Blastic plasmacytoid dendritic cell neoplasm (BPDCN) is a rare, aggressive hematologic malignancy characterized by skin lesions and involvement of the bone marrow and lymph nodes. Patients with BPDCN are treated with chemotherapy but often develop resistant disease, underscoring the need to develop more effective targeted therapeutic strategies. Recent gene expression analysis highlighted the antiapoptotic gene $BCL2$ as overexpressed in BPDCN, suggesting that BPDCN may be functionally dependent on $BCL2$. Using BH3 profiling, which measures changes in mitochondrial permeability to determine the level of apoptotic priming in a sample, Montero, Stephansky, and colleagues found that BPDCN cells were indeed dependent on $BCL2$, and that BPDCN cell lines and primary BPDCN cells were sensitive to pharmacologic inhibition of $BCL2$ with venetoclax. Of note, BPDCN cells exhibited a greater decrease in apoptotic threshold in response to venetoclax treatment compared with normal bone marrow cells, indicating a potential therapeutic window. Consistent with this idea, venetoclax treatment resulted in decreased disease burden and prolonged survival in BPDCN patient-derived xenograft models. Furthermore, two patients with relapsed/refractory BPDCN who received venetoclax off-label experienced substantial antitumor responses without evidence of toxicity. These findings identify BPDCN as dependent on $BCL2$ and support clinical trials of venetoclax, either alone or in combination with other therapies, for patients with BPDCN.

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Therapy and radiation induce senescence in tumor cells and the tumor microenvironment, resulting in the acquisition of a proinflammatory senescence-associated secretory phenotype (SASP) that can promote tumor progression and adverse side effects. Demaria and colleagues used a transgenic mouse model (p16-3MR) they had previously developed, in which senescent host cells can be selectively ablated, to ascertain whether noncancerous host cells exhibit therapy-induced senescence and evaluate the role of senescent host cells in the response to chemotherapy. Similarly, it was shown that patients with breast cancer with a high level of p16-positive senescent T cells were more likely to develop chemotherapy-induced fatigue. Treatment of p16-3MR mice with chemotherapeutic drugs induced the expression of proinflammatory SASP factors, decreased levels of hematopoietic progenitor cells, reduced spontaneous physical activity, and induced cardiotoxicity. Consistent with these findings, depletion of senescent host cells in chemotherapy-treated mice resulted in reduced expression of SASP genes, bone marrow recovery, and increased physical activity and strength. Further, depletion of senescent host cells in p16-3MR mice orthotopically implanted with metastatic murine mammary carcinoma cells resulted in delayed tumor recurrence. Together, these results demonstrate that chemotherapy-induced senescent noncancerous cells contribute to adverse events associated with chemotherapy and suggest that ablation of senescent host cells may be a potential therapeutic strategy to reduce chemotherapy-associated morbidities.

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Patients with postpartum breast cancer, diagnosed within 5 years of childbirth, have an increased risk of metastasis. In rodent models, weaning has been shown to induce mammary gland involution, which promotes early stages of breast cancer metastasis. Goddard and colleagues used rodent models to determine if breast cancer cells also have a metastatic advantage at secondary sites. The liver has an increased metabolic output during pregnancy and lactation, and, in rats and mice, liver weights increased during pregnancy and returned to normal after weaning. Liver weight gain was associated with enhanced hepatocyte proliferation during pregnancy and hepatocyte hypertrophy during lactation. The post-weaning weight loss was associated with increased hepatocyte apoptosis, altogether indicating a previously unrecognized weaning-induced liver involution. Liver involution was accompanied by stromal remodeling, including increased deposition of extracellular matrix components and an influx of myeloid cells, stromal changes previously associated with prometastatic microenvironments. In vivo, mice with post-weaning liver involution had an increase in tumor cell seeding in the liver, but not at other sites, indicating a metastatic advantage in the liver after weaning. Moreover, patients with postpartum breast cancer had a greater risk of developing liver metastases for up to 10 years after giving birth, but did not have an increased risk of metastasis to other sites. Altogether, these findings suggest that post-weaning liver involution creates a microenvironment permissive for breast cancer metastases, which may contribute to the poor prognosis in patients with postpartum breast cancer.

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-JAK1/2 Mutations Promote Innate Resistance to Anti–PD-1 Therapy-

