Drug Resistance

Major finding: BET inhibitor–resistant cells undergo transcriptional rewiring to reactivate MYC gene expression.

Mechanism: Compensatory activation of WNT/β-catenin binding at MYC enhancer regions drives resistance.

Impact: WNT pathway activation may represent a predictive biomarker of BET inhibitor response in AML.

TRANSCRIPTIONAL REPROGRAMMING UNDERLIES BET INHIBITOR RESISTANCE

Epigenetic regulators, such as the bromodomain and extra terminal (BET) family of proteins, have been increasingly implicated in cancer initiation and maintenance, and have led to the development of small-molecule inhibitors targeting the BET domain, such as I-BET and JQ1. Although BET inhibitors have shown early success in acute myeloid leukemia (AML), little is known about the underlying molecular mechanisms that govern resistance to BET inhibition. To address this question, Fong and colleagues generated a model of BET inhibitor resistance using MLL–AF9-expressing primary murine hematopoietic stem and progenitor cells treated with I-BET. I-BET–resistant cells were characterized by decreased expression of the lineage markers GR1 and CD11B and were enriched for leukemia stem cells in limiting-dilution experiments. Although I-BET–resistant cells shared few genetic aberrations, transcriptional profiling revealed increased expression of the BRD4 target gene MYC, despite an overall decrease in BRD4 chromatin binding, and enhanced activation of the WNT transcriptional program. Mechanistically, β-catenin replaced BRD4 at MYC regulatory sequences to drive increased MYC expression in I-BET–resistant cells. In a second report, Rathert, Roth, and colleagues revealed through an RNAi screen that suppression of the polycomb repressive complex 2 subunit SUZ12 promotes JQ1 resistance in a BET inhibitor–sensitive AML mouse model. Under long-term JQ1 treatment, SUZ12-deficient AML cells restored transcription of BRD4-dependent genes such as MYC through an adaptation process involving the remodeling of enhancer landscapes and the activation of WNT signaling. In line with this result, JQ1-resistant human leukemia cell lines and primary samples displayed similar MYC enhancer profiles and an increased expression of genes associated with WNT signaling. Suppression of WNT targets reactivated cells to JQ1 in vitro, whereas WNT activation drove de novo JQ1 resistance in vivo. Together, these data suggest that compensatory activation of transcriptional pathways, such as WNT–MYC, may underlie BET inhibitor resistance in AML.


Leukemia

Major finding: PPARγ agonists synergize with the BCR–ABL inhibitor imatinib to deplete the CML stem cell pool.

Mechanism: PPARγ agonists inhibit the PPARγ–STAT5–HIF2α–CITED2 pathway, driving CML stem cell apoptosis.

Impact: Combination PPARγ agonist and TKI therapy shows early clinical efficacy in phase II trials.

PPARγ AGONISTS DEPLETE THE CHRONIC MYELOID LEUKEMIA STEM CELL POOL

In chronic myeloid leukemia (CML), BCR–ABL tyrosine kinase inhibitors (TKI) such as imatinib improve patient survival but rarely achieve complete molecular response (CMR) because of their inability to eradicate quiescent CML stem cells. It has previously been shown that the antidiabetic drugs pioglitazone and rosiglitazone, which function as agonists of peroxisome proliferator-activated receptor γ (PPARγ), impair hematopoiesis in CD34+ CML cell lines. Prost and colleagues found that pioglitazone and rosiglitazone synergized with imatinib to decrease the number of colony-forming cells in patients with chronic-phase CML. Imatinib reduced the number of progenitor cells, whereas pioglitazone reduced the number of immature leukemia stem cells, and in combination these agents depleted both proliferating and nonproliferating CD34+ CML cells. Mechanistically, pioglitazone decreased expression of STAT5, which is transcriptionally repressed by PPARγ, and the downstream targets hypoxia-inducible factor 2α (HIF2α) and CITED2, key genes that regulate the stemness of hematopoietic stem cells. Whereas imatinib acted rapidly to prevent STAT5 phosphorylation, pioglitazone acted slowly to decrease STAT5 RNA and protein levels and prevented the induction of CITED2 and its target genes by imatinib in TKI-resistant chronic-phase CML cells. To assess the efficacy of this combination in humans, pioglitazone was added to imatinib therapy in three patients who had never achieved CMR. In response to dual treatment, all three patients reached CMR, which was maintained for up to 4.7 years after withdrawal of pioglitazone. Early results of a multicenter phase II clinical trial of the imatinib–pioglitazone combination showed sustained CMR in 57% of patients, which was associated with decreased STAT5 expression and CD34+ cell clonogenicity. These results suggest that CML stem cells have a non-oncogene addiction to the PPARγ–STAT5 pathway and that combination therapy with PPARγ agonists and BCR–ABL TKIs may result in cancer eradication in patients with chronic phase CML via gradual erosion of the CML stem cell pool.
