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The mitogen-activated protein kinase signaling module as a therapeutic target in hematologic malignancies
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Abstract
Important insights into the cellular and molecular biology of cancer in general and of hematologic malignancies in particular have been gained in the past two decades. The genes, and their protein products, involved in the transformation of cells from normal to neoplastic, as well as in the progression of neoplastic cells to a more aggressive, therapy-resistant phenotype, are being elucidated in great detail. However, most hematologic malignancies, particularly adult acute leukemias, remain associated with high mortality rates and new therapeutic approaches are urgently needed. The challenge is therefore to carefully and efficiently translate the information gained into effective therapeutic strategies. The clinical success achieved by tyrosine kinase inhibitors, such as ST1571 in chronic myelogenous leukemia, has stimulated interest for kinase-based signaling pathways as therapeutic targets in hematologic malignancies. The mitogen-activated protein kinase (MAPK) pathway is a common point of convergence of many different mitogenic and anti-apoptotic signal transduction pathways in hematopoietic, as well as epithelial, cancer cells and can now be clinically targeted by highly selective small molecule inhibitors. The mounting preclinical evidence of anti-leukemic activity of MAPK inhibitors, alone or in combination with pro-apoptotic small molecules or with conventional chemotherapeutic agents provides rationale that MAPK inhibition-based treatment strategies could soon enrich our therapeutic armamentarium against human leukemias.