RNA-seq analysis of murine liver to identify breast cancer metastatic potential during liver involution
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Background

Postpartum breast cancer cases have increased risk of liver metastasis:
- Postpartum breast cancer (PBBC) is defined as breast cancer diagnosed within 10 years of last lactation.
- PBBC patients have an increased risk of developing liver metastases compared to never pregnant (nulliparous) patients (Fig 1).
- Frequency of liver metastases in nulliparous and PBBC patients from a University of Colorado young women's cohort (n=646, p<0.05). B) Frequency of metastases to the liver, lung, brain, and bone in nulliparous and PBBC patients that had metastases

Post-wean period is a key window for tumor advantage:
- The liver undergoes tissue remodeling in response to a reproductive cycle
- Nulliparous or regressed states. Tumors were examined and quantified 5 weeks post-injection

Research Questions & Methods

1. What can we learn about liver involution from an unbiased liver RNA-seq approach?
2. Can we find further evidence for why the involution supports a metastatic niche?

Liver RNA-seq data show evidence of a classic reproductive cycle:
- Fig 7. A) PCA of 9000 variable genes across all groups. B) Hierarchical clustering of the top 500 most differentially expressed genes (DEG) vs. C) Multiple group comparison by single sample gene set enrichment analysis (ssGSEA) on four hallmark pathways.

Fig 8 cont. C) ssGSEA identified cell death as enriched as early as ID2, with stronger signal at ID4 and ID6.

Lung vs ID2

Lung vs ID4

Lung vs ID6

Gene signatures associated with poor outcomes in breast cancer are found in the normal involving liver:
- Previous studies have shown:
  - Mammary gland involution gene signatures associate with poor breast cancer outcomes
  - Immune cells, especially myeloid derived cells, associate with the liver metastatic niche
  - Extracellular matrix (ECM) and ability to remodel ECM promotes tumor growth

Conclusion

The involuting liver has features of the involuting mammary gland, but has distinct differences that may provide further insight into the liver metastatic niche. Two areas of interest for further investigation are the role of immune suppressive macrophages and ECM remodeling.

Acknowledgements & References

Unpublished data: Please do not share/post