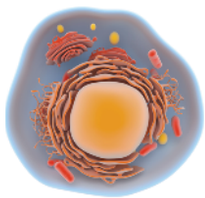
Immunotherapy

Major finding: XBP1 promotes ovarian cancer progression via dysregulation of tumor-associated dendritic cells (tDC).

Mechanism: XBP1 activation by peroxidized lipids impairs tDC lipid homeostasis and antigen presentation.

Impact: Inhibition of ER stress in tDCs is a potential strategy to enhance antitumor T-cell immunity.

THE ER STRESS FACTOR XBP1 INHIBITS ANTITUMOR IMMUNE RESPONSES



Activation of endoplasmic reticulum (ER) stress responses, including the transcription factor X-box binding protein 1 (XBP1), has been shown to directly promote tumor growth, metastasis, and drug resistance in various cancers. Cubillos-Ruiz and colleagues hypothesized that the ER stress sensor XBP1 also drives ovarian cancer progression by inhibiting dendritic cells (DC), which induce T-cell–mediated protective antitumor responses and are often dysregulated in ovarian tumors. In support of this idea, enhanced activation of XBP1 in tumor-associated dendritic cells (tDC) was observed in mice bearing aggressive ovarian tumors and in human ovarian cancer samples. Specific depletion of *Xbp1* in DCs inhibited primary and metastatic tumor growth and prolonged survival in multiple preclinical mouse models of ovarian cancer, demonstrating that expression of XBP1 in tDCs is necessary for disease progression. Constitutive activation of XBP1 in tDCs was mediated by reactive oxygen species–dependent generation of intracellular lipid peroxidation byproducts and induction of sustained ER stress, and resulted in increased expression of XBP1-controlled triglyceride biosynthetic genes in tDCs. Ovarian cancer–infiltrating DCs lacking XBP1 exhibited decreased intracellular lipid and triglyceride levels, which have been implicated in the regulation of DC-mediated antitumor immune responses. Indeed, reduced lipid accumulation in XBP1-deficient tDCs increased their antigen-presenting capacity, resulting in enhanced T-cell infiltration and activation at tumor sites. Similarly, nanoparticle-mediated XBP1 silencing in tDCs augmented T-cell–dependent antitumor immunity, decreased metastasis, and increased survival in tumor-bearing mice. These results identify XBP1 as a key regulator of DC lipid homeostasis and function and suggest the ER stress response as a potential therapeutic target to improve the immune response to cancer. ■

Cubillos-Ruiz JR, Silberman PC, Rutkowski MR, Chopra S, Perales-Puchalt A, Song M, et al. ER stress sensor XBP1 controls anti-tumor immunity by disrupting dendritic cell homeostasis. Cell 2015;161:1527–38.

Prostate Cancer

Major finding: Abiraterone is converted to Δ^4-abiraterone (D4A), a metabolite with more potent antitumor activity.

Concept: D4A inhibits multiple steroidogenic enzymes in addition to CYP17A1 and is a competitive AR antagonist.

Impact: D4A may be more effective than abiraterone in patients with castration-resistant prostate cancer.

METABOLIC CONVERSION OF ABIRATERONE CONTRIBUTES TO ITS ANTITUMOR EFFECTS

Castration-resistant prostate cancer (CRPC) arises when tumors acquire the ability to synthesize the steroid androgen hormone 5α-dihydrotestosterone (DHT), which binds and activates the androgen receptor (AR). Abiraterone is a 17α-hydroxylase/17,20-lyase (CYP17A1) inhibitor that blocks DHT synthesis and increases overall survival in patients with CRPC. Given that abiraterone is itself a steroid with structural similarities to steroid precursors known to be metabolized by 3β-hydroxysteroid dehydrogenase (3βHSD) in the DHT biosynthetic pathway, Li and colleagues hypothesized that 3βHSD would convert abiraterone to a structurally related Δ^4,3-keto compound called Δ^4-abiraterone (D4A). Indeed, the authors detected D4A in the sera of abiraterone-treated mice and patients with CRPC who were receiving abiraterone. Unlike abiraterone, which is only a potent inhibitor of CYP17A1, D4A inhibits multiple enzymes required for androgen synthesis in addition to CYP17A1, including 3βHSD and steroid-5α-reductase (SRD5A). Moreover, D4A has a significantly greater binding affinity for both wild-type and mutant AR than abiraterone, and competitive AR antagonism by D4A is comparable to the nonsteroidal AR antagonist enzalutamide. Consistent with these findings, D4A is a more potent inhibitor of AR target gene expression than abiraterone and suppresses DHT-induced PSA expression to the same extent as enzalutamide in prostate cancer cell lines *in vitro* and *in vivo*. Compared with abiraterone and enzalutamide, D4A also significantly delays growth of prostate cancer xenografts without causing the increase in deoxycorticosterone that is associated with adverse events in patients treated with abiraterone. The observation that abiraterone is converted into a more active metabolite that can simultaneously and directly inhibit androgen synthesis and AR activity suggests that D4A may contribute to the clinical activity attributed to abiraterone and raises the possibility that direct use of D4A may provide more clinical benefit than abiraterone therapy. ■

Li Z, Bishop AC, Alyamani M, Garcia JA, Dreicer R, Bunch D, et al. Conversion of abiraterone to D4A drives anti-tumour activity in prostate cancer. Nature 2015 Jun 1 [Epub ahead of print].