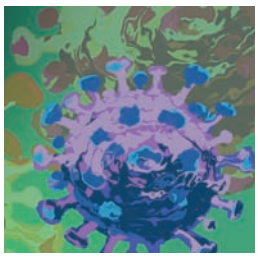
Age, Sex, Comorbidities, and Cancer Stage Influence COVID-19 Risk

- An observational study of 890 patients with cancer and COVID-19 aimed to find factors associated with risk.
- In patients with cancer, risk of COVID-19 death was correlated with male sex, greater age, and comorbidities.
- Receipt of anticancer treatments, regardless of type, was not associated with altered risk of COVID-19 death.

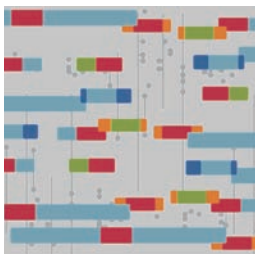


COVID-19 is particularly dangerous for patients with cancer, but information about individual factors associated with clinical outcome in patients with simultaneous COVID-19 and cancer is generally lacking. In an observational study of 890 patients from 19 centers in four European countries, Pinato and colleagues identified several risk factors for death from COVID-19 in patients with cancer. In agreement with findings from the general population, male sex, age greater than or equal to 65 years, and presence of two or more comorbidities other than cancer (most commonly hypertension, cardiovascular diseases, or diabetes mellitus) were all independently associated with greater risk of death. Active cancer (as opposed to cancer in remission) and advanced-stage cancer were independently associated with higher risk of death. Ongoing cancer treatment with chemotherapy, immunotherapy, endocrine therapy, or targeted therapy was not associated with increased risk of death; however, a possible confounder is that treated patients tended to be younger, which could mask a potential deleterious effect of anticancer therapy. Among COVID-19 treatments, only the antimalarials chloroquine and hydroxychloroquine showed a positive correlation with survival after adjusting for sex, age, and tumor stage; however, caution should be taken in interpreting this result as other factors (e.g., baseline COVID-19 severity) may have influenced prescribing, and the results of randomized controlled trials in patients without cancer do not support the use of antimalarials for COVID-19 in the general population. In summary, this timely work provides a glimpse into factors worth considering when assessing, treating, and studying patients with COVID-19 and cancer. ■

See article, p. 1465.

Chemotherapy Resistance–Conferring Mutations Present Vulnerability

- Tumor sensitivity to PARP inhibitors and platinum-based drugs can be overcome by reversion mutations.
- This work provides insight into how reversions restore function of DNA-repair genes, such as *BRCA1* and *BRCA2*.
- Resistance-conferring reversion mutations may lead to neoantigen generation, presenting immunotherapy targets.

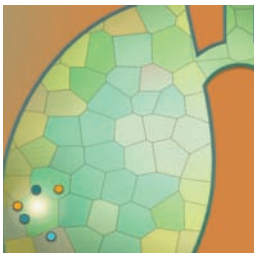


PARP inhibitors and platinum-based drugs are approved to treat breast and ovarian cancers with defects in homologous recombination machinery (e.g., due to mutations in *BRCA1/2*, *RAD51C/D*, or *PALB2*), but the development of resistance is common. Platinum-resistant tumors are often cross-resistant to PARP inhibitors, raising the question of whether homologous recombination is restored via reversion of mutations affecting DNA-repair genes in these doubly resistant tumors. In an analysis of 29 case reports and small cohort studies describing 308 gene-reversion events affecting homologous recombination genes in 91 patients, Pettitt and colleagues found that most reported reversions affected *BRCA1* (29%) or *BRCA2* (68%). Patients in the study had a wide range of different pathogenic mutations, but even patients who shared a pathogenic mutation most often acquired unique reversion mutations, with the exception of a handful of reported reversions to wild-type. This suggests that, for a given pathogenic mutation, no particular reversion mutation is favored. Notably, the type of mutation played a role in reversion frequency, with missense mutations and splice-site mutations, as well as mutations at the *C* terminus of BRCA2, typically resisting reversion. Mechanistically, reversion mutations appeared to depend most often on DNA-repair processes that fix double-strand breaks using microhomology; however, this was not always the case, indicating that reversion proceeds via multiple mechanisms. Many reverted proteins would have out-of-frame sequences or new amino acid breakpoint junctions, presenting potential sources of neoantigens that could be targeted using immunotherapies. Collectively, this work characterizes a mechanism of resistance to traditional treatments and suggests a treatment modality to overcome it. ■

See article, p. 1475.

