Targeted Therapy

Major finding: Sustained mutant p53 is required for tumor maintenance and is a therapeutic target *in vivo*.

Clinical relevance: Targeting HSP90-mediated stabilization of mutant p53 inhibits tumor growth and prolongs survival.

Impact: Exploiting tumor dependence on gain-of-function mutant p53 may be an effective therapeutic strategy.

DESTABILIZATION OF MUTANT p53 PROTEINS SUPPRESSES TUMOR GROWTH

Missense mutations in the tumor suppressor *TP53* are frequently expressed in human tumors and result in constitutive stabilization of gain-of-function oncogenic mutant p53 proteins within tumors. To assess whether destabilization of mutant p53 is an effective therapeutic strategy *in vivo*, Alexandrova, Yallowitz, and colleagues generated a mouse model with conditional inactivation of mutant *Trp53*^{R248Q}, a hotspot mutation present in many sporadic cancers and associated with Li–Fraumeni syndrome. Li–Fraumeni patients born with this mutation show accelerated tumor onset, higher tumor numbers, and shorter tumor-free survival compared with Li–Fraumeni patients with p53 loss. Ablation of mutant p53 suppressed the growth of allograft T-cell lymphomas and extended survival, indicating that sustained expression of stabilized mutant p53 is necessary for tumor maintenance. Consistent with this idea, genetic inactivation of mutant *Trp53*^{R248Q} induced regression or stagnation of autochthonous tumors due to increased apoptosis and inhibited lung metastasis, resulting in significantly longer median overall and T-cell lymphoma–specific survival. Pharmacologic inhibition of the HSP90 chaperone and its positive regulator histone deacetylase 6, which are overexpressed in tumors and required for stabilization of mutant p53, via combined treatment with 17DMAG and SAHA prevented T-cell lymphoma formation and prolonged survival in mutant *Trp53*$^{R172H/R172H}$ mice, but not *Trp53*-null mice, suggesting that, in a mutant p53 context, the efficacy of HSP90 inhibition is largely dependent on destabilization of mutant p53 protein. Similarly, single-agent long-term treatment with the more potent HSP90 inhibitor ganetespib specifically destabilized mutant p53 and triggered apoptosis in mutant p53–expressing T-cell lymphoma cells, which resulted in suppression of T-cell lymphoma formation and prolonged survival in both *Trp53*$^{R248Q/-}$ and *Trp53*$^{R172H/R172H}$ mice, but not *Trp53*-null mice. These findings underscore the dependence of tumors on sustained expression of gain-of-function mutant p53 and suggest destabilization of mutant p53 protein via targeted inhibition of HSP90 as a potential therapeutic strategy. ■

Alexandrova EM, Yallowitz AR, Li D, Xu S, Schulz R, Proia DA, et al. Improving survival by exploiting tumour dependence on stabilized mutant p53 for treatment. Nature 2015 May 25 [Epub ahead of print].

Splicing

Major finding: MYC-mediated maintenance of proper mRNA splicing is essential for lymphomagenesis.

Mechanism: MYC directly upregulates the expression of core small ribonucleoprotein particle assembly genes.

Impact: Spliceosome-targeted therapy may prove effective in MYC-driven hematologic malignancies.

MYC REGULATES EXPRESSION OF PRE-mRNA SPLICING MACHINERY IN LYMPHOMA

The *MYC* oncogene drives tumor proliferation in multiple cancer types by influencing gene transcription, protein translation, and DNA replication. However, current therapeutic strategies to target MYC have thus far been unsuccessful. Koh, Bezzi, and colleagues found that MYC directly induces the transcription of genes encoding core spliceosome machinery components in both human and murine lymphoma models. Among the upregulated targets were small nuclear ribonucleoprotein particle (snRNP) assembly genes, including the gene encoding the critical enzymatic subunit protein arginine methyltransferase 5 (PRMT5). Expression of these genes correlated with high *MYC* levels in human lymphoma and leukemia, and *PRMT5* levels accurately predicted poor prognosis and decreased survival in patients with large diffuse B-cell lymphomas. In addition, lymphoma development in *Eμ-myc;Prmt5*$^{+/-}$ mice was delayed, implicating PRMT5 in MYC-driven tumorigenesis. Consistent with this finding, acute deletion of *Prmt5* reduced the viability of *Eμ-myc* B cells and increased G_1 arrest and apoptosis *ex vivo*, and PRMT5 was required for the maintenance of MYC-driven lymphomas *in vivo*. Deletion of *Prmt5* in both murine and human lymphoma cell lines resulted in decreased methylation of Sm proteins and increased aberrant splicing of pre-mRNAs with weak 5′ donor sites via exon skipping and intron retention. Similarly, depletion of MYC in lymphoma cell lines decreased PRMT5 levels and resulted in aberrant splicing events, supporting the idea that MYC-dependent regulation of PRMT5 is essential for proper mRNA splicing in lymphoma. Forced expression of alternatively spliced transcripts regulated by MYC/PRMT5, including *Atr*, *Ep400*, and *Dvl1*, using antisense oligonucleotides decreased *Eμ-myc* B-cell viability and increased apoptosis, mimicking the effects of PRMT5 depletion. Overall, these results provide evidence that MYC regulates the core splicing machinery to maintain the fidelity of mRNA splicing during lymphomagenesis and suggest that targeted inhibition of spliceosome components may be effective in MYC-driven tumors. ■

Koh CM, Bezzi M, Low DH, Ang WX, Teo SX, Gay FP, et al. MYC regulates the core pre-mRNA splicing machinery as an essential step in lymphomagenesis. Nature 2015 May 11 [Epub ahead of print].