The Hepatocyte-like Oenocyte of the Host, as a Central Hub for Systemic Lipid Metabolism, is Altered by Tumor Progression and Cachexia.

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1. Introduction

- According to the American Cancer Society, cancer continues to be the second leading cause of death in the US, after heart disease.
- Cancer is a complex and dynamic cellular mechanism that leads to the over-proliferation of cells within the body.
- Cachexia, or wasting syndrome, is defined as a general state of weakness caused by muscle and weight loss.
- This study focuses on the interaction between tumor and host metabolism, where the hepatocyte-like oenocyte serves as a central hub for systemic lipid metabolism, contributing to the unraveling of the mechanisms of organ wasting induced by tumors.
- Oenocytes are large, specialized cells found along the cuticle of insects that are involved in the metabolism of very long chain fatty acids (VLCFA), hormone synthesis, and detoxification processes.

Fig. 1

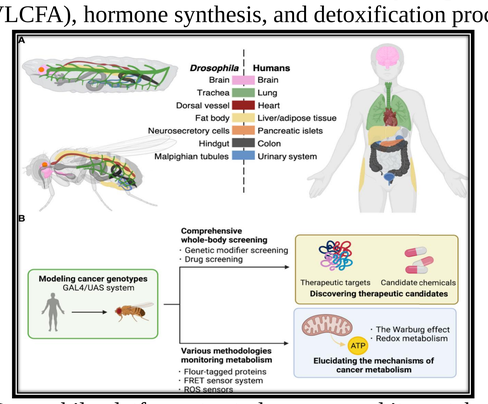


Figure 1 Drosophila platforms to study cancer and its metabolism. (A), Corresponding tissues/organs regarding their structures and functions between Drosophila and humans. (B), The GAL4/UAS system enables induction of genes of interest in target fly tissues.

2. Methods

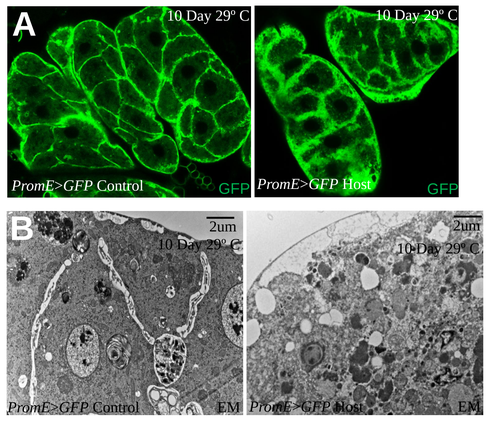
- Cachexia was induced in adult female flies by transplanting Actin>NICD tumors. The flies were allowed to remain at room temperature for 8-12 hours following injection.
- Flies were then incubated at 29º C for 10-14 days before being dissected and stained.
- Four different genotypes of flies were injected with tumors in this study:
  - *wild type* (Bloomington Line: W1118)
  - *PromE>GFP*
  - *PromE>GFP* x *UAS-mCherry-Atg8a* (Bloomington Line: 37750)
  - *PromE>GFP* x *UAS-Spin-RFP*.
- Host flies were cultured at 25º C and allowed to mature to adulthood before being injected with the tumor.

3. References

1. ACS Medical Content and News Staff. “2022 Cancer Facts & Figures Cancer: Cancer Death Rate Drops.” 2022 Cancer Facts & Figures Cancer | Cancer Death Rate Drops | American Cancer Society, 12 Jan. 2022, www.cancer.org/research/acs-research-news/facts-and-figures-2022.html#:~:text=Cancer%20continues%20to%20be%20the,about%201%2C670%20deaths%20a%20day.
2. Jiang H, Kimura T, Hai H, Yamamura R and Sonoshita M (2022) Drosophila as a toolkit to tackle cancer and its metabolism. Front. Oncol. 12:982751. doi: 10.3389/fonc.2022.982751

