LINKING SEPTIN9 ISOFORM EXPRESSION TO THERAPEUTIC RESPONSE IN BREAST CANCER

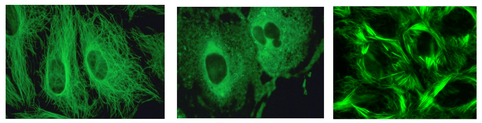
UT Health San Antonio | Mays Cancer Center

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American Cancer Society

Introduction

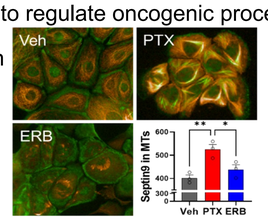
Microtubule targeting agents (MTAs), including stabilizers (paclitaxel, doxetaxel) and destabilizers (eribulin, vinorelbine) are used to treat breast cancer with no biomarkers of response

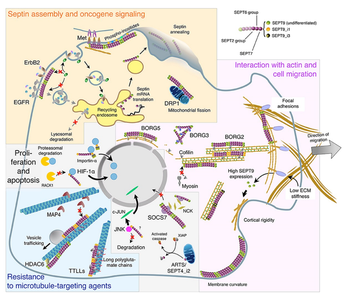


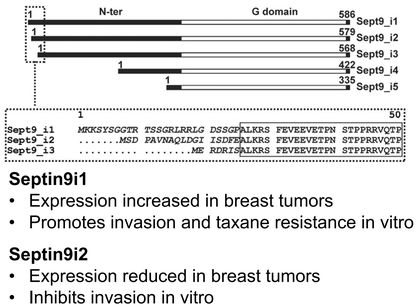
Control Microtubules | Microtubule destabilizers (eribulin, vincas) | Microtubule stabilizers (taxanes)

Septins are cytoskeletal proteins that may mediate MTA response

- Septins coordinate microtubules and actin to regulate oncogenic processes
- MTAs differentially affect septin localization
- Septin 9 in particular has been associated with breast cancer progression
- Septin 9 isoforms can promote (SEPT9i1) or inhibit (SEPT9i2) cancer cell invasion





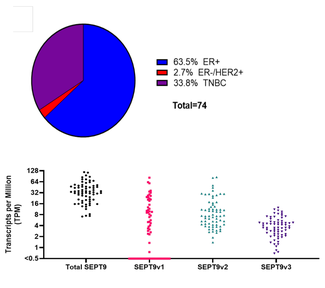


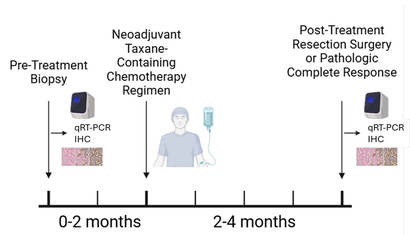
Septin9i1
- Expression increased in breast tumors
- Promotes invasion and taxane resistance in vitro

Septin9i2
- Expression reduced in breast tumors
- Inhibits invasion in vitro

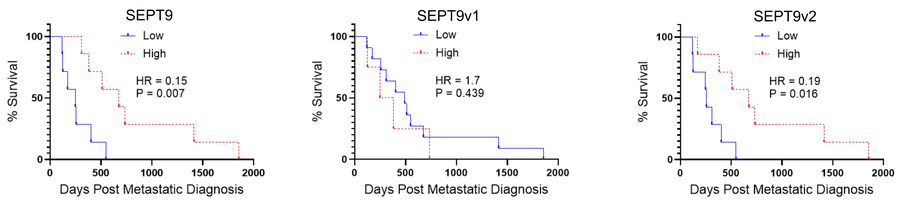
Hypothesis: Test the correlation of septin9 isoform expression with the response of breast cancer patients to taxane-containing chemotherapy regimens

- Retrospective study in advanced breast cancer patients who had whole transcriptome sequencing by Caris Life Sciences
- Prospective study of taxane response in the neoadjuvant setting



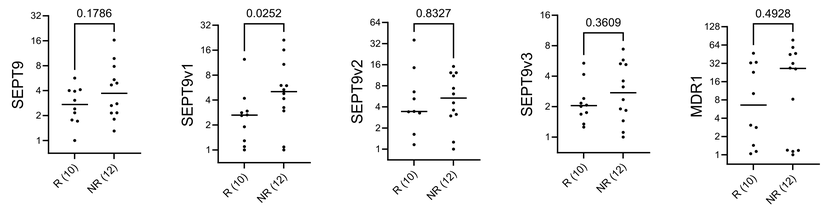


Retrospective Study – Overall Survival Post Metastatic Diagnosis



Levels of SEPT9v2 expression correlate with increased survival post-metastatic diagnosis specifically in TNBC patients

