Cell Biology

Major Finding: Transcytosis from cancer cells into fibroblasts triggered the cGAS–STING pathway.

Concept: Downstream induction of inflammatory modulators limited the efficacy of oncolytic virus treatment.

Impact: This uncovers a means by which cancer cells alter the environment to undermine therapeutic efficacy.

CONTACT WITH CANCER CELLS INDUCES INFLAMMATORY PATHWAYS IN FIBROBLASTS

Cancer-associated fibroblasts (CAF) can produce inflammatory substances that may contribute to resistance to anticancer therapies, including oncolytic-virus treatment. To investigate the mechanisms underlying CAFs' production of inflammatory modulators and their potential link to resistance to treatment with oncolytic viruses, Arwert, Milford, Rullan, and colleagues started by determining the results of contact between cancer cells and CAFs or fibroblasts from normal tissue. In normal tissues, direct contact between epithelial cells and fibroblasts is prevented by the basement membrane, but this barrier to interaction is disrupted in tumors. Direct coculture of cancer cells with fibroblasts led to induction of genes encoding cytokines and chemokines along with interferon-stimulated genes (ISG), all encoding inflammatory modulators. Among these, *IFNB1*, encoding interferon-β1, was rapidly upregulated in a subset of CAFs, triggering ISG transcription in both CAFs and cancer cells. The induction of *IFNB1* and consequent upregulation of ISGs was dependent on interferon regulatory factor 3 (IRF3), a transcription factor involved in the innate-immune response to viral infection, which was found at elevated levels in nuclei of CAFs in contact with cancer cells. Interestingly, the IRF3 activation caused by cancer cell–CAF contact appeared to be dependent on cGAS–STING signaling, which is normally triggered by the presence of cytosolic DNA; this finding raised the question of how cell–cell contact would affect this pathway. Further experiments revealed small amounts of cytoplasmic material from cancer cells were transcytosed into CAFs upon direct cell–cell contact, providing a mechanism for the transfer of both cGAMP, the second messenger in cGAS–STING signaling, and cytosolic DNA fragments generated as a result of the genomic stress present in cancer cells. Importantly, the transcriptional programs triggered by activation of this pathway reduced the efficacy of oncolytic viruses in killing cancer cells *in vitro* and their suppression of tumor growth *in vivo*. In summary, this work provides an intricate characterization of the effects of cancer cell–CAF contact at the molecular scale and shows how this dynamic can interfere with the therapeutic effects of oncolytic viruses. ■

Arwert EN, Milford EL, Rullan A, Derzsi S, Hooper S, Kato T, et al. STING and IRF3 in stromal fibroblasts enable sensing of genomic stress in cancer cells to undermine oncolytic viral therapy. Nat Cell Biol 2020;22:758–66.

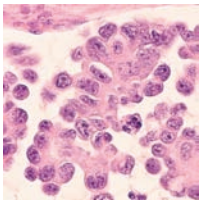
Clinical Trial

Major Finding: Berzosertib upped survival in those with platinum-resistant tumors and short platinum-free intervals.

Concept: Brief platinum-free intervals may have mattered with this ATR inhibitor due to high replication stress.

Impact: Data from this randomized phase II trial suggest that a larger study of the combination is warranted.

BERZOSERTIB MAY SYNERGIZE WITH GEMCITABINE IN SEROUS OVARIAN CANCER



Replication stress is characteristic of high-grade serous ovarian cancers, which may render these tumors sensitive to inhibition of the serine/threonine protein kinase ATR, a key factor in the cellular response to replication stress. In light of preclinical evidence suggesting that the selective ATR inhibitor berzosertib may exhibit synergy with the chemotherapy drug gemcitabine, which inhibits DNA repair, Konstantinopoulos and colleagues conducted a phase II, randomized, open-label clinical trial of berzosertib plus gemcitabine versus gemcitabine alone in patients with recurrent, platinum-resistant high-grade serous ovarian, primary peritoneal, or fallopian tube cancer. Randomization was stratified by platinum-free interval (less than or equal to three months versus three to six months) and resulted in 36 patients being placed in the arm receiving gemcitabine alone and 34 patients being placed in the arm receiving combination therapy. Both progression-free survival and overall survival data indicated that the combination treatment was more effective in patients with platinum-free intervals of three months or less. A significant overall survival benefit from the addition of berzosertib was observed in the patients with shorter platinum-free intervals, with median overall survival in the combination therapy group being 84.4 weeks versus 40.4 weeks in the group receiving gemcitabine alone. In contrast, there was no statistically significant benefit in patients with longer platinum-free intervals. This disparity may be explained by the fact that tumors from patients with shorter platinum-free intervals have indicators of greater replicative stress and thus may be more likely to respond to ATR inhibition. The addition of berzosertib to gemcitabine was generally well tolerated, with similar side-effect profiles in both groups. Overall, the results of this trial support further investigation of berzosertib plus gemcitabine in a larger, phase III study. Further, it may be worth testing the combination in patients with other tumor types that exhibit high replication stress, such as serous uterine cancers or small-cell lung cancers. ■

Konstantinopoulos PA, Cheng SC, Wahner Hendrickson AE, Penson RT, Schumer ST, Doyle LA, et al. Berzosertib plus gemcitabine versus gemcitabine alone in platinum-resistant high-grade serous ovarian cancer: a multicentre, open-label, randomised, phase 2 trial. Lancet Oncol 2020;21:957–68.