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

Abstract

Cancer is a complex and dynamic cellular mechanism that causes significant changes to the biochemical pathways and affects the organs of its host. One of the hallmarks of cancer is cachexia, or wasting syndrome, defined as a general state of weakness caused by muscle and weight loss. The occurrence of cancer cachexia is largely attributed to systemic metabolic changes stimulated by tumors. 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, making them essential for maintaining homeostasis. Oenocyte cells are highly enriched with smooth endoplasmic reticulum and peroxisomes, highlighting the functional similarity in lipid metabolism between oenocytes and hepatocytes. Oenocytes perform similar processes to the human liver, making them an ideal model for studying diseases like obesity, insulin resistance, non-alcoholic fatty liver disease (NAFLD), and cancer.

Many genes are involved in the production, regulation, and metabolism of lipids within the fly. Knocking down these genes yielded changes in lipid metabolism and transport within the oenocyte, leading to increased lipid uptake similarly seen in starved flies. Cachexia was induced by transplanting Actin/NICD tumors into adult female flies. After incubation at 29 ℃ for 10-12 days, flies developed the “bloating” phenotype as a sign of cachexia. The flies were dissected and stained for markers of autophagy, necrosis, mitochondrion, vesicles, and other metabolic indicators. Hosts accumulated lipid droplets along the periphery of oenocyte cells. These lipid droplets are few and larger than normal. Furthermore, hosts had higher expression of ATP5A than control samples. ATP5A is a gene that encodes the alpha subunit of the mitochondrial F1F0 ATP synthase complex. This indicated that hosts had more mitochondria in their cells and therefore higher levels of lipid metabolism. Yet, within the oenocytes there were little to no lipid droplets, so coupled with the higher number of mitochondria this indicates that in the early stages of cachexia, the oenocytes are metabolizing lipids, but as the disease progresses, the lipids are exported elsewhere, out of the oenocytes. Finally, nuclear staining showed fragmentation and warping of the nuclear membrane which could indicate unhealthy cell function. While there is still much unknown about the effects of cancer and what it means for the host, we can conclude that the effects of cachexia cause oenocytes and other organs to function improperly and eventually lead to death. Understanding cancer-related cachexia and its effects can give us a better picture of oncogenic pathways and ways to combat the illness.