PH'ALL CELLS ARE SUSCEPTIBLE TO DUAL TARGETING OF BCL2 AND ABL/LYN

Philadelphia chromosome–positive acute lymphoblastic leukemia (Ph’ALL) is an aggressive subtype characterized by the BCR–ABL translocation. Targeted therapy against the ABL kinase with tyrosine kinase inhibitors (TKI) achieves short-term responses, but resistance often develops, in part through upregulation of BCL2 family antiapoptotic proteins. The BCL2 inhibitor venetoclax is effective in multiple hematologic malignancies, prompting Leonard and colleagues to investigate its use in Ph’ALL. A Ph’ALL cell line and two patient samples showed sensitivity to venetoclax plus dasatinib; these cells exhibited a high ratio of BCL2 to MCL1, an antiapoptotic protein not inhibited by venetoclax, compared with insensitive cells. Further, venetoclax synergized BCR-ABL TKIs to enhance apoptosis of Ph’ALL cells. The highest degree of synergy was observed with the multikinase inhibitors ponatinib and dasatinib, both of which induced expression of the proapoptotic protein BIM. Ponatinib and dasatinib inhibit multiple kinases in addition to ABL, including LYN, and knockdown of ABL or LYN had similar effects to the inhibitors and resulted in enhanced apoptosis and synergy with venetoclax, suggesting that multikinase inhibitors synergize with venetoclax by suppressing both ABL and LYN. Combined treatment with venetoclax and dasatinib was well tolerated in a mouse model of Ph’ALL and reduced the disease burden more effectively than either single agent. Moreover, resistance to venetoclax, which can occur via upregulation of MCL1, was prevented by dasatinib and ponatinib, which blocked LYN activity to reduce STAT5 phosphorylation and prevent MCL1 upregulation, indicating that inhibitors that target both ABL and LYN may prevent venetoclax resistance in Ph’ALL. The finding that inhibition of BCL2 and ABL/LYN synergize to promote Ph’ALL cell apoptosis and prevent resistance to venetoclax provides a rationale for further clinical investigation of this drug combination in this disease.


Epigenetics

Fumarate promotes EMT by downregulating antimetastatic miRNAs

Fumarate is a metabolite of the tricarboxylic acid cycle that also inhibits α-ketoglutarate–dependent dioxygenases such as TET enzymes involved in DNA demethylation and has been shown to promote cellular transformation. Mutations in fumarate hydratase (FH), which catalyzes the conversion of fumarate to malate, result in fumarate accumulation and are associated with aggressive renal cell cancers with poor clinical outcomes. To discover how loss of FH promotes tumorigenesis, Sciacovelli and colleagues analyzed the proteome and transcriptome of FH-deficient cells and found that vimentin was overexpressed. Vimentin is a marker of epithelial-to-mesenchymal transition (EMT), and, accordingly, reintroduction of FH reduced vimentin expression, increased expression of the epithelial marker E-cadherin, promoted an epithelial morphology, and suppressed cell motility, altogether indicating that FH loss may promote EMT. Moreover, several key EMT transcription factors were upregulated in FH-deficient cells, including SNAI2, ZEB1, and ZEB2, which are known to be suppressed by antimetastatic miRNAs in the miR-200b-429 miRNA cluster, which includes miR-200a, miR-200b, and miR-429 and was also downregulated in FH-deficient cells. miR-200 expression can be repressed by CpG island hypermethylation, and fumarate suppressed TET activity, resulting in increased methylation of the regulatory CpG43 CpG island of miR-200b-429 and reduced miR-200b-429 expression. Consistent with these findings, in patients with renal cancer, loss of FH was associated with an EMT signature with high expression of vimentin and low expression of E-cadherin and reduced patient survival. These results suggesting that fumarate accumulation may promote EMT by epigenetic downregulation of an antimetastatic miRNA cluster provide insight into the etiology of FH-deficient tumors.

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