Immune Surveillance Promotes Regression of Preinvasive Lung Lesions

- Spontaneous regression of preinvasive lung carcinoma *in situ* was associated with high CD8$^+$ T-cell infiltration.
- Progressive lesions had impaired antigen presentation and altered transcription of some immune system genes.
- The observed differences between progressive and regressive lesions did not apply to the surrounding stroma.



Progression from high-grade lung carcinoma *in situ* to lung squamous cell carcinoma is not inevitable, and 30% of these preinvasive lesions spontaneously regress. Recent work has indicated a possible role for immune surveillance in regression, but the mechanism remains incompletely characterized. Pennycuick, Teixeira, and colleagues found that regressive lesions had more infiltrating CD8$^+$ cytotoxic T cells than progressive lesions, but there were no differences in the number of CD4$^+$ helper T cells or FOXP3$^+$ regulatory T cells. Almost all cold (poorly infiltrated by T cells) lesions progressed to cancer; however, some hot lesions did as well. Progressive lesions harbored more somatic mutations and copy-number alterations affecting genes in pathways involving antigen presentation by major histocompatibility complexes, antigen processing, and stimulation and inhibition of T-cell responses, and the mutations in at least four of these genes (*B2M*, *CHUK*, *KDR*, and *CD80*) bore the hallmarks of positive selection. Progressive lesions also exhibited upregulation of *CCL27* and *CCR10*, which is of note because CCL27–CCR10 signaling is associated with immune escape in melanoma and downregulation of *TNFSF9*, which encodes a protein that promotes T-cell and natural killer–cell activation. Collectively, these results indicate a role for poor CD8$^+$ T-cell infiltration, defective antigen processing, and aberrant expression of *CCL27*, *CCR10*, and *TNFSF9* in progression from lung carcinoma *in situ* to invasive lung carcinoma. The differences observed between progressive and regressive lesions did not apply to the surrounding stroma, so these findings provide potential targets for therapies for preventing progression of preinvasive lung lesions. ■

See article, p. 1489.

LSD1 Inhibitor Efficacy Is Influenced by Cell of Origin in Leukemia

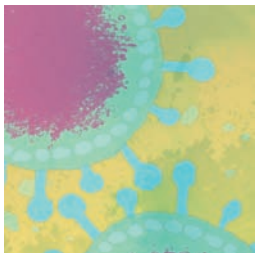
- Hematopoietic stem cell (HSC)–derived acute myeloid leukemia (AML) cells were resistant to LSD1 inhibition.
- Granulocyte–monocyte progenitor–derived AML was more sensitive to LSD1 inhibition and proapoptotic stimuli.
- The BH3 mimetic venetoclax enhanced LSD1 inhibitor sensitivity in HSC-derived AML cells.

