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BIOLOGY AND BIOCHEMISTRY

# The Role of Androgen Receptor Modification in the Development of Drug-Resistant Breast Cancer

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## ABSTRACT

Tamoxifen is the most common treatment option for pre-menopausal women with breast cancer (BCa). However, nearly half of those women develop resistance and treatment options become limited to highly toxic chemotherapy. Our aim is to characterize the development of resistance to Tamoxifen. We investigated the role that Androgen Receptor (AR) modification has on the development of this drug resistance. SUMO (small ubiquitin like modifiers), a mechanism which allows for hyperactivity of the AR, was assessed following Tamoxifen treatment to determine expression of modified AR at the protein and RNA levels. Cell viability was also assessed to determine when the resistance to Tamoxifen occurs. We found Tamoxifen resistance to develop following seven days post treatment and increased expression of modified AR at subsequent time intervals.

## BACKGROUND

Breast cancer is the second leading cause of death in women. Tamoxifen (Tam), a form of endocrine therapy, is the primary treatment for pre-menopausal patients with BCa.[3] Half of those receiving Tam develop resistance and suffer life-threatening metastases.[3] The AR is emerging as a potential new therapeutic target for drug-resistant BCa patients.[1] Higher AR expression correlates with better survival for BCa patients that are sensitive but not resistant to Tam therapy (Fig 1). Why is there a difference in this correlation between patients? Our lab investigated the role of AR in resistant BCa. In Tam-resistant cells, AR is hyperactive. One mechanism that allows for this hyperactivity is SUMO (small ubiquitin like modifiers). Results from our lab showed that increased expression of SUMO-2/3 coexists with hyperactive AR in Tam-resistant cells. Also, SUMO binds AR and stimulates its activity. In this study, we hypothesis that AR SUMOylation supports the development of resistance to the drug tamoxifen.

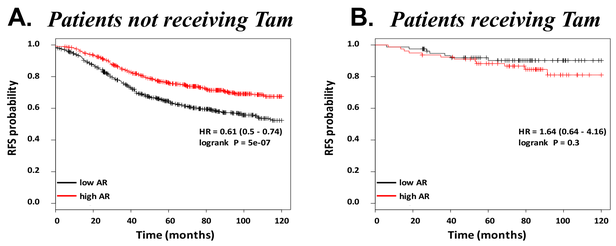
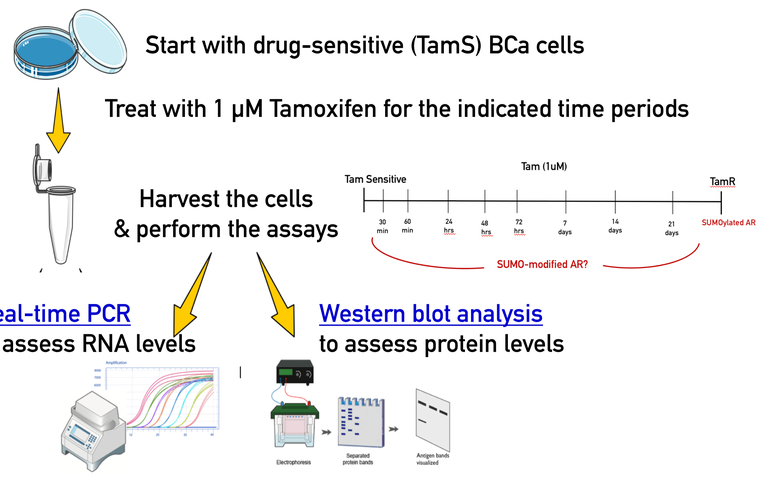



***Figure 1.*** *Higher AR expression in breast cancer patients treated with Tamoxifen correlate with higher disease reoccurrence.*

