Enhancing the radiosensitivity of triple-negative breast cancer by targeting VEGF/Neuropilin-2

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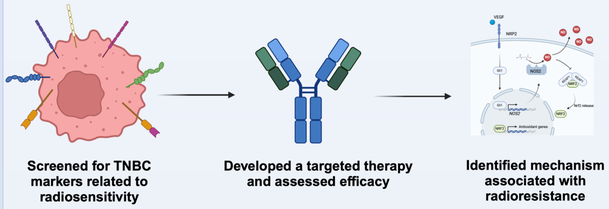
INTRODUCTION

- Triple-negative breast cancer (TNBC) is highly aggressive and is associated with a poor prognosis compared to other breast cancer subtypes[1].
- Radiation therapy is often the last line of defense to prevent locoregional recurrence, but TNBC patients still have higher relapse rates[2,3].
- Current radiosensitizers for TNBC include immune checkpoint inhibitors and DNA repair inhibitors which are often non-specific, and efficacy is variable among patients[4-6].

OBJECTIVE

- Explore intrinsic molecular factors of TNBC that mediate radioresistance
- Develop a targeted approach with an antibody to enhance the radiosensitivity of the tumor while limiting toxicity to healthy tissue
- Uncover the mechanistic role of this targeted therapy

METHODS



Screened for TNBC markers related to radiosensitivity

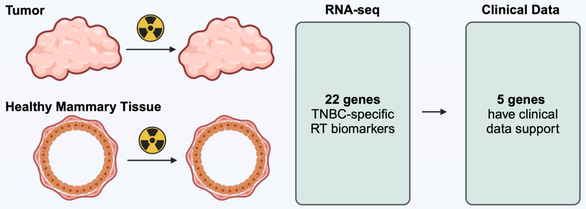
Developed a targeted therapy and assessed efficacy

Identified mechanism associated with radioresistance

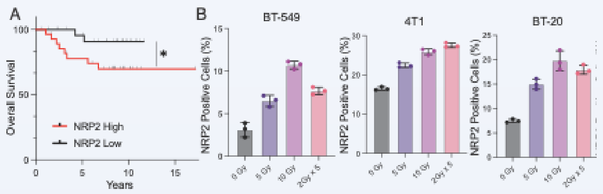
1. Screened for surface proteins that are specific to TNBC after radiotherapy
2. Developed an antibody that blocks the function of the protein and tested its efficacy both *in vitro* and *in vivo*
3. Used biotechnological tools to identify mechanism associated with radioresistance

RESULTS

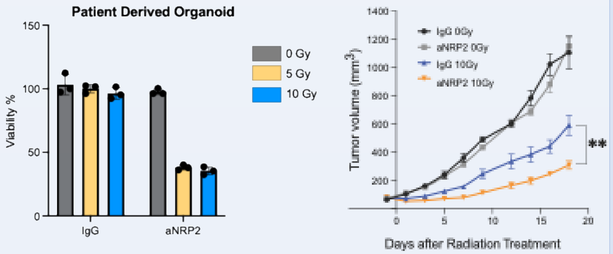
Screening for TNBC-specific biomarkers of radiation response



Neuropilin-2 (NRP2) was top hit and was validated *in vitro*

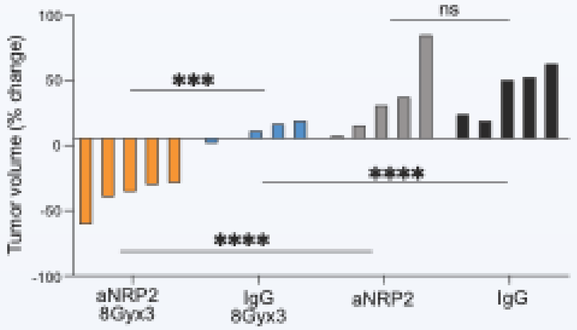


VEGF/NRP2 inhibition (aNRP2) sensitizes TNBC to radiotherapy *in vitro* and *in vivo*

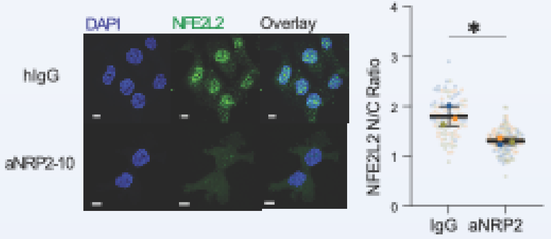


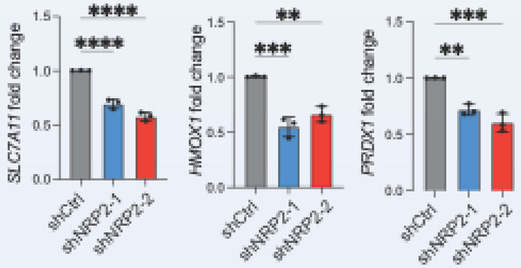
RESULTS

Radiotherapy with aNRP2 induces tumor regression



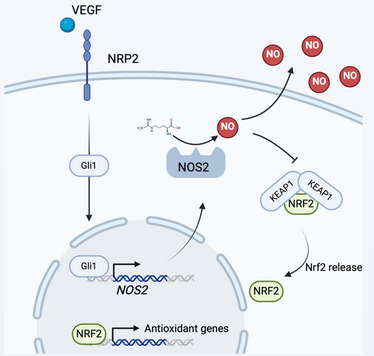
NRP2-expressing cells mitigate radiation-induced oxidative stress by inducing Nrf2-mediated antioxidant genes





CONCLUSIONS

- VEGF/NRP2 is a critical mediator of radioresistance in triple negative breast cancer
- The mechanism involves initiating Nrf2-mediated antioxidant genes and limit radiation-induced oxidative stress
- The NRP2 function-blocking antibody we developed is effective to induce radiosensitivity of TNBC in various settings



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