Hematopoietic stem cell (HSC)–derived acute myeloid leukemia (AML) is typically more aggressive, exhibits greater resistance to cytotoxic chemotherapy, and has higher expression of the transcription factor EVI1 than granulocyte–monocyte progenitor (GMP)–derived AML. Cai and colleagues investigated the potential impact of cell of origin on the effects of pharmacologic inhibition of LSD1, a histone demethylase that is involved in the DNA-damage response and p53 pathway and is being investigated as a therapeutic target in AML. In mouse leukemia cells in which transformation was driven by the *MLL–AF9* fusion gene, treatment with an LSD1 inhibitor was more effective in GMP-derived leukemia cells than HSC-derived leukemia cells, and LSD1 inhibition extended life span in mice transplanted with GMP-derived leukemia cells but not HSC-derived leukemia cells. LSD1 inhibitor treatment increased apoptosis in mouse GMP-derived leukemia cells but not HSC-derived leukemia cells, and human GMP-derived *MLL–AF9* primary leukemia cells were more prone to apoptosis than HSC-derived leukemia cells overall. Human and mouse GMP-derived leukemia cells had higher p53 protein levels than HSC-derived leukemia cells, *Evi1* knockdown increased p53 levels in mouse HSC-derived leukemia cells, and higher p53 levels were associated with increased sensitivity to LSD1 inhibition. Finally, LSD1 inhibitor treatment efficacy was enhanced by the proapoptotic drug venetoclax in *Evi1*^{hi} mouse AML cells. Together, these findings demonstrate that HSC-derived AML is resistant to LSD1 inhibition—but also that this resistance can be overcome by combination therapy. ■

See article, p. 1500.

COVID-19 Treatments Do Not Improve Mortality in Patients with Cancer

- In a large observational study, COVID-19 treatment generally did not affect survival in patients with cancer.
- An exception was hydroxychloroquine plus any other treatment, which was correlated with higher mortality.
- Although observational, this study controlled for variables such as comorbidities and baseline COVID-19 severity.

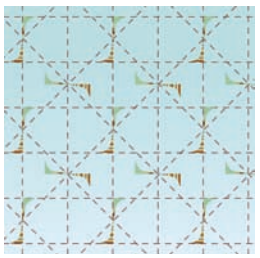


The average 30-day all-cause mortality is estimated to be at least 15% in patients with active or prior cancer and SARS-CoV-2 infection—much higher than the mortality in the general population. Given the widespread use of numerous treatments for COVID-19, including in patients with cancer, Rivera, Peters, and colleagues conducted an observational study including 2,186 adults in the United States with invasive cancer and laboratory-confirmed COVID-19 in search of any correlations between COVID-19 treatment use and 30-day all-cause mortality. Patients received the following COVID-19 treatments, alone or in combination: hydroxychloroquine (25%), azithromycin (22%), remdesivir (6%), high-dose corticosteroids (5%), tocilizumab (4%), or any other therapy (4%). Sixty percent of patients received no COVID-19 treatments. After adjusting for several potentially confounding variables, including but not limited to other comorbidities, baseline COVID-19 severity, and cancer status (in remission, stable or responding disease, or progressive disease), no individual treatment was associated with a statistically significant increased or decreased risk of mortality. However, receipt of hydroxychloroquine plus any other treatment was correlated with increased mortality. Overall, these findings do not provide strong support for the use of any of the investigated therapies for COVID-19 treatment in patients with cancer, although a numeric (non–statistically significant) decrease in mortality was seen with remdesivir, a result that may be worth investigating further. Although interpretation is restricted by the intrinsic limitations of observational studies, the difficulty of enrolling patients with cancer into randomized controlled trials necessitates studies of this type, which provide useful insights during this rapidly evolving pandemic. ■

See article, p. 1514.

Combined AKT and PARP Inhibition Shows Early Clinical Signs of Synergy

- The PARP inhibitor olaparib plus the AKT inhibitor capivasertib showed efficacy against advanced solid tumors.
- Patients had germline *BRCA1/2* mutations or *BRCA1/2*–wild-type tumors with or without DDR or PI3K–AKT alterations.
- This supports preclinical data suggesting synergy with inhibition of PARP and AKT; further trials are under way.

