Pre-existing TOP2A/E2F-High Cells Drive Resistance to Trastuzumab Deruxtecan in HER2+ Breast Cancer

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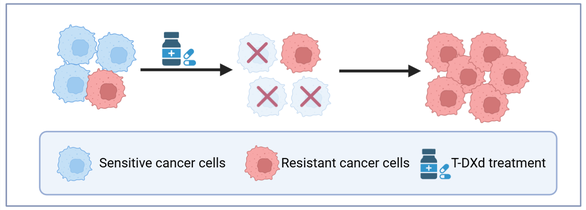
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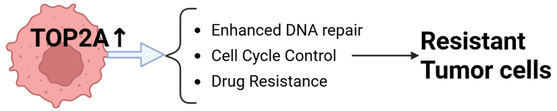
Abstract

Acquired resistance to trastuzumab deruxtecan (T-DXd) limits its efficacy in HER2 positive(HER2$^{+)}$ breast cancer and the underlying mechanisms driving this resistance are not fully understood. We performed whole transcriptome analysis of resistant cell lines (TDXd-R SUM190 and TDXd-R HCC1954) and revealed activation of DNA-repair and E2F signaling with high topoisomerase Ⅱ alpha (TOP2A) expression. With single-cell RNA-seq datasets, we found distinct TOP2A^{+} HER2^{+} cell cluster present at baseline in all examined HER2+ cell lines and patient tumors prior to T-DXd exposure, indicating a potential innate resistance. This cluster was also characterized with high E2F activity. Drug screening and validation identified LUCANTHONE and CDK2 inhibitor as effective synergetic-drugs in reducing T-DXd resistance. It suggests that resistance is related to TOP2A^{+} HER2^{+} cells, which can be therapeutically targeted to improve the treatment response.

Introduction

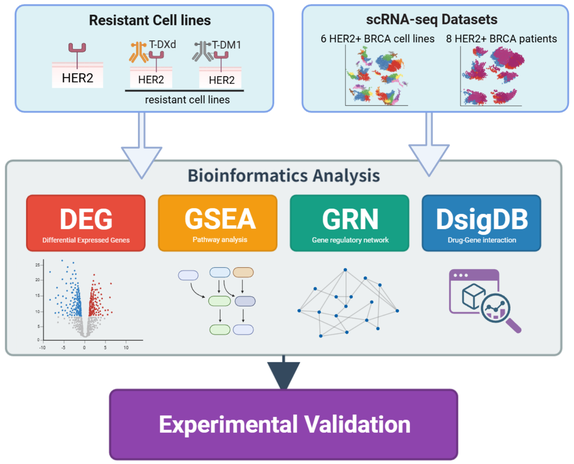
Tumor cell heterogeneity :
Emerging evidence suggests that T-Dxd resistance may arise from pre-existing tumor cell heterogeneity[1].





Topoisomerase Ⅱ alpha (TOP2A) :
a key enzyme in DNA topology and replication, is associated with poor prognosis and treatment resistance[2,3].

Methods and Materials



*Resistant cell lines : SUM190-TDXd-R, HCC1954-TDXd-R
*Single cell RNA sequencing datasets (scRNA-seq) [4,5,6]

Results

Figure 1: Distinct **TOP2A^{+} HER2^{+} cell epithelial subpopulation** present prior to T-DXd treatment in all scRNA-seq HER2^{+} patient samples.

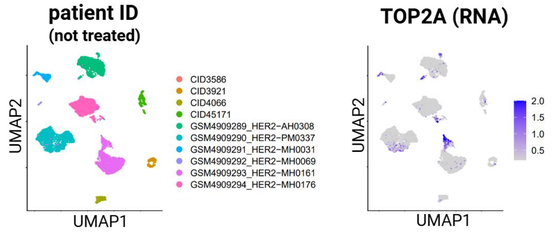


Figure 2: Distinct TOP2A^{+} HER2^{+} subpopulation present in scRNA-seq HER2 positive breast cancer cell lines.