4. Results

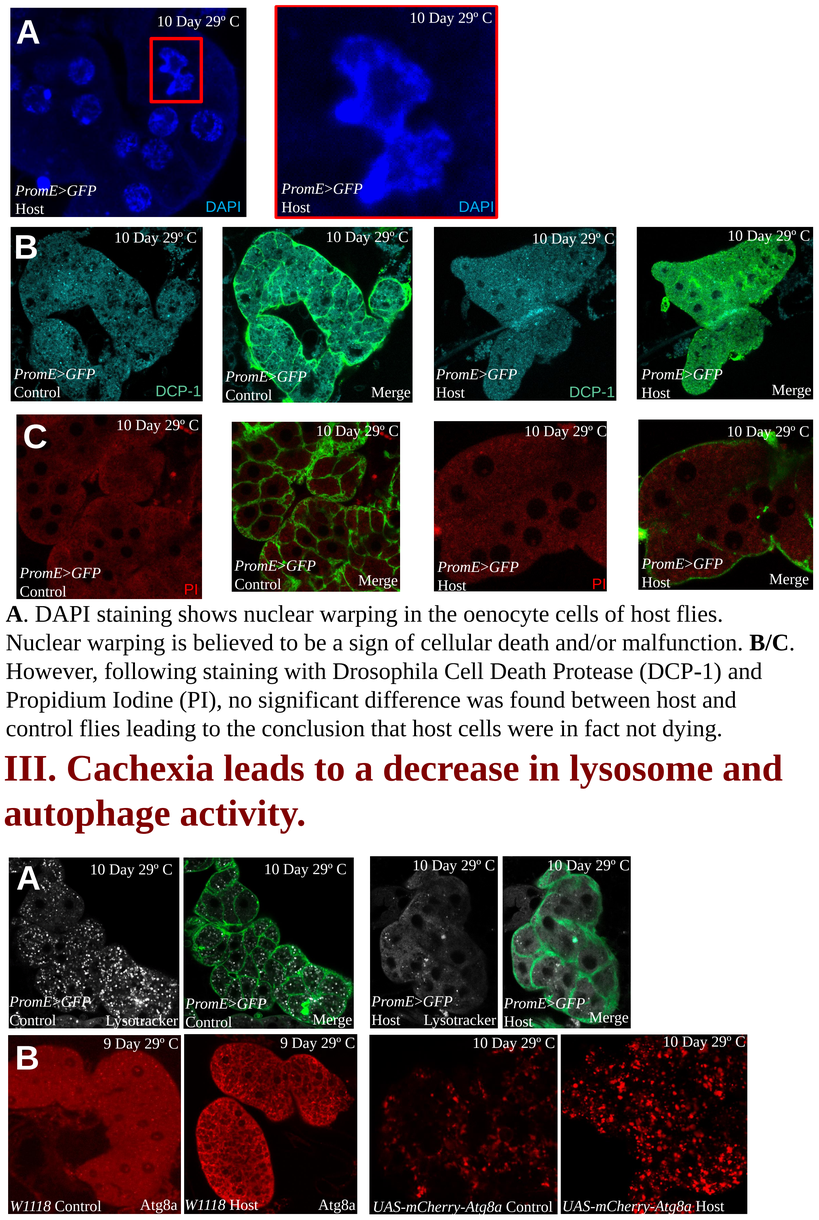
I. Tumor presence causes cellular membrane expansion in the oenocyte.



A. GFP expressed in the cellular membrane shows cachexia host flies (right) exhibit a thicker oenocyte cellular membrane when compared to control flies (left). Nuclear fragmentation is believed to be a sign of cellular death and/or malfunction.

