Beyond NOTCH Inhibition in T-ALL

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Studies have shown that multiple genes encoding proteins involved in the PI3K pathway are mutated in human cancers, making this pathway a priority in the development of targeted therapy. The earliest and most compelling evidence of the involvement of the PI3K pathway in cancer came from studies involving deletion of phosphatase and tensin homologue (*PTEN*) tumor-suppressor gene in multiple cancer types. In parallel, the recent discovery of novel activating mutations in NOTCH1 in more than 50 percent of human T-cell lymphoblastic leukemia (T-ALL) samples has made it clear that NOTCH1 is far more important in human T-ALL pathogenesis than previously suspected. NOTCH1 receptor is therefore a promising target for drugs such as gamma-secretase inhibitors (GSIs), which block NOTCH1 activation in cancer and in T-ALL particularly. However, enthusiasm for these therapies has been tempered by tumor resistance and the paucity of information on the oncogenic programs regulated by NOTCH1.

In the Plenary Session yesterday, Dr. Ferrando et al. reported that mutational loss of *PTEN* induces resistance to NOTCH1 inhibition in T-ALL. NOTCH1 signaling regulates *PTEN* expression and AKT signaling in leukemic T cells. Activation of NOTCH signaling and activation of the PI3K-AKT pathway showed marked synergism in tumor formation. Thus, inhibition of NOTCH1 with GSIs resulted in transcriptional upregulation of *PTEN* and concomitant downregulation of PI3K/AKT signaling in T-ALL, since regulation of *PTEN* is mediated by HES1, a transcriptional repressor directly controlled by NOTCH1. Importantly, activation of AKT reversed the growth defect phenotype induced by the loss of NOTCH signaling, highlighting the importance of the interaction between these two pathways for the control of cell growth.

In this study, the authors identify that the loss of the *PTEN* tumor suppressor gene and activation of the PI3K-AKT signaling pathway are critical factors that determine the resistance of T-ALL cells to inhibition of NOTCH1 signaling with GSIs. They also show that mutational loss of *PTEN* induces an oncogene addiction switch from NOTCH to AKT. Thus, as tumor cells become resistant to NOTCH inhibitor therapies they turn more sensitive to AKT inhibitors. These results are of importance as they provide the molecular sequelae of resistance to NOTCH inhibitor therapies in T-ALL, and the basis for the use of a targeted alternative therapy with PI3K/AKT pathway inhibitors that are in clinical trials in several other malignancies.