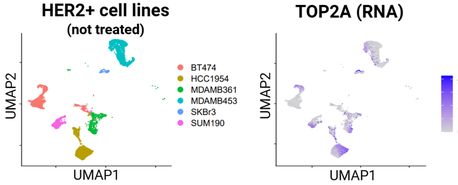


Table1 : DEGs of TOP2A^{+} HER2^{+} cells

Gene	Avg_log2FC	P_val_adj
TOP2A	6.1148	0.0000
CDK1	6.7625	4.026e-09
UBE2C	6.7509	0.0000
TFDP1	1.1717	1.839e-32

Figure 3 : Enrichment scores of DNA repair pathway in TOP2A^{+} HER2^{+} cells.

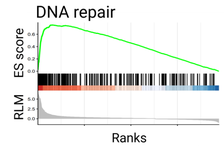
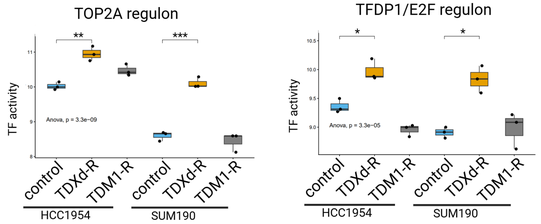


Figure 4. Increased TOP2A, TFDP1/E2FTF activities in resistant cell line (orange)



Discussion

1. **Pre-existing heterogeneity** appears in scRNA-seq datasets of HER2 positive breast cancer, even prior to T-DXd exposure.
2. DEG and GRN analysis revealed the **TOP2A-high / E2F-active state** in HER2^{+} breast cancer which can defines a resistant subpopulation.
3. Enrichment analysis and GRN analysis identified **Lucanthone** and **CDK2 inhibitors** as promising agents capable of sensitizing resistant cells.
4. These insights support the rationale for combination strategies to prevent resistance emergence in HER2^{+} breast cancer with T-DXd.

Figure 5: High TOP2A and E2F/TFDP1 regulon activity and potential synergistic therapeutic agents, including LUCANTHONE and CDK2 inhibitor.

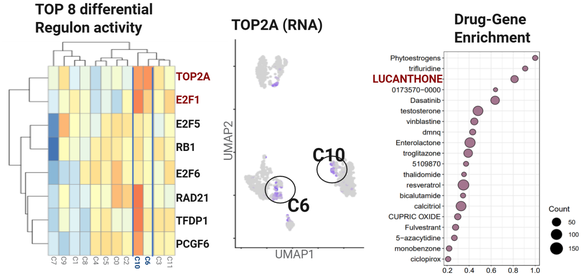
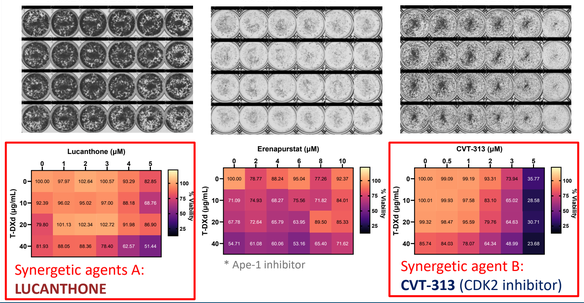


Figure 6. Cell viability of combination therapy with T-DXd and potential agents



Conclusions

Our findings suggest that resistance to T-DXd in HER2 positive breast cancer can be associated with selection/enrichment of a pre-existing cancer cell subpopulation, defined by high TOP2A expression and elevated E2F-associated regulon activity. This TOP2A-high/E2F-high signature may serve as a biomarker for innate resistance. Furthermore, these data support T-DXd in combination with agents, such as Lucanthone and CDK2 inhibitors to overcome T-DXd resistance. Further functional validation and clinical translation are warranted.

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