103. Treatment of malignant neoplasms

(University of Basel)

Asset Overview

Product Type	Others
Disease Area	Oncology
Indication	Malignant neoplasm
Current Stage	Lead Optimization
Target	MDM2
MoA	MDM2 as a therapeutic target in the substantial cohort of ER-positive, GATA3-mutant breast cancer patients. With MDM2 inhibitors widely available, our findings can be rapidly translated into clinical trials to evaluate in-patient efficacy.
Brief Description	• Capitalizing on a newly identified synthetic lethal interaction between GATA3 and MDM2, this invention provides for an innovative new approach to pharmacologically inhibit MDM2 with the ultimate goal of targeting GATA3 deficiency in cancer treatment. • Inhibition of MDM2 hampers cell proliferation and induces apoptosis in cells with reduced GATA3 activity. Since GATA3 deficiency has been identified in breast, bladder or prostate cancer, the technology offers the potential to develop treatments for various neoplasms, in particular malignant neoplasms. • The invention includes the use of a number of MDM2 inhibitors, and correlates GATA3 status as a predictive biomarker of response. The approach has been confirmed in vitro and in animal models.
Intellectual Property	WO2021228814A1
Publication	GATA3 and MDM2 are synthetic lethal in estrogen receptor-positive breast cancers. Communications Biology, (2022)
Inventors	Salvatore Piscuoglio, Charlotte K. Y. Ng, Hesam Montazer, and Gaia Bianco (Dept. Biomedicine, University of Basel), Sumana Srivatsa, and Niko Beerenwinkel (D-BSSE, ETH Zürich)

Highlights

- GATA3 and MDM2 are synthetic lethal in ER-positive breast
- GATA3 status determines response to MDM2 inhibitors in vitro.
- GATA3 expression determines response to MDM2 inhibitor in vivo.
- The synthetic lethality between GATA3 and MDM2 is TP53 dependent.
- GATA3 mutational status predicts response to MDM2 inhibitors in ER-positive breast cancer patient-derived organoids (PDOs) and patient-derived xenograft (PDX).
- The synthetic lethality between GATA3 and MDM2 acts via the PI3K-Akt-mTOR signaling pathway.

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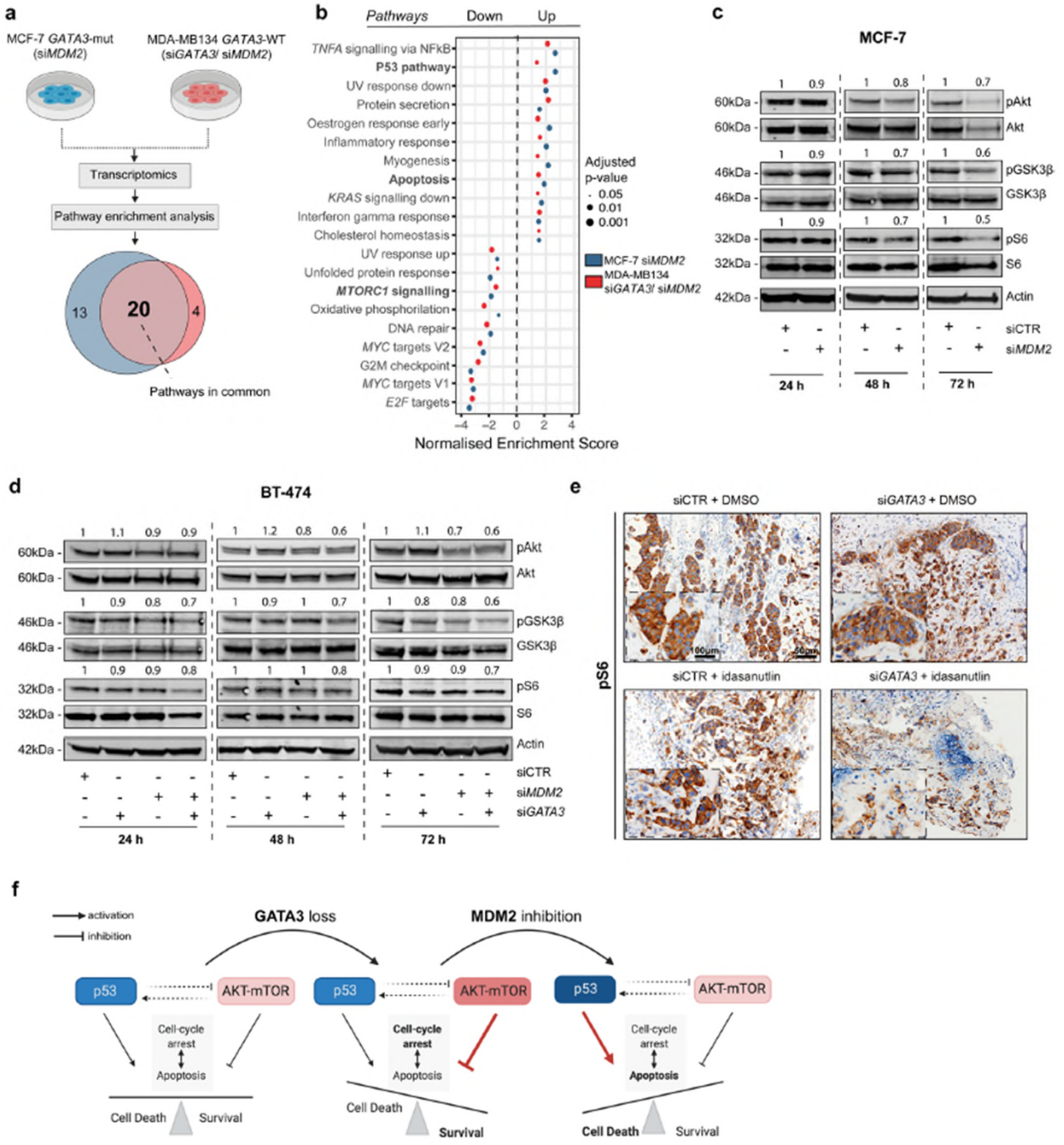
Key Data

The synthetic lethality between GATA3 and MDM2 acts via the PI3K-Akt-mTOR signaling pathway



a Schematic representation of the RNA-seq experimental setup to identify gene expression changes induced by concurrent GATA3 loss and MDM2 inhibition. Venn diagram shows the number of pathways enriched in both MCF-7 with MDM2 siRNA and MDA-MB134 with GATA3 siRNA and MDM2 siRNA. **b** Normalized enrichment scores of significantly up- and down-regulated pathways identified by gene set enrichment analysis in both MCF-7 and MDA-MB134. The size of the dots is proportional to the adjusted p-value as indicated in the legend. **c**, **d** Immunoblot showing markers of mTOR signaling pathway activation at 24, 48, and 72 h post-siRNA transfection in **c** MCF-7 cells upon MDM2 silencing and **d** BT-474 cells upon GATA3 and/or MDM2 silencing (see also Supplementary Fig. 6a, c, d). For all the western blots, quantification is relative to the loading control (actin) and normalized to the corresponding siCTR. **e** Representative immunohistochemistry micrographs of phospho-S6 stainings in BT-474 tumors extracted four days post-implantation in the CAM model. **f** Schematic representation of the mechanistic hypothesis. Scale bars: **e** 50 and 100 µm. Statistical significance was determined for **b** by fgsea. **a**, **f** were created with BioRender.com.