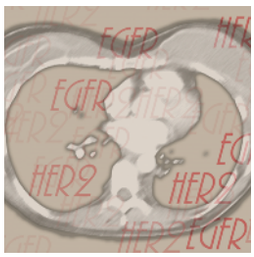
IN THIS ISSUE

An Actionable *HER2* Mutation Is Identified in Li-Fraumeni Syndrome

- All tumors of a patient with Li-Fraumeni Syndrome had oncogenic alterations of *EGFR* or *HER2*.
- *HER2*^{V659E} had not previously been identified in humans and was sensitive to lapatinib.
- Treatment with lapatinib improved the patient's symptoms and led to a radiologic response.

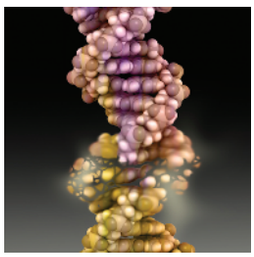


The identification of actionable genetic alterations in tumors can guide personalized use of targeted therapies. Serra and colleagues report the case of a patient with recurrent breast and lung tumors that harbored a germline *TP53* mutation and was diagnosed with Li-Fraumeni Syndrome. Whole-exome sequencing of the patient's tumors and metastases identified alterations in either *EGFR* or *HER2* in each sample, suggesting that convergent evolution toward human epidermal growth factor receptor (HER) activation conferred a selective advantage. The patient's most recent tumor had a *HER2*^{V659E} mutation, an allele that had not previously been found in humans but is orthologous to the mutation found in rats that led to the discovery of *HER2* as an oncogene. Overexpression of *HER2*^{V659E} in human mammary epithelial cells induced HER2 hyperphosphorylation and activation of downstream signaling, and cells expressing *HER2*^{V659E} were sensitive to clinically relevant concentrations of lapatinib, a small-molecule inhibitor of HER2 and EGFR. Based on these findings, lapatinib therapy was initiated in combination with paclitaxel, and led to symptom improvement and a radiologic response within 2 months. After paclitaxel was discontinued due to toxicity and amplified *HER2* was detected in circulating tumor cells, trastuzumab was added, and disease stabilization continued for 6 more months. These results suggest that anti-HER2 therapies may also have clinical activity in tumors with *HER2* mutations and raise the possibility that activation of HER family receptor tyrosine kinases contributes to the pathogenesis of Li-Fraumeni Syndrome. ■

See article, p. 1238.

Antiandrogens Prevent AR-Mediated Regulation of DNA Damage

- AR induces the expression of DNA repair genes and confers prostate cancer radioresistance.
- Antiandrogen treatment decreases DNA repair and reduces cell viability following radiotherapy.
- Antiandrogen therapy disrupts AR-mediated regulation of classical nonhomologous end-joining.

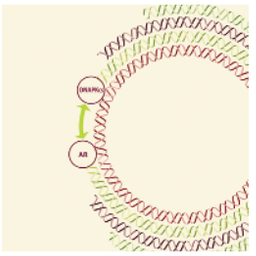


The standard of care for men with high-risk prostate cancer is the combination of androgen deprivation therapy (ADT) and radiotherapy, which increases prostate cancer cell death and improves overall survival compared with radiotherapy alone. However, the molecular mechanisms underlying this therapeutic synergy and how androgen receptor (AR) activity promotes resistance to radiotherapy remain poorly understood. Polkinghorn and colleagues found that treatment with the second-generation antiandrogen ARN-509 decreased the expression of DNA repair genes in castration-resistant prostate cancer xenografts, suggesting that AR positively regulates DNA damage repair. In support of this idea, canonical AR transcriptional output was associated with enrichment of a DNA repair gene signature in primary, castration-sensitive human prostate cancer samples; 32 of these 144 genes were stimulated by androgen and directly regulated by AR binding. Androgen deprivation or treatment with ARN-509 decreased DNA repair *in vitro*, resulting in accumulation of DNA damage and reduced prostate cancer cell viability in response to ionizing radiation, whereas stimulation with androgens enhanced repair of radiation-induced DNA damage and conferred resistance to radiotherapy. This antiandrogen-stimulated increase in radiosensitivity was mediated by a reduction in DNA double-strand break repair via classical nonhomologous end-joining but not homologous recombination. These results establish AR as an important transcriptional regulator of DNA repair gene expression and suggest that inhibition of AR-driven DNA repair underlies the synergistic effects of ADT and ionizing radiation in men with prostate cancer. ■

See article, p. 1245.

