TYK2-STAT1-BCL2 Pathway Dependence in T-cell Acute Lymphoblastic Leukemia.

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Public Summary: In recent years, “pathway dependence” has been revealed in specific types of human cancer, which can be important because they pinpoint proteins that are particularly vulnerable to antitumor-targeted inhibition (so-called Achilles’ heel proteins). Here, we use RNAi technology to identify a novel oncogenic pathway that involves aberrant activation of the TYK2 tyrosine kinase and its downstream substrate, STAT1, which ultimately promotes T-ALL cell survival through the upregulation of BCL2 expression. Cancer Discov; 3(5); 564–77. ©2013 AACR.

Scientific Abstract: Targeted molecular therapy has yielded remarkable outcomes in certain cancers, but specific therapeutic targets remain elusive for many others. As a result of two independent RNA interference (RNAi) screens, we identified pathway dependence on a member of the Janus-activated kinase (JAK) tyrosine kinase family, TYK2, and its downstream effector STAT1, in T-cell acute lymphoblastic leukemia (T-ALL). Gene knockdown experiments consistently showed TYK2 dependence in both T-ALL primary specimens and cell lines, and a small-molecule inhibitor of JAK activity induced T-ALL cell death. Activation of this TYK2-STAT1 pathway in T-ALL cell lines occurs by gain-of-function TYK2 mutations or activation of interleukin (IL)-10 receptor signaling, and this pathway mediates T-ALL cell survival through upregulation of the antiapoptotic protein BCL2. These findings indicate that in many T-ALL cases, the leukemic cells are dependent upon the TYK2-STAT1-BCL2 pathway for continued survival, supporting the development of molecular therapies targeting TYK2 and other components of this pathway.

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