## METHODOLOGY




## RESULTS

### Breast cancer cells develop resistance with continuous drug (Tam) treatments

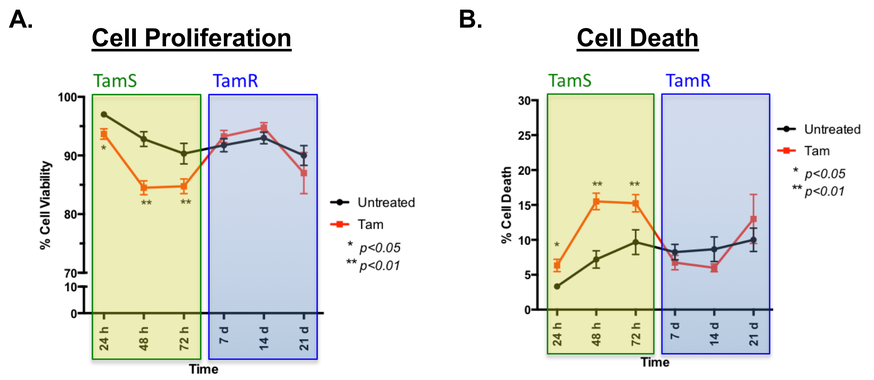
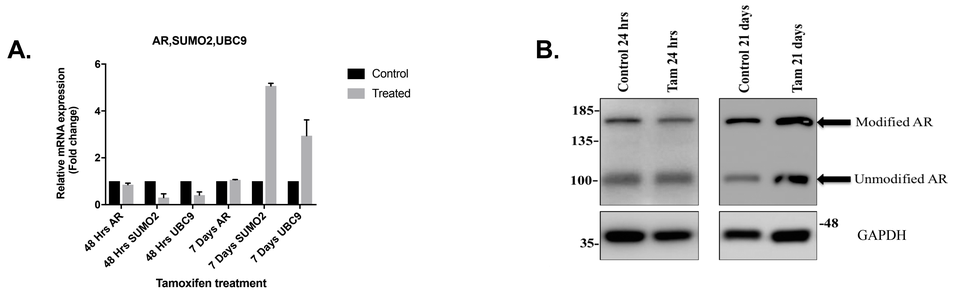



***Figure 2.*** *BCa cells were treated with Tam consistently up to 21 days. Two zones are illustrated; sensitive (green) and resistant (blue).*

### Drug-resistant BCa alters SUMO machinery & favors AR modification

***Tam treatments for short periods***




***Tam treatments for for >6 months***

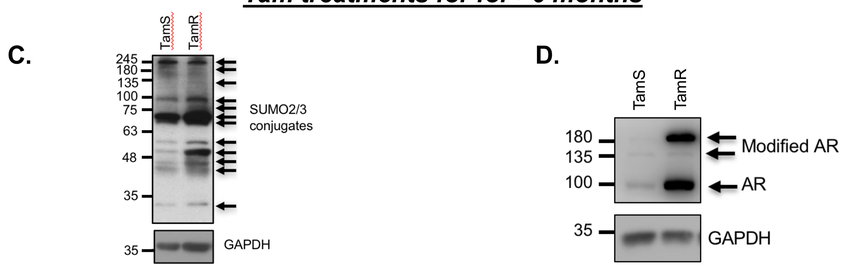



***Figure 3.*** ***(A)*** *RNA levels were assessed for AR, SUMO2, and SUMO conjugating enzyme UBC9.* ***(B-D)*** *Western blot analysis of indicated proteins.*

### Inhibiting SUMO decreases 3D-growth of drug-resistant BCa

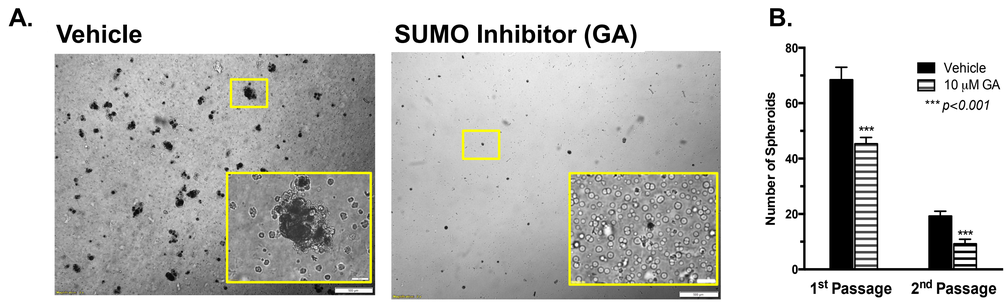



***Figure 4.*** *Therapeutically resistant cancer stem cells were treated with a SUMO inhibitor and number of spheroids were counted.*

## CONCLUSIONS

- We defined two "zones" of responses to tamoxifen (Fig. 2A & B):
  - The green zone from 0 to 7 days indicates Tamoxifen sensitivity.
  - The blue zone from 7 to 21 days indicates Tamoxifen resistance.
- Tamoxifen treatments increase SUMO and favors AR modification.

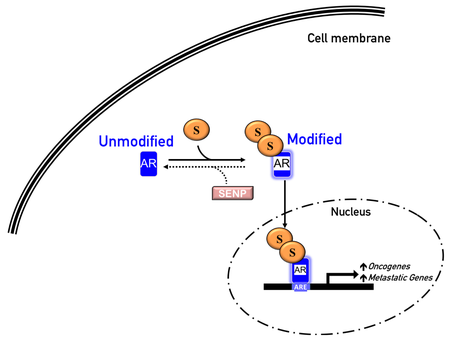



***Figure 5.*** *Schematic representation of AR modification by SUMO in TamR-BCa*

## FUTURE WORK

In the future, we aim to find a better approach for preventing resistance to tamoxifen &/or decreasing growth of cells that are already resistant. We will screen 3D spheroids of resistant cells using different combinations of SUMO inhibitors and AR antagonists.

## REFRENCES

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