

Conference Abstracts

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Targeting SEMA7A in pre-clinical models of treatment resistant Breast Cancer

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Abstract

Background

Breast cancer risk increases with age in all women. While childbirth ultimately confers long-term protection against breast cancer for women whose first pregnancy occurs before age 30, those who give birth after age 30 experience a persistent increase in lifetime breast cancer risk. Moreover, breast cancers diagnosed within 10 years of childbirth, termed postpartum breast cancers (PPBCs), exhibit disproportionately high rates of metastasis. We and others have demonstrated that normal postpartum mammary gland involution generates a wound-healing-like microenvironment that promotes tumor progression and metastasis. Semaphorin 7A (SEMA7A), a mediator of tissue remodeling and cell survival during involution, has emerged as a potential driver of recurrence in PPBC. We have also identified elevated SEMA7A expression in breast tissue from women aged >30 regardless of parity status, suggesting a broader role for SEMA7A in age-associated breast cancer risk and progression.

Methods

We employed models of normal mammary gland development, postpartum involution, and breast cancer to investigate the role of SEMA7A in tumor progression and therapy resistance. In

addition, we developed a novel monoclonal antibody targeting SEMA7A and evaluated its therapeutic potential in models of PPBC and treatment-resistant breast cancer.

Results

SEMA7A-deficient mice demonstrated accelerated mammary gland involution together with reduced tumorigenesis and metastasis, findings that were reproduced by treatment with our novel anti-SEMA7A antibody. In ER⁺ breast cancer models, SEMA7A expression was initially driven by ER signaling; however, long-term estrogen deprivation, such as that induced by anti-estrogen therapy, resulted markedly increased SEMA7A expression alongside ER downregulation and resistance to endocrine therapies. Notably, treatment with our anti-SEMA7A monoclonal antibody restored ER expression and reversed endocrine resistance. In ER⁻ models SEMA7A conferred resistance to cell death induced by chemotherapy and activation of tumor promotional stromal remodeling. In both ER⁺ and ER⁻ breast cancer models, SEMA7A induced multiple pro-survival pathways, including resistance to apoptosis and promotion of autophagy, epithelial-mesenchymal transition (EMT), immunosuppression and vascular recruitment, all of which are associated with metastatic progression. Our novel anti-SEMA7A monoclonal antibody not only reversed these

phenotypes but also induced complete tumor regression and significantly reduced metastasis across multiple experimental models.

Conclusion

Our findings identify SEMA7A as a critical mediator of breast cancer progression during postpartum involution, aging-associated susceptibility, and therapy resistance. We have also identified that SEMA7A is a biomarker for

recurrence in PPBCs, ER+BC and ER-BC suggesting that targeting SEMA7A could have broad clinical applications. In collaboration with Pearl Scientific, we have developed a humanized monoclonal antibody for advancement to the clinic. Therapeutic targeting of SEMA7A may represent a novel strategy to reduce recurrence, overcome treatment resistance, and prevent metastasis in breast cancer patients.

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