Risk of RAS in relapsed childhood ALL

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In this issue of Blood, Irving et al report a high frequency of rat sarcoma (RAS) signaling pathway mutations in relapsed childhood B-cell precursor acute lymphoblastic leukemia (BCP ALL) and present detailed data on the clonal evolution of RAS mutation-positive blasts from diagnosis to first, and, in some cases, second relapse.1 This study is important for 2 reasons; first because it adds to our understanding of the complex genetic mechanisms involved in chemoresistant ALL and second because the authors also present data from in vitro and in vivo experiments indicating that the mitogen-activated protein kinase kinase (MEK) inhibitor selumetinib could be a novel treatment option in relapsed ALL with activation of the RAS pathway (see figure).

Although ALL usually displays 1 dominant clone—ie, identical somatic mutations in the majority of blast cells—at diagnosis, next-generation sequencing and xenografts have recently revealed that cases frequently also harbor mutations that are present in only a subset of the cells, indicating a previously unrecognized genetic heterogeneity.2,3 Evidence pointing in the same direction has come from comparisons of ALL at diagnosis and relapse, where microdeletions and mutations present only at relapse have been backtracked to minor subclones in the corresponding diagnostic sample.1,5 Genetic heterogeneity at diagnosis may be one of the underlying factors when the leukemia relapses, because small subclones may survive the treatment that eradicates the main diagnostic clone and subsequently lead to disease recurrence. Irving et al investigate mutations affecting the RAS signaling pathway in samples from 206 relapsed BCP ALLs. Mutations in this pathway are among the most common somatic changes in human malignancies and are found in a wide range of tumors. In pediatric ALL, mutations of the KRAS, NRAS, PTPN11, and FLT3 genes, all involved in the RAS pathway, are seen in ~35% of cases at diagnosis, with varying frequency in different genetic
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