The Power of *Drosophila* in Modeling Cancer Cachexia

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Abstract

Late-stage cancer patients often exhibit cachexia, a wasting syndrome characterized by the loss of muscle and adipose tissues. However, the extent to which these wasting effects directly contribute to mortality remains unclear. *Drosophila*, a well-conserved model organism, has been instrumental in demonstrating systemic energy wasting and mortality in the context of tumors, similar to mice and humans. Research in *Drosophila* has elucidated the underlying mechanisms by which tumor-associated secreted proteins cause muscle atrophy and lipid loss, ultimately leading to energy wasting. Nevertheless, emerging evidence in both *Drosophila* and mammals challenges the notion that blocking energy loss in muscle or fat is sufficient to improve tumor-associated mortality, suggesting the existence of additional pathogenic factors in cancer cachexia. This raises two critical questions: how do tumors disrupt the physiological functions of other organs besides muscle and fat, and to what extent do these organ dