

Approximately 25% of newly diagnosed breast cancer cases are non—invasive or pre-invasive breast cancers known as ductal carcinoma in situ (DCIS). DCIS can progress to invasive ductal carcinoma (IDC), conferring a more dangerous prognosis; however, there is a gap in knowledge regarding what ultimately causes this transition. Understanding epithelial invasion in the mammary gland will provide insight on how DCIS progresses to IDC. Our lab has found that DCIS transforms to IDC under the “wound-healing” pressure of postpartum tissue remodeling—termed postpartum mammary gland involution. This invasive transformation is dependent, in part, on collagen-induced cyclooxygenase (COX2) expression. We identified that a membrane-bound signaling molecule, semaphorin-7a (SEMA7A), promotes both collagen deposition and COX-2 expression and therefore DCIS progression (Tarullo S, et al. *Oncogene* 2020). SEMA7A is also naturally upregulated in mammary epithelial cells during postpartum involution (Rutherford T, et al. *Cell Death & Disease* 2021) and in DCIS relative to normal epithelium (Tarullo 2020). We have identified that inhibition or silencing of SEMA7A can inhibit DCIS invasion (Tarullo 2020). While this demonstrates that SEMA7A expression is sufficient to promote innate capacity for tumor cell invasiveness, we have yet to investigate how SEMA7A interacts with the tumor microenvironment (TME) to promote stromal changes known to advance this transition, such as collagen remodeling or immune cell recruitment. We have demonstrated a potential role for DCIS-associated macrophages in facilitating this transition. We have found that SEMA7A polarizes macrophages in between an M1- and M2-like state and can promote macrophage remodeling of the lymphatic vasculature as well as tumor cell entry into lymphatic vessels (Elder A, et al. *Cancer Res* 2018). Furthermore, we have shown that SEMA7A promotes expression of matrix remodeling enzymes. Our results suggest that SEMA7A mediates DCIS invasion through both intrinsic and extrinsic mechanisms, which could facilitate progression to metastasis. By understanding how SEMA7A regulates DCIS progression we can begin to introduce potential targets for preventative therapies for development of invasive disease—including targeting SEMA7A itself. Since SEMA7A is low in most adult tissues it is expected that such a therapeutic would be less toxic for patients than the current therapies.