Understanding resistance to the SMAC mimetic birinapant in triple-negative breast cancer

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BACKGROUND

Triple-Negative Breast Cancer (TNBC)

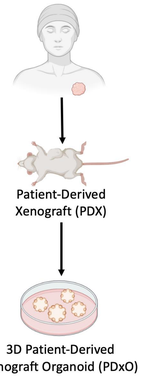


Triple-Negative Breast Cancer (TNBC) has the lowest 5-year survival rate among subtypes at 77% [1,2]

TNBC shows no expression of the Estrogen & Progesterone Receptors (ER-& PR-) and is HER2-, significantly limiting availability of targeted therapies[3]

The 5-year survival rate for TNBC patients drops to 12% after distant metastasis[1,2]

Patient-Derived models retain clinical biology



TNBC PDX and PDxO models show differential responses to the small-molecule therapy birinapant[4]

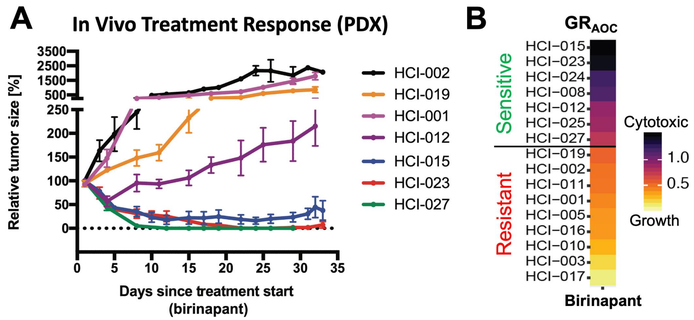
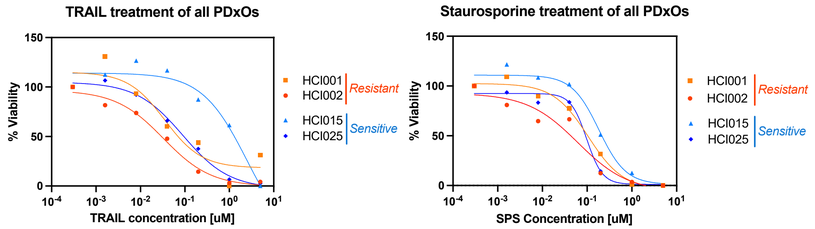


Figure 1. Birinapant response in a subset of PDX and PDxO models. **A)** *In vivo* response of PDX models to birinapant treatment (35 days) reveals distinct responders and non- responders. **B)** Birinapant sensitive and resistant PDxO lines categorized via GR_{AOC} values from Cell Titer Glo birinapant response curves.

Birinapant-resistant PDxOs can die via alternate pathways



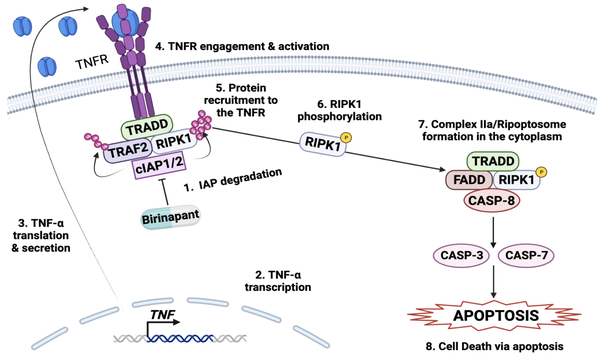
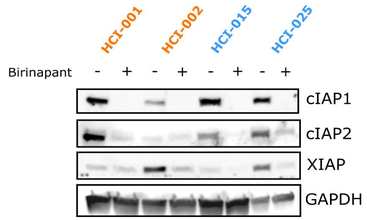


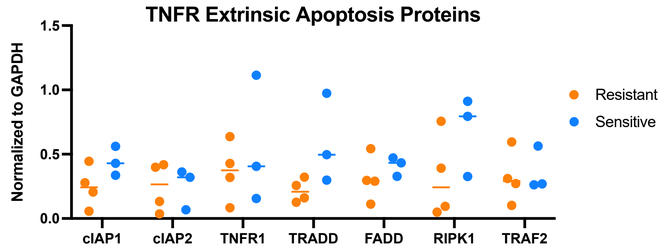
Figure 2. Birinapant's mechanism of action in the TNFR pathway.

RESULTS

Birinapant degrades IAPs in all TNBC PDxOs tested

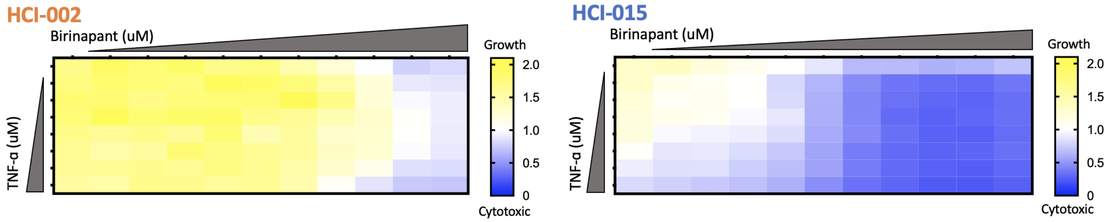


Birinapant-resistant PDxOs express extrinsic apoptosis proteins

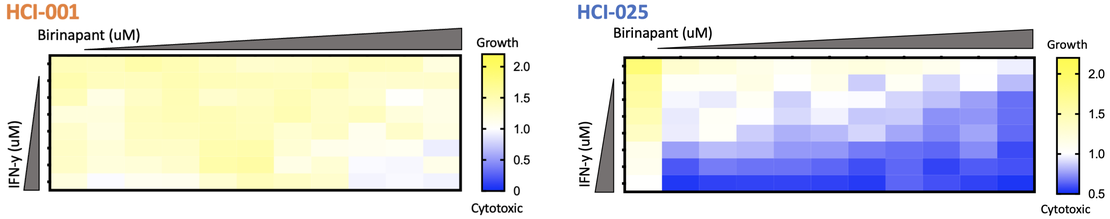


Birinapant-resistant PDxOs only remain resistant to TNFR-mediated cell death pathways

Apoptosis



Necroptosis



CONCLUSIONS

Using PDxOs, inability to execute TNFR-mediated apoptosis signaling was identified as a mechanism of birinapant-resistance in TNBC. This regulation protects TNBC tumors from birinapant-induced cell death and is likely protective against all SMAC mimetics. These data suggest that identifying and restoring the potentially missing step in TNFR-mediated apoptosis within birinapant-resistant PDxOs can sensitize them to birinapant and expand the patient population that could benefit from SMAC mimetics.



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