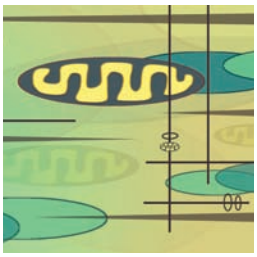


Preclinical evidence suggests that there may be synergy between PARP inhibitors and AKT inhibitors, potentially enabling the limitations of each class—development of resistance and low single-agent efficacy, respectively—to be bypassed. In a phase I clinical trial, Yap and colleagues treated 64 patients with advanced solid tumors with a combination of the PARP inhibitor olaparib and the AKT inhibitor capivasertib. Twenty patients were enrolled in the dose-escalation cohort and 44 patients who had germline *BRCA1/2* mutations or actionable mutations affecting the DNA-damage response or PI3K–AKT pathway were enrolled in the dose-expansion cohort. Most patients (39%) had ovarian cancer; the second-largest group (28%) had breast cancer. Among the 56 patients whose disease was evaluable for efficacy, 25% had partial responses and 20% had stable disease lasting four months or longer, demonstrating a clinical benefit rate of 45%. Although small numbers limit the analysis, signs of greater benefit were seen in patients with germline *BRCA1/2* mutations; among these patients, five of seven (71%) of those with breast cancer and seven of 10 (70%) of those with ovarian cancer exhibited clinical benefit. Antitumor responses were also observed in patients who had previously developed disease progression on PARP and PI3K pathway inhibitors. Pharmacodynamic studies demonstrated a reduction in phosphorylated GSK3β, increase in phosphorylated ERK, and decrease in BRCA1, providing evidence substantiating the expected mechanisms of action. In summary, this work provides preliminary clinical evidence of synergy between PARP inhibitors and AKT inhibitors, a combination that is being investigated in further trials. ■

See article, p. 1528.

CD39 Activates Mitochondrial Stress Response to Aid Resistance in AML

- CD39^{+} acute myeloid leukemia cells were present at baseline and expanded after cytarabine treatment.
- CD39 conferred cytarabine resistance by activating the cell survival–promoting mitochondrial stress response.
- Depletion or inhibition of CD39 improved cytarabine sensitivity *in vivo*, supporting ongoing clinical trials.

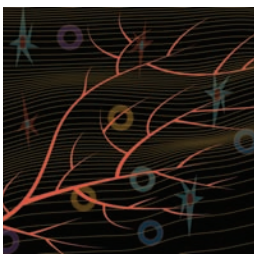


In acute myeloid leukemia (AML), relapse with chemotherapy-resistant disease frequently occurs. In an investigation of the basis of cytarabine resistance in AML, Aroua, Boet, Ghisi, and colleagues found that AML cells with high expression of CD39 (also known as ENTPD1) exhibited high intrinsic resistance to cytarabine. CD39^{hi} cells were present prior to cytarabine exposure and expanded after cytarabine treatment *in vivo*. In patients, CD39 was a marker of minimal residual disease after chemotherapy and adverse prognosis, with high numbers of CD39^{+} cells after chemotherapy correlating with shorter disease-free survival, higher short-term relapse rates, and poorer clinical outcome. CD39 was a positive regulator of oxidative phosphorylation in AML cells, and this was mediated at least in part by controlled expression of the transcriptional activators NRF1 and PGC1a, which drive mitochondrial biogenesis. *In vitro*, pharmacologic inhibition of CD39 increased AML susceptibility to cytarabine, likely via regulation of mitochondrial function to limit the metabolic reprogramming associated with the acquisition of cytarabine resistance. Mechanistically, there was evidence of a positive feedback loop linking CD39 to the cAMP–PKA signaling axis in resistant cells: With parallel activation of the ROS–ATF4 axis, activation of the survival-promoting mitochondrial stress response occurred. In mice, CD39 depletion or inhibition decreased tumor-cell burden in bone marrow following cytarabine treatment and extended survival. Collectively, these findings identify a previously unknown contributor to cytarabine resistance in AML, uncover a noncanonical function for CD39 that enables intrinsic cytarabine resistance, and support investigation of CD39 antibodies or inhibitors with chemotherapy in clinical trials. ■

See article, p. 1544.

New Model Enables Characterization of Two Pancreatic Cancer Subtypes

- Human pancreatic ductal adenocarcinoma (PDAC) organoids were transplanted into mouse pancreatic ducts.
- These organoids grew into tumors that faithfully recapitulated the two prognosis-associated PDAC subtypes.
- Slow-growing tumors could progress into fast-growing tumors via activation of KRAS signaling genes.

