Angiogenesis

Major finding: Anti-EGFL7 antibodies enhance the antiangiogenic and antitumor activity of anti-VEGF therapy.

Mechanism: EGFL7 promotes endothelial cell adhesion and survival under anti-VEGF therapy-induced stresses.

Impact: Circulating progenitor cells represent a biomarker of anti-EGFL7 activity in mice and patients.

EGFL7-TARGETING ANTIBODIES SUPPRESS TUMOR ANGIOGENESIS

Prolonged treatment with VEGF-targeted therapies such as the monoclonal antibody bevacizumab has been shown to inhibit the growth of various solid tumors and to provide increased survival benefit. Suppression of tumor angiogenesis generates a nutrient- and oxygen-deprived microenvironment, suggesting that inhibition of factors that promote endothelial cell survival under these stress conditions may enhance the long-term efficacy of anti-VEGF therapy. Johnson and colleagues found that EGF-like domain 7 (EGFL7), an extracellular matrix–associated protein expressed by tumor blood vessels, protected endothelial cells from apoptosis in response to hypoxia or nutrient deficiency. Treatment with anti-EGFL7 antibodies inhibited EGFL7-stimulated endothelial cell adhesion and survival *in vitro* and augmented the antiangiogenic activity of anti-VEGF antibody in xenograft tumor models, resulting in a greater reduction in microvascular density and enhanced suppression of tumor growth. Furthermore, anti-EGFL7 improved the durability and efficacy of anti-VEGF therapy in a genetically engineered mouse model of non–small cell lung cancer, in which tumor blood vessels express EGFL7 in the context of the autochthonous microenvironment; this enhanced antitumor effect was dose dependent and was associated with prolonged progression-free survival and overall survival. To enable assessment of anti-EGFL7 activity, the authors characterized a population of human $CD34^+$ circulating progenitor cells (CPC) in the peripheral blood that expressed high levels of *EGFL7* mRNA compared with circulating endothelial cells and were capable of differentiating into endothelial cells. Anti-EGFL7 treatment specifically reduced the number of CPCs in preclinical mouse models as well as in patients from a phase I clinical trial examining anti-EGFL7 as a single agent or in combination with bevacizumab. This integrated preclinical and clinical analysis suggests a pharmacodynamic biomarker for anti-EGFL7 response and defines an optimal dose for future clinical trials of anti-EGFL7. ■

Johnson L, Huseni M, Smyczek T, Lima A, Yeung S, Cheng JH, et al. Anti-EGFL7 antibodies enhance stress-induced endothelial cell death and anti-VEGF efficacy. J Clin Invest 2013;123:3997–4009.

Prostate Cancer

Major finding: Mutation of 3β-hydroxysteroid dehydrogenase type 1 (3βHSD1) enhances DHT production in CRPC.

Mechanism: The N367T mutation inhibits 3βHSD1 ubiquitination and enhances its protein stability.

Impact: Inhibition of mutant 3βHSD1 may suppress intratumoral androgen synthesis and limit CRPC growth.

A GAIN-OF-FUNCTION MUTATION IN A STEROIDOGENIC ENZYME PROMOTES CRPC

The outgrowth of castration-resistant prostate cancer (CRPC) following androgen deprivation therapy is dependent on increased androgen synthesis within tumors and sustained androgen receptor (AR) signaling. Although treatment with inhibitors of androgen synthesis such as abiraterone limits CRPC growth, dihydrotestosterone (DHT) can be synthesized from residual amounts of the steroid precursor dehydroepiandrosterone (DHEA). However, the mechanisms that enhance DHT production from DHEA and promote abiraterone resistance in CRPC remain poorly understood. Chang and colleagues identified a nonsynonymous point mutation in hydroxy-delta-5-steroid dehydrogenase, 3 beta- and steroid delta-isomerase 1 (*HSD3B1*), which encodes an enzyme, 3β-hydroxysteroid dehydrogenase type 1 (3βHSD1), that is required for the initial rate-limiting step of DHT synthesis from DHEA, in a subset of CRPC cell lines. In addition, the N367T substitution was detected in human CRPC tumor samples as a somatic mutation or in association with LOH and increased expression of mutant 3βHSD1 in patients with germline heterozygous inheritance and was selected for in xenograft tumors treated with abiraterone, supporting a role in abiraterone resistance. *HSD3B1* mutation did not alter the enzymatic activity of 3βHSD1 but rather prevented its polyubiquitination by the E3 ubiquitin ligase autocrine mobility factor receptor and degradation via the endoplasmic reticulum–associated protein degradation (ERAD) pathway, resulting in increased 3βHSD1 protein accumulation in mutant CRPC cells. Expression of mutant 3βHSD1 augmented the flux of DHEA to DHT, enhanced expression of AR-regulated genes in CRPC cells, and accelerated the development of CRPC tumors *in vivo*, whereas depletion of the mutant protein impaired DHT synthesis, diminished prostate cancer cell proliferation, and inhibited CRPC xenograft growth. These findings show that 3βHSD1 mutation facilitates enhanced DHT synthesis following androgen deprivation and suggest that inhibition of this steroidogenic enzyme may limit prostate cancer progression and overcome abiraterone resistance in CRPC. ■

Chang KH, Li R, Kuri B, Lotan Y, Roehrborn CG, Liu J, et al. A gain-of-function mutation in DHT synthesis in castration-resistant prostate cancer. Cell 2013;154:1074–84.