DNA Repair

Major finding: AKT reduces NHEJ efficiency by phosphorylating XLF, which dissociates XLF from LIG4 and XRCC4.

Mechanism: Phosphorylation of XLF promotes its binding to 14-3-3β, which sequesters XLF in the cytoplasm.

Impact: Oncogenic AKT activation may promote genomic instability in part through impairment of NHEJ.

AKT IMPAIRS NHEJ BY PHOSPHORYLATING XLF

Aberrant accumulation of DNA double-strand breaks (DSB) caused by impairment of homologous recombination (HR)– or nonhomologous end-joining (NHEJ)–mediated repair can lead to genomic instability and ultimately promote tumorigenesis. Liu, Gan, and colleagues found that hyperactive AKT signaling increased DSB accumulation and markedly reduced NHEJ-mediated DSB repair efficiency. AKT activation specifically led to phosphorylation of X-ray repair cross-complementing protein 4 (XRCC4)–like factor (XLF), which forms a complex with XRCC4 and DNA ligase IV (LIG4) that mediates the ligation of damaged DNA ends. AKT1, but not AKT2 or other related kinases, directly phosphorylated XLF on threonine 181 (T181), which subsequently led to dissociation of XLF from XRCC4 and LIG4 and retention of XLF in the cytoplasm by inducing binding to 14-3-3β and reducing binding to importin complexes. In the cytoplasm, casein kinases further phosphorylated XLF to facilitate its association with an E3 ubiquitin protein ligase complex containing β-transducin repeat containing protein 1 (β-TRCP1), which led to ubiquitination of XLF and its subsequent proteasomal degradation. NHEJ efficiency and cell survival after irradiation were significantly reduced in XLF-deficient cells expressing a phosphomimetic T181E mutant, providing further evidence that AKT1-mediated phosphorylation of XLF negatively regulates the NHEJ repair pathway. Of note, an XLF^{R178Q} mutation within the AKT phosphorylation motif identified in a patient with colorectal cancer blocked T181 phosphorylation, which enhanced NHEJ efficiency and conferred resistance to DSB-inducing chemotherapy, suggesting that evasion of AKT-dependent NHEJ inhibition could possibly represent a chemoresistance mechanism. Although further characterization of the dynamics of XLF regulation by AKT1 in both normal and tumor cells is needed, these findings highlight the connection between AKT signaling and DNA repair, which may have implications for tumorigenesis and response to cancer therapies. ■

Liu P, Gan W, Guo C, Xie A, Gao D, Guo J, et al. Akt-mediated phosphorylation of XLF impairs non-homologous end-joining DNA repair. Mol Cell 2015 Feb 5 [Epub ahead of print].

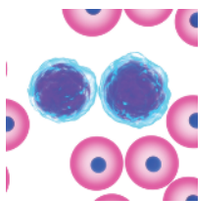
Leukemia

Major finding: CD19 ligand (CD19L)–soluble TRAIL (sTRAIL) shows potent antileukemic activity in preclinical models.

Concept: CD19L fusion increases the potency of sTRAIL and induces apoptosis via activation of CD19 and TRAILR.

Impact: CD19L–sTRAIL may be effective in patients with relapsed B-cell precursor acute lymphoblastic leukemia.

A CD19L–sTRAIL FUSION TARGETS B-CELL PRECURSOR ACUTE LYMPHOBLASTIC LEUKEMIA



Although chemotherapy is often effective in treating B-cell precursor acute lymphoblastic leukemia (BPL), a subset of patients experience tumor relapse, underscoring the need to develop additional therapeutic strategies for these patients. The soluble extracellular domain of TNF-related apoptosis-inducing ligand (sTRAIL) selectively induces apoptosis in tumor cells; however, its clinical utility is limited by a short plasma half-life and rapid release from its receptors (TRAILR). In an attempt to increase the potency of sTRAIL, Uckun and colleagues generated a fusion protein consisting of sTRAIL fused to a natural ligand (CD19L) of the CD19 receptor, which is expressed by leukemic cells from patients with high-risk BPL but not normal cells. Recombinant human CD19L–sTRAIL selectively bound to primary human $CD19^+$ BPL cells and patient-derived leukemic xenograft clones *in vitro* and induced apoptosis more potently than sTRAIL, even at very low concentrations, via activation of CD19- and TRAILR-dependent signaling. Treatment with CD19L–sTRAIL, but not CD19L or sTRAIL alone, suppressed leukemia development in patient-derived xenograft models, suggesting that this fusion protein targets leukemia-initiating cells. Furthermore, administration of low-dose CD19L–sTRAIL exhibited potent antileukemic activity in xenograft models of relapsed human BPL, resulting in prolonged event-free survival compared with untreated leukemia-bearing mice. Importantly, CD19L–sTRAIL was well tolerated *in vivo* and showed a superior pharmacokinetic profile compared with that of sTRAIL, including a higher plasma concentration and a longer plasma half-life. These results support the idea that fusion to CD19L enhances the potency of sTRAIL to induce apoptosis by promoting its stable anchoring to the membrane of leukemic cells and simultaneously activating the CD19 and TRAILR pathways. In addition, these preclinical studies suggest that recombinant human CD19L–sTRAIL may be clinically effective in patients with chemotherapy-resistant relapsed BPL. ■

Uckun FM, Myers DE, Qazi S, Ozer Z, Rose R, D'Cruz OJ, et al. Recombinant human CD19L-sTRAIL effectively targets B cell precursor acute lymphoblastic leukemia. J Clin Invest 2015 Jan 26 [Epub ahead of print].