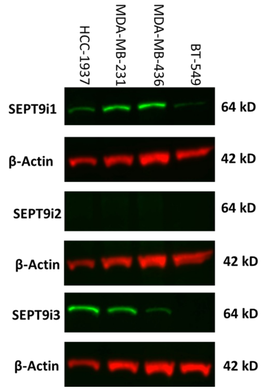
Prospective Study – Pathological Response to Neoadjuvant Taxane



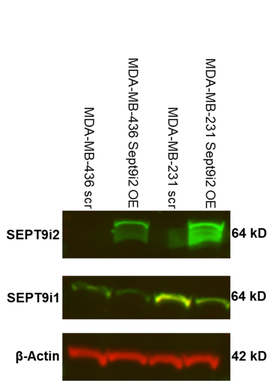
Patients who have a complete pathological response to neoadjuvant taxane chemotherapy have lower levels of SEPT9v1 in tumors pretreatment

Development and validation of isogenic models

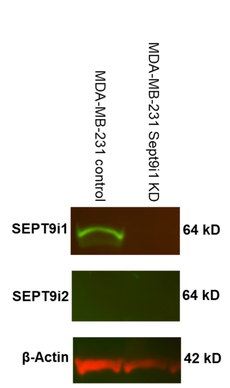
Baseline expression



Overexpressing isoforms

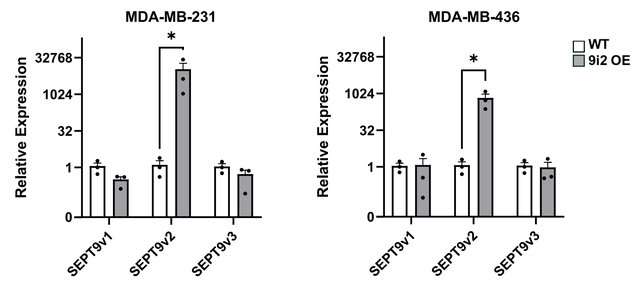


Knocking down isoforms



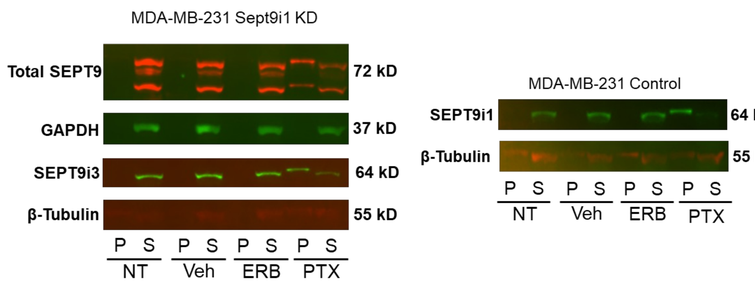
Overexpression of SEPT9i2 results in decreased SEPT9i1, suggesting SEPT9i1 and SEPT9i2 could be functionally linked

Overexpressing SEPT9i2 does not reduce SEPT9i1 at the mRNA level

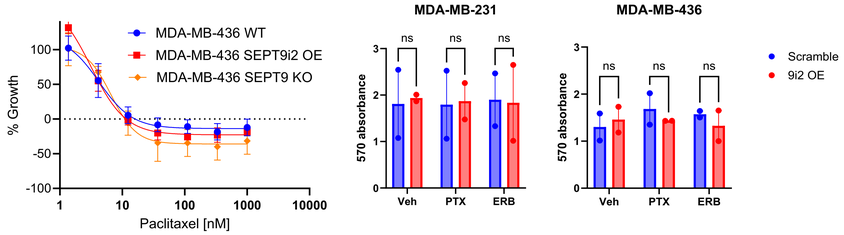


Overexpression of SEPT9i2 results in decreased SEPT9i1 post-transcriptionally

Paclitaxel treatment causes SEPT9 isoforms to associate with microtubules regardless of SEPT9i1 expression



Ongoing studies to investigate overexpression of SEPT9i2 on antiproliferative potency, cytotoxic efficacy and invasiveness of breast cancer cells



Summary and Future Directions

- SEPT9 isoforms demonstrates to be correlated with response in patients to taxane chemotherapy
- In vitro findings present limitations on SEPT9 isoform correlative studies
- Next steps include to perform in vivo evaluations of isogenic tumor models to better understand SEPT9 isoforms correlation with response to MTAs.

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