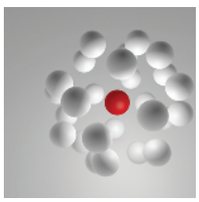
Bladder Cancer

Major finding: Recurrent PGE_2-induced proliferation of CSCs leads to bladder cancer chemoresistance.

Mechanism: Chemotherapy-induced apoptosis stimulates a PGE_2/COX2 wound-healing response and CSC repopulation.

Impact: Early PGE_2/COX2 inhibition during cytotoxic chemotherapy abrogates bladder cancer chemoresistance.

PGE_2 BLOCKADE PREVENTS CSC REPOPULATION AND BLADDER CANCER CHEMORESISTANCE



Many advanced carcinomas, including bladder urothelial carcinomas, are treated using multiple cycles of cytotoxic chemotherapy aimed at killing unsynchronized proliferating cancer cells while allowing normal tissues to recover between cycles. However, over time, a subset of patients progressively becomes unresponsive due to repopulation of cancer stem cells (CSC) that have a survival advantage. Using bladder carcinoma xenografts, Kurtova and colleagues found that gemcitabine/cisplatin chemotherapy treatment resulted in enrichment of undifferentiated cytokeratin 14–positive ($CK14^+$) cancer cells with sphere-forming and tumorigenic potential, consistent with a CSC survival advantage. Unexpectedly, these $CK14^+$ cancer cells actively proliferated in response to chemotherapy-induced apoptosis *in vitro*. These findings were validated *in vivo* via pulse-chase double labeling, revealing that quiescent label-retaining $CK14^+$ cancer cells were actively recruited to undergo cell division after chemotherapy treatment. Mechanistically, the hormone-like lipid prostaglandin E_2 (PGE_2) and the enzyme that mediates PGE_2 production, cyclooxygenase-2 (COX2), were increased in response to chemotherapy-induced apoptosis of proliferative cells, which stimulated neighboring $CK14^+$ cancer cells to repopulate residual tumors. PGE_2-containing supernatant from chemotherapy-treated cells induced sphere formation of CSCs, whereas a PGE_2-neutralizing antibody and the COX2 inhibitor celecoxib reduced sphere formation. Furthermore, combination treatment with celecoxib and chemotherapy reduced the expansion of $CK14^+$ cancer cells, enhanced responsiveness to successive chemotherapy treatment cycles, and diminished metastasis to the lung in mice harboring advanced bladder cancer xenografts, including a primary tumor derived from a patient who was resistant to chemotherapy. In addition, expression profiling of chemoresistant bladder carcinomas demonstrated a wound-response gene signature, including upregulation of COX2, which was abolished by combination treatment with celecoxib. Together, these findings highlight a mechanism of progressive chemoresistance in which CSCs actively proliferate upon recurrent cytotoxic chemotherapy treatment, reminiscent of wound-healing responses, and suggest that inhibition of PGE_2/COX2 signaling may abrogate tumor repopulation. ■

Kurtova AV, Xiao J, Mo Q, Pazhanisamy S, Krasnow R, Lerner SP, et al. Blocking PGE_2-induced tumour repopulation abrogates bladder cancer chemoresistance. Nature 2015;517:209–13.

Autophagy

Major finding: PI(5)P production by PIKFYVE is required for VPS34-independent autophagosome biogenesis.

Concept: PI(5)P rescues autophagy in PI(3)P-deficient cells and mediates glucose starvation–induced autophagy.

Impact: Components of this alternative autophagy pathway may represent potential therapeutic targets.

PI(5)P INDUCES NONCANONICAL AUTOPHAGY

Autophagosomes are double-membraned vesicles that deliver damaged proteins and organelles and other cytoplasmic material to lysosomes during autophagy. The class III phosphatidylinositol 3-kinase VPS34 induces autophagosome formation by producing phosphatidylinositol 3-phosphate [PI(3)P], which in turn mediates membrane recruitment of proteins required for autophagosome biogenesis such as DFCP1 and WIPI2. However, noncanonical VPS34-independent autophagy has been observed, suggesting that other lipids and lipid kinases may regulate autophagy in certain contexts where PI(3)P is dispensable. Vicinanza and colleagues show that another phosphoinositide, phosphatidylinositol 5-phosphate [PI(5)P], which is synthesized by the type III PI(5)P kinase PIKFYVE, is present at early autophagic membranes and promotes autophagosome biogenesis in HeLa cells. Inhibition of PIKFYVE or overexpression of PI(5)P 4-kinases (PI5P4K2), which convert PI(5)P to phosphatidylinositol 4,5-bisphosphate, impaired autophagy, further pointing to a role of PI(5)P in autophagy initiation. In cells in which PI(3)P was depleted through inhibition or knockdown of VPS34, exogenous PI(5)P rescued autophagy and was also capable of recruiting DFCP1 and WIPI2. PI(5)P synthesis also was necessary for glucose starvation–induced autophagy in HeLa cells, whereas production of PI(3)P was not. The identification of PI(5)P as a regulator of autophagosome biogenesis provides insight into noncanonical autophagy mechanisms and may have potential therapeutic implications, as components of this pathway may contribute to resistance to inhibitors of VPS34-mediated autophagy currently in clinical development and possibly represent targets to inhibit autophagy-dependent prosurvival mechanisms employed by cancer cells in response to nutrient starvation. ■

Vicinanza M, Korolchuk VI, Ashkenazi A, Puri C, Menzies FM, Clarke JH, et al. PI(5)P regulates autophagosome biogenesis. Mol Cell 2015 Jan 8 [Epub ahead of print].