A Positive Feedback Loop Links Hormone Signaling and DNA Repair

- AR is activated by DNA damage and promotes resistance to radiation-induced genotoxic insult.
- AR promotes double-strand break repair via stimulation of DNA damage repair genes.
- DNAPKcs is required for AR-mediated DNA repair and potentiates AR transcriptional activity.

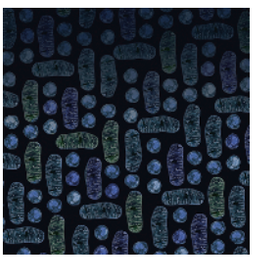


Increased activity of DNA damage repair pathways such as nonhomologous end-joining has been implicated in tumor progression and resistance to radiation therapy, which induces DNA double-strand breaks. Clinical studies have shown that the combination of androgen deprivation therapy (ADT) and radiation therapy improves survival in men with prostate cancer, suggesting that androgen receptor (AR) activity may affect the response to radiation-induced DNA damage and radiosensitivity. Goodwin and colleagues found that ADT or pharmacologic AR inhibition decreased the growth and survival of castration-resistant prostate cancer (CRPC) cells and xenografts in response to radiation, and that this effect was rescued by androgen supplementation, indicating that AR activity promotes radioresistance. Consistent with this idea, AR signaling was activated in CRPC cells in response to DNA damage and promoted resolution of radiation-induced DNA double-strand breaks, independent of the role of AR in cell-cycle progression and apoptosis. AR-mediated DNA repair was dependent on direct induction of genes involved in DNA damage repair, in particular the gene encoding DNAPKcs (DNA-dependent protein kinase catalytic subunit). AR stimulated both the expression and activation of DNAPKcs in CRPC cells; DNAPKcs inhibition impaired DNA repair following radiation and reduced AR transcriptional activity, whereas androgen supplementation partially rescued double-strand break repair and enhanced radioresistance. These findings identify a positive feedback loop linking AR-mediated regulation of DNAPKcs to DNA damage repair and tumor progression and suggest that inhibition of this signaling axis may overcome radioresistance in CRPC. ■

See article, p. 1254.

Autophagy Supports *Braf*^{V600E}-Driven Lung Tumor Growth

- Deletion of the autophagy gene *Atg7* extends survival of mice with *Braf*^{V600E}-driven lung tumors.
- *Atg7* loss promotes formation of benign tumors characterized by mitochondrial defects.
- Autophagy supports *Braf*^{V600E}-driven lung tumor cell survival by maintaining mitochondrial metabolism.



Autophagy, a catabolic process in which unnecessary or defective cellular components are engulfed and lysosomally degraded, sustains cell survival by recycling metabolites for biosynthesis and eliminating damaged proteins and organelles. Whether autophagy limits or promotes tumorigenesis is unclear, although increasing evidence suggests the role of autophagy in cancer is context-dependent. Strohecker and colleagues evaluated the role of autophagy in tumor establishment and progression using a mouse model in which intranasal administration of adenoviral Cre recombinase simultaneously enabled expression of the *Braf*^{V600E} allele and deleted the essential autophagy gene *Atg7* in the lung. Interestingly, inhibition of autophagy via *Atg7* deletion initially induced oxidative stress and accelerated the formation of *Braf*^{V600E}-driven lung tumors, but progressive mitochondrial dysfunction eventually limited tumor proliferation and prolonged survival. *Atg7* deficiency altered progression of *Braf*^{V600E}-driven tumors from adenomas and adenocarcinomas to benign oncocytomas that accumulated morphologically and functionally defective mitochondria, suggesting that defects in mitochondrial metabolism may suppress tumor growth. Analysis of tumor-derived cell lines revealed that *Atg7*-deficient cells were significantly more sensitive to starvation than *Atg7*–wild-type cells. Moreover, loss of *Atg7* conferred dependence on exogenously supplied glutamine for survival. Taken together, these data suggest that *Braf*^{V600E}-driven tumors may become addicted to autophagy as a means to sustain proper mitochondrial function and meet their increased biosynthetic demands and, as a result, may be sensitive to compounds that block this process. ■

See article, p. 1272.