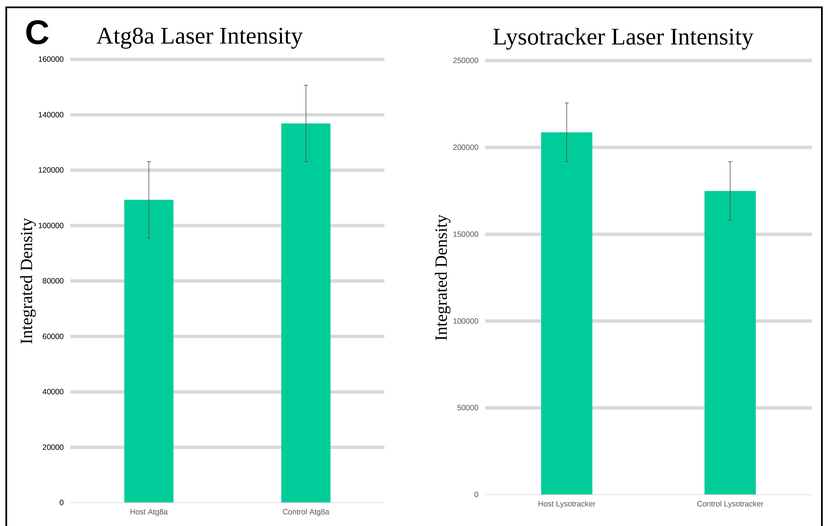
B. Electron Microscope (EM) data shows large gaps in the cellular membrane possibly related to increases in the exportation of intracellular molecules caused by cachexia.

II. Nuclear warping is not a signal of cell death.



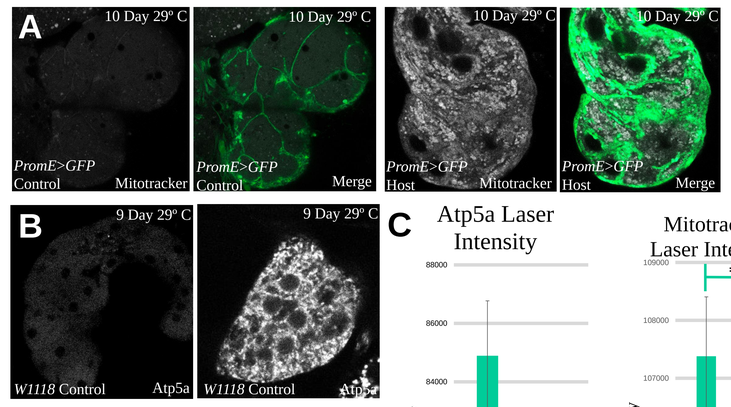
A. DAPI staining shows nuclear warping in the oenocyte cells of host flies. Nuclear warping is believed to be a sign of cellular death and/or malfunction. **B/C**. However, following staining with Drosophila Cell Death Protease (DCP-1) and Propidium Iodine (PI), no significant difference was found between host and control flies leading to the conclusion that host cells were in fact not dying.

III. Cachexia leads to a decrease in lysosome and autophage activity.



A. Lysotracker staining showed a greater number of lysosomes in control samples when compared to the cachexia host. The decrease in lysosomes in cachexia hosts may play a role in progressing cachexia. **B.** Like lysosomes, there was a decrease in the intensity of Atg8a staining (autophagy) as well as *mCherry* expression in cachexia hosts when compared to the control samples. **C.** Quantification of confocal laser intensity shows similar results.

IV. Cachexia requires an increase in the number and activity of mitochondria.



A. Mitotracker staining showed greater mitochondrial activity in cachexia tumor-host flies when compared to control flies. **B.** ATP5A staining showed a related increase in the number of mitochondria. **C.** Quantification of laser intensity matched with observations. *P Value=0.037944133.

5. Conclusion

- Cancer cachexia causes membrane expansion and an increase in mitochondrial activity, but a decrease in autophagy and lysosome activity.
- Earlier stages of cachexia may have increased lysosome and autophagy activity, but this study only looked at the later stages of the disease.
- Lipid metabolism is also a significant metabolic indicator in the oenocyte which should be studied further.
- We do know that cachexia causes organism-wide metabolic dysregulation.
- This study requires further research as cancer and cachexia are very dynamic processes.

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