Anti–PD-1 therapy has been efficacious against highly metastatic or hypermutated cancers, in part by upregulating antitumor IFNγ signaling. However, IFNγ signaling can also induce tumor-specific PD-L1 expression to promote acquired resistance to anti–PD-1 therapy. Shin and colleagues, who previously showed that patients with advanced melanomas harboring concomitant loss-of-function mutations in JAK1/2 and LOH of the wild-type JAK1/2 allele developed acquired resistance to anti–PD-1 blockade, evaluated the role of JAK1/2 mutations in innate resistance to anti–PD-1 therapy. Whole-exome sequencing (WES) of pretreatment biopsies from 23 patients with metastatic melanoma treated with anti–PD-1 therapy revealed the presence of a concomitant loss-of-function JAK1P429S mutation and amplification of the JAK locus in one of nine nonresponders. Similarly, evaluation of WES data from 16 pretreatment biopsies from 16 patients with metastatic colon cancer identified a patient with a concomitant homozygous truncating JAK1 mutation and LOH at the JAK1 locus who did not respond to anti–PD-1 treatment. Evaluation of IFNγ signaling in patient-derived melanoma cell lines revealed that loss-of-function JAK1/2 mutations ablated IFNγ-mediated signaling and subsequent upregulation of PD-L1. Further, analysis of data from the Cancer Cell Line Encyclopedia and The Cancer Genome Atlas showed that truncating JAK1/2 mutations occurred in multiple types of cancers and were associated with significantly decreased overall survival in patients with melanoma or breast, prostate, or lung cancer. Together, these results describe an immunoediting mechanism by which loss-of-function kinase mutations induce primary resistance to anti–PD-1 therapy.

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IN THIS ISSUE

Loss of DAB2IP and RASAL2 Drive Metastasis in Luminal B Breast Cancer

- Loss of expression of two RasGAPs, DAB2IP and RASAL2, underlies the aggressiveness of luminal B tumors.
- Loss of DAB2IP and RASAL2 promote invasion via RAS activation and EMT via NF-κB activation.
- DAB2IP and RASAL2 may have potential as predictive biomarkers in patients with luminal B tumors.

Luminal B breast cancer is an aggressive subtype that frequently metastasizes and recurs; however, the mechanism underlying the aggressive behavior of these tumors has not been fully elucidated. The RAS pathway is hyperactivated in the majority of breast cancers, but RAS mutations are rare, prompting Olsen and colleagues to investigate expression of RasGAPs, which hydrolyze RAS-GTP to inactivate RAS. The RasGAP DAB2IP was frequently downregulated in luminal B breast tumors, and reduced expression was associated with DAB2IP promoter hypermethylation and with a reduction in relapse-free survival in patients with luminal B tumors. DAB2IP depletion activated RAS signaling in breast cancer cell lines, enhanced anchorage-independent growth, and reduced the growth of breast cancer xenografts. Of 63 primary luminal B tumors, 43% displayed loss of expression of DAB2IP, and 21% exhibited loss of both DAB2IP and another RasGAP, RASAL2. Combined suppression did not enhance the growth of tumor xenografts compared with DAB2IP or RASAL2 loss alone. However, concomitant loss of DAB2IP and RASAL2 enhanced the invasiveness of breast cancer cells, induced expression of genes associated with epithelial-to-mesenchymal transition (EMT), and increased metastasis in vivo. Concomitant loss of DAB2IP and RASAL2 promoted invasion via activation of RAS signaling, and induced EMT and metastasis by activating NF-κB signaling. Collectively, these results suggest that loss of RasGAP expression might represent an alternative mechanism to activate RAS, and expression of DAB2IP and RASAL2 may serve as potential prognostic biomarkers in patients with luminal B breast cancer.


APC/C Impairment Prevents Excessive Chromosomal Instability in Cancer

- Partial inhibition of the APC/C complex limits chromosome segregation errors and excessive CIN.
- Cancer cells may avoid the deleterious effects of excessive CIN via mitotic lengthening.
- APC/C impairment may promote resistance to drugs that increase chromosome segregation errors.

Chromosomal instability (CIN) can promote tumorigenesis and drug resistance, but excessive CIN may suppress tumorigenesis. To identify mechanisms that allow cancer cell survival under excessive CIN, Sansregret and colleagues performed an siRNA screen in cells where chromosome segregation errors were induced using a small-molecule inhibitor of the spindle assembly checkpoint (SAC). This approach revealed that partial inhibition of the anaphase-promoting complex/cyclosome (APC/C), which delayed mitotic progression by a few minutes, efficiently reduced the rate of chromosome segregation errors. Partial APC/C inhibition reduced the frequency of lagging chromosomes in conditions where the SAC was not compromised, and APC/C impairment also gave cells more time to efficiently form a bipolar spindle after genome-doubling. CDC27 is the most frequently mutated APC/C subunit in human cancer, and several cancer-associated mutations in CDC27 and other subunits are predicted to be deleterious. In cancer cell lines, monoallelic disruption of CDC27 reduced the frequency of lagging chromosomes. Prolonged treatment of cell lines with various inhibitors of the SAC kinase MPS1 led to the enrichment of clones with monoallelic mutations in APC/C subunits and the selection of cells with delayed mitosis. APC/C disruption and mitotic lengthening might thus promote resistance to drugs that increase chromosome segregation errors. The finding that changes in APC/C activity induce mild changes in mitotic duration suggests a mechanism by which tumors may reduce segregation errors to prevent excessive CIN, and further suggests that APC/C impairment may promote resistance to therapies targeting the SAC.

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