Leukemia

Major finding: Stabilization of MLL fusions through proteasome inhibition induces pro-B MLL leukemia cell death.

Clinical relevance: Bortezomib showed activity in two patients with pro-B MLL leukemia.

Impact: Oncogenes with latent tumor-suppressive properties may be exploitable for treatment strategies.

PROTEASOME INHIBITOR-STABILIZED MLL FUSIONS SUPPRESS PRO-B MLL LEUKEMIA

Translocations involving the mixed-lineage leukemia (*MLL*) gene induce aggressive leukemias, but high expression of MLL fusion proteins is rarely observed, suggesting that accumulation of MLL fusion products may negatively affect leukemia cell survival. Liu and colleagues found that MLL and MLL fusion protein accumulation increased upon proteasome inhibition in human leukemia cell lines and that the proteasome inhibitors bortezomib and carfilzomib caused a significant dose-dependent reduction in viability specifically in progenitor B-cell (pro-B) leukemia cells with MLL fusions but not pro-B non-MLL leukemias or MLL fusion-positive myeloid leukemias. Bortezomib-induced cell death in pro-B MLL leukemia cells was dependent on MLL fusion protein accumulation, as death was prevented by MLL fusion protein depletion and overexpression of MLL fusion proteins in non-MLL pro-B leukemia lines increased sensitivity to proteasome inhibition. Mechanistically, bortezomib activated a mitochondrial apoptotic pathway in pro-B MLL leukemia cells through upregulation of caspase 8 that led to the cleavage and activation of pro-apoptotic BID. In addition to apoptosis, bortezomib treatment also induced a potent cell-cycle arrest in G_2/M that was dependent on induction of the p27 gene *CDKN1B* by bortezomib-stabilized MLL fusion proteins, which promoted transcription via recruitment of the positive transcription elongation factor b complex and interaction with the B cell-specific transcription factor PAX5. Bortezomib treatment significantly inhibited pro-B MLL leukemia tumor progression in a mouse xenograft model, providing evidence that proteasome inhibitors have activity against pro-B MLL leukemia *in vivo*. Based on these findings, 5 adult patients with MLL leukemia received bortezomib through compassionate use. Consistent with the preclinical findings, responses were only observed in the patients with pro-B leukemia; one patient had a complete remission lasting longer than 1 year. Taken together, these results indicate that exploitation of latent tumor-suppressive properties of oncogenes could be effective in cancer treatment, particularly for pro-B MLL leukemias. ■

Liu H, Westergard TD, Cashen A, Piwnica-Worms DR, Kunkle L, Vij R, et al. Proteasome inhibitors evoke latent tumor suppression programs in pro-B MLL leukemias through MLL-AF4. Cancer Cell 2014;25:530–42.

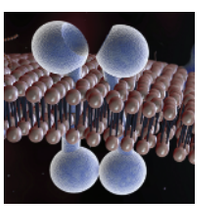
Breast Cancer

Major finding: Combined inhibition of EGFR and HER3 sensitizes TNBC to PI3K–AKT pathway inhibitors.

Concept: PI3K–AKT pathway inhibitors induce HER3 upregulation and heterodimerization with EGFR.

Impact: Targeting EGFR and HER3 in combination with PI3K–AKT inhibitors may be beneficial in EGFR-positive TNBC.

HER3 LIMITS THE ANTITUMOR ACTIVITY OF PI3K–AKT INHIBITORS IN TNBC



Overexpression of the EGF receptor (EGFR) and hyperactivation of the phosphoinositide 3-kinase (PI3K) pathway occur in a large fraction of triple-negative breast cancers (TNBC). However, EGFR or PI3K inhibitors have not led to durable responses in TNBC, possibly due to compensatory activation of other receptor tyrosine kinases. Tao and colleagues found that the PI3K inhibitor GDC-0941 and the AKT inhibitor GDC-0068 each increased human EGF receptor 3 (HER3) abundance and induced HER3 and EGFR phosphorylation in EGFR-positive, *PTEN*-null TNBC cell lines. Combining MEHD7945A, an antibody that targets both EGFR and HER3, with either GDC-0941 or GDC-0068 impeded ligand-induced EGFR and HER3 activation and significantly impaired TNBC cell proliferation when compared with PI3K–AKT inhibition alone. Consistent with this finding, combined MEHD7945A and either GDC-0941 or GDC-0068 treatment markedly impaired tumor growth of TNBC patient-derived xenografts compared with monotherapy and prevented HER3 and EGFR activation in tumor xenograft samples. Moreover, pharmacologic or genetic inhibition of HER3 was significantly more effective than the anti-EGFR antibody cetuximab in sensitizing TNBC cells to PI3K–AKT inhibitors *in vitro*, and combined cetuximab and GDC-0941 or GDC-0068 treatment did not significantly enhance tumor xenograft growth inhibition compared with single-agent treatment, suggesting that HER3 activation limits the efficacy of PI3K pathway inhibitors in TNBC. Notably, high pretreatment EGFR expression was associated with an increased probability of achieving pathologic complete response (pCR) following combination anti-EGFR and chemotherapy treatment in patients with TNBC, and of those patients that did not achieve pCR, a statistically significant increase in HER3 expression and HER3–EGFR heterodimerization was observed in the majority of residual tumors examined. Together, these findings implicate HER3 as a compensatory mechanism to PI3K–AKT inhibition and provide a rationale for clinical evaluation of combined EGFR, HER3, and PI3K–AKT inhibition in patients with EGFR-positive TNBC. ■

Tao JJ, Castel P, Radosevic-Robin N, Elkabets M, Auricchio N, Aceto N, et al. Antagonism of EGFR and HER3 enhances the response to inhibitors of the PI3K-Akt pathway in triple-negative breast cancer. Sci Signal 2014;7:ra29.