencing, Sequenom mass spectrometry–based genotyping assays, next-generation targeted sequencing, and Illumina MiSeq for regions in BRAF, NRAS (MAPK pathways), and PIK3CA and AKT1 (PI3K/akt/mTOR pathways). Like LCH, they detected BRAFV600E mutations in >50% of samples (46/80). Unlike LCH, they detected mutations in NRAS and PIK3CA. Notably, they did not specifically test for MAP2K1 mutations. In addition, the Chakraborty group, using WES only, analyzed only 1 patient with ECD (and found no mutations), so the incidence of mutations outside the RAS-RAF-MEF-ERK and RAS-PI3K-akt-mTOR pathways in patients with ECD remains unknown.

Another important difference in ECD is that additional mutations are present not infrequently in patients with BRAFV600E mutations (not just wild-type BRAFV600E); 4 of 46 BRAFV600E mutants had coexistent PIK3CA mutations.

Of note, both of these studies provide evidence that these are activating mutations and generally result in phosphorylation of ERK. Thus, they are very likely to be clinically relevant in the pathogenesis of their respective diseases. Supportive of these mutations being pathologically important “driving mutations” is the finding by the authors that there is a remarkably low frequency of somatic mutations in LCH lesions, with a median of 1 mutation per sample. Of note, with respect to LCH, it seems that ERK activation is a universal end point in LCH from the various pathologic activation of upstream signaling proteins. At this time, the same cannot necessarily be said for ECD. Only further studies will determine whether mutations outside the ERK axis have the same clinical and treatment-response implications as those within the MAPK-ERK pathway (ie, BRAFV600E).

Taken together, targeting these various mutations beyond the BRAFV600E is no doubt a worthwhile objective. We have already found this with the BRAF inhibitors and it is hoped that, given the relatively low incidence of multiple mutations, resistance to therapy may be relatively less common than that observed in melanoma. Indeed, recent consensus guidelines confirm the need for routine mutational analysis to guide the treatment of ECD.9 What, then, about targeting other mutations? The in vitro studies by Chakraborty et al support the premise that MEK inhibition may be therapeutically useful, but more studies are needed. Finally, both studies demonstrated that in a significant minority of patients, no mutations are identified. In part this may be caused by the relative impurity of the sample with respect to the clonal cell. Indeed, Emile et al and others have demonstrated that both BRAFV600E and NRAS mutations can be found in monocytes in the peripheral blood.5,10 Thus, with analysis of samples that are of higher purity and enriched for the clonal cells, we may in the future be able to identify mutations in the vast majority of patients with ECD or LCH. Moreover, such “mutational profiling” may align with different clinical patterns of disease; we already recognize that the clinical presentation of LCH and ECD is very heterogeneous, and mutational analysis may help subclassify clinical patterns of disease/response (although the authors were unable to find such associations with their small sample size).

These 2 articles confirm that every patient with LCH or ECD should have mutational analysis for at least the BRAFV600E mutation, and the mutational panel will continue to grow as we explore for other mutations in the MAPK and PI3K-akt pathways.

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Identifying mutant pathways in the histiocytoses

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