Knocking out SEMA7A disrupts normal epithelial invasion during pubertal mammary gland development

Figure 1: Knocking out SEMA7A in mice shows reduced ductal elongation during pubertal mammary gland development. (A) Representative mammary gland carmine alum whole mount images from C57BL/6-background SEMA7A KO mice compared to wild type (WT) at 5 weeks of age. (B) Quantification of ductal elongation at 5 weeks of age normalized to Wild type (WT) KO mice. Ductal elongation quantified in millimeters length beyond lymph node, taken as a percentage of millimeter length of mammary gland at 5 weeks of age; (right) H&E images of ducts at 5 weeks of age. (C) Quantification of ductal branching at 5, 8, and 12-13 weeks of age. Branching in KO mice shows reduced ductal elongation during pubertal mammary gland development.

Figure 3: Treatment of RAW264.7 macrophages with SEMA7A promotes a unique mRNA-expression pattern.

Figure 4: Treatment of RAW264.7 macrophages with SEMA7A promotes protein expression of macrophage polarization markers.

Figure 6: Treatment of mice DCS tumors with a SEMA7A-blocking antibody decreases DCS progression and invasion-promoting phenotypes. Female SnGc mice were subcutaneously injected with 250,000 MCF7/BD2 cells in the left and right mammary gland flaps. Mice were killed at weekly intervals, followed by whole mammary gland dissection. The tumors were dissected and homogenized and used for protein or RNA extraction. The protein was denatured by proteinase K and then separated using a Bio-Rad protein affinity gel. An equal amount of protein 

Conclusions and Future Directions

- We have shown a potential delay in pubertal development in SEMA7A KO mice, demonstrated through a decrease in ductal length starting at 6 weeks of age (Fig 1A-B), sustained macrophage remodeling in the pubertal mammary gland (Fig 1C), and (bottom) Tumor necrosis factor alpha (TNFα).
- The tumors also had decreased collagen intensity from the tumor border (Fig 1C) and changes in collagen orientation (Fig 1E) that suggest a less invasive phenotype. Interestingly, we found an increase of macrophages in the tumor-adjacent mammary gland (Fig 1E).
- Overall, we have shown that SEMA7A facilitates cell invasion by altering structural components and macrophage function that assist in cell invasion. We hypothesize that SEMA7A promotes macrophage accumulation around DCIS tumors, priming macrophages to be tumor-promotional and remodel the collagen around the myoepithelial to assist in DCIS cell invasion. SEMA7A shifts from DCIS cells promotes macrophage MMP expression, to remodelling the tumor-associated matrix and assist in the invasive potential of SEMA7A+ DCIS tumors. Blocking SEMA7A signaling may decrease DCIS progression of these tumors. Our next steps are to characterize cytokine expression in macrophages after SEMA7A treatment and further explore upstream mechanisms of SEMA7A regulation.