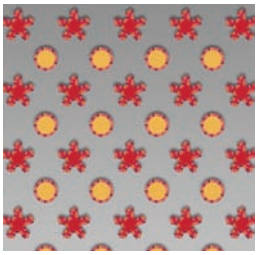


Pancreatic ductal adenocarcinoma (PDAC) can be classified into two molecularly distinct subtypes. The basal-like (or squamous) subtype is poorly differentiated, exhibits upregulation of epithelial-to-mesenchymal transition (EMT) genes and the transcription factor genes *MYC* and *TP63*, and carries a poor prognosis, whereas the classical (or progenitor) subtype is better differentiated, is characterized by expression of endodermal identity marker genes such as *HNF4* and *GATA6*, and is associated with better prognosis. Characterization of these subtypes has been hindered by a lack of preclinical models that accurately recapitulate them, prompting Miyabayashi and colleagues to develop a murine model in which patient-derived PDAC organoids are transplanted into the pancreatic ducts, where pancreatic intraepithelial neoplasms develop into invasive PDAC in humans. Like human PDAC, these intraductally engrafted organoids (IGO) came in two varieties, one with a more indolent phenotype (classical-like) and one characterized by faster growth, shorter host survival, and upregulation of EMT, proliferation, and cell-cycle genes along with KRAS- and mTORC1-pathway genes (basal-like). Tumor-cell plasticity, perhaps with influence from the tumor microenvironment, mediated switching between the two IGO subtypes. The transition from a classical-like to a basal-like IGO was marked by activation of KRAS signaling genes, which caused upregulation of EMT, axon guidance, and extracellular matrix remodeling genes. In summary, these findings shed light on the molecular basis of the two subtypes of PDAC and provide a novel mouse model as a platform to further study them. ■

See article, p. 1566.

Reversion to Fetal Intestinal–Like State Promotes WNT Independence

- In colorectal cancer organoids, a combination of cancer-associated mutations promoted WNT-independent growth.
- Priming by TGFβ, abundant in the tumor microenvironment, was required to initiate WNT-signaling independence.
- This work identifies a possible resistance mechanism to PORCN inhibitors, which are now in clinical trials.



Hyperactivation of WNT signaling is the primary driver of colorectal cancer, and mechanisms by which colorectal cancers can escape WNT signaling dependence are unknown—a topic of interest given ongoing phase I trials of inhibitors of PORCN (an enhancer of WNT signaling). Han and colleagues created murine intestinal organoid lines harboring the oncogenic *Ptprk–Rspo3* fusion and $Kras^{G12D}$ (or $Braf^{V600E}$) and inactivating mutations in the tumor-suppressor genes *Trp53* and/or *Smad4*. Among these lines, only the quadruple mutants could proliferate in the presence of PORCN inhibitors. Some of these organoid lines exhibited downstream activation of the WNT pathway (e.g., 25-fold amplification of *Ctnnb1*, which encodes β-catenin), but 16 of 20 resistant organoid lines had low WNT-target gene expression when cultured with a PORCN inhibitor, indicating WNT-independent growth. Notably, priming by TGFβ (which is abundant in the tumor microenvironment), used to select for *Smad4*-mutant populations, was required for initiation of WNT independence but not to sustain WNT independence after it was established. In contrast, *Trp53* disruption was required for both initiation and maintenance of WNT independence. *In vivo*, the tumor microenvironment alone was sufficient to establish WNT-independent growth. WNT independence was associated with transcriptional reprogramming to a fetal intestinal–like state, and signaling by the paralogous transcriptional coactivators YAP1 and TAZ (of the Hippo pathway) was necessary and sufficient for this observed lineage reversion and associated WNT-independent growth. Collectively, this work identifies a possible mechanism of resistance to WNT inhibition that is of particular importance given the advancement of WNT pathway inhibitors in clinical trials. ■

See article, p. 1590.

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In This Issue

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