Synovial Sarcomas Are Dependent on WNT/β-catenin Signaling

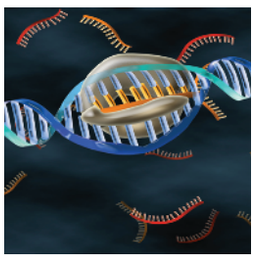
- WNT/β-catenin signaling is required for initiation and maintenance of synovial sarcoma *in vivo*.
- CK1α activators block synovial sarcoma formation and induce regression of established tumors.
- SYT–SSX transcriptionally activates an autocrine WNT/β-catenin signaling loop.

Synovial sarcoma, an aggressive cancer lacking effective therapies, is distinguished by a chromosomal translocation that fuses *SYT* (also known as *SS18*) on chromosome 18 with one of three *SSX* genes (*SSX1*, *SSX2*, or *SSX4*) on the X chromosome. The SYT–SSX fusion product has been shown to disrupt the activity of chromatin remodeling complexes and deregulate gene expression, but exactly how SYT–SSX drives tumorigenesis remains unclear. Using murine models of synovial sarcoma, Barham and colleagues show that activation of the WNT pathway is essential for the initiation and progression of synovial sarcoma. Deletion of β-catenin abrogated tumor formation in a conditional transgenic mouse model expressing human *SYT–SSX2*, and expression of the WNT receptor antagonist DKK1 or depletion of the WNT receptor LRP6 suppressed synovial sarcoma xenograft growth. Moreover, pharmacologic inhibition of the WNT pathway with activators of casein kinase 1α (CK1α), which stabilizes axin and promotes β-catenin turnover, significantly reduced human synovial sarcoma cell line growth *in vivo* and induced regression of established tumors. Activation of β-catenin activity by SYT–SSX was dependent on the same N-terminal segment necessary for interactions with chromatin remodelers that regulate gene expression, and expression of SYT–SSX led to transcriptional activation of many WNT pathway components in an autocrine manner. The finding that synovial sarcomas are dependent on SYT–SSX-induced WNT/β-catenin signaling suggests that targeting this pathway may improve clinical outcomes. ■

See article, p. 1286.

Dual Targeting of EPHA2 Augments Tumor Suppression in Ovarian Cancer

- miR-520d-3p targets EPHA2 and EPHB2 to inhibit ovarian cancer growth, migration, and invasion.
- Combined treatment with miR-520d-3p enhances the antitumor activity of *EPHA2*-targeted siRNA.
- Inverse expression levels of EPHA2/EPHB2 and miR-520d-3p are prognostic in ovarian cancer.



The oncogenic receptor tyrosine kinase EPH receptor A2 (EPHA2) is frequently overexpressed in ovarian cancer and has been associated with increased tumor growth and decreased overall survival, implicating EPHA2 as a potential therapeutic target. Although treatment with *EPHA2*-targeted siRNA decreases tumor growth in mouse models, the clinical efficacy of this approach has been limited, suggesting that additional targeting of the EPH pathway may boost the antitumor activity of *EPHA2* siRNA. Nishimura and colleagues characterized a tumor-suppressive microRNA (miRNA, miR), miR-520d-3p, as a favorable prognostic factor in patients with ovarian cancer that directly targeted EPHA2. Restoration of miR-520d-3p expression in ovarian cancer cells downregulated EPHA2 expression, resulting in reduced proliferation, migration, and invasion *in vitro* and impaired tumor formation and angiogenesis in an orthotopic model of ovarian cancer. Moreover, combined treatment with *EPHA2* siRNA and miR-520d-3p further enhanced the suppression of ovarian cancer cell proliferation and migration and synergistically inhibited tumor growth and angiogenesis *in vivo* compared with single-agent therapy. This increased antitumor efficacy was mediated in part by the ability of miR-520d-3p to also directly repress the expression of the EPH receptor EPHB2; low EPHA2/EPHB2 expression and high miR-520d-3p levels were associated with prolonged survival, suggesting that this prognostic signature may facilitate stratification of patients with ovarian cancer. These results establish combined siRNA and miRNA treatment as a potential strategy to improve therapeutic efficacy in ovarian cancer and potentially other tumors. ■

See article, p. 1302.

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