Therapeutic targeting of sunitinib-induced androgen receptor (AR) phosphorylation in renal cell carcinoma

Adelaiye-Ogala R, Damayanti NP, Orillion AR, Arisa S, Chintala S, Titus MA, Kao C, Pili R (2018) *Cancer Res* 78:2886–2896.

Androgen receptor (AR) expression is known to play a critical role in the development and progression of solid tumors, including prostate cancer [1] and renal cell carcinoma (RCC) [2-6]. However, the biological role of AR signaling and its potential as a target for treatment of RCC is not well understood and is of great interest to researchers.

Pili and his team at Indiana University utilized a range of technologies—including protein array, gene silencing, western blot, and immunofluorescence cell imaging—to identify the phosphorylation target within the AR protein that correlated with AR activation and to examine how alterations with key therapeutics could be used to effectively treat RCC [7]. Phosphorylation of AR by cyclin-dependent kinase 1 (CDK1) at serine 81 results in AR activation; inhibition of this phosphorylation decreases AR activity [8]. Sunitinib is a receptor tyrosine kinase inhibitor (RTKi) that is an effective treatment for RCC; however, in sunitinib-resistant cell models for RCC, AR expression and activity are elevated (Figure 1). To counter this resistance, Adelaiye-Ogala and coworkers treated the sunitinib-resistant cells with enzalutamide, an AR antagonist that acts by preventing androgen binding to AR as well as AR transcription. This antagonist also degrades any phosphorylated AR, restoring the sensitivity of RCC cells to sunitinib treatment.

This team also reported that resistance to sunitinib may result in an increase in CDK1, and that kinome alterations arising from constant inhibition by RTKi may lead to acquired resistance in RCC [9]. Because AR expression is observed to increase as cells become resistant to sunitinib treatment, they treated cells with a combination of enzalutamide and sunitinib. This drug cocktail proved to be more effective in inhibiting AR expression and reducing the observed tumor size than treatment with either drug alone. These results suggest that AR may be a key target for therapeutic drugs capable of mitigating a poor response to RTK inhibitors in RCC. ■

References

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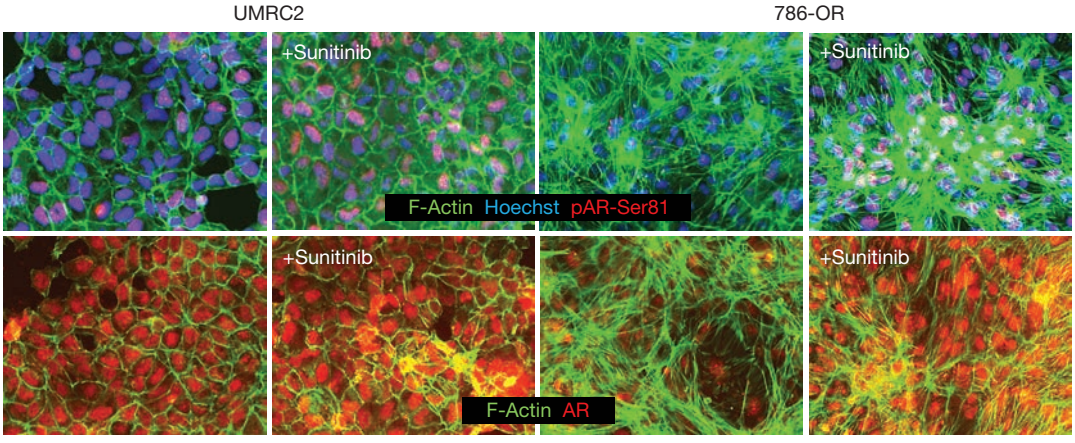

Figure 1. Increased sunitinib-induced AR expression is associated with activation of AR-targeted genes and increased AR phosphorylation. The renal cell carcinoma (RCC) cell line UMRC2 and the sunitinib-resistant cell line 786-OR were left untreated or exposed to sunitinib for 48 hr, and then immmunostained (after a 3–4 week sunitinib washout) for AR phosphorylated at serine 81 (pAR-Ser81) or for the AR C-terminal domain. Primary antibodies were visualized with fluorescent Invitrogen™ Alexa Fluor™ or FITC secondary antibody conjugates (red). F-actin and nuclei were stained with Invitrogen™ ActinGreen™ 488 ReadyProbes™ Reagent (green, Cat. No. 37110) and Hoechst™ 33258 (blue), respectively. Cells were analyzed using the Invitrogen™ EVOS™ FL Imaging System. Reprinted from Adelaiye-Ogala R, Damayanti NP, Orillion AR, Arisa S, Chintala S, Titus MA, Kao C, Pili R (2018) *Cancer Res* 78:2886–2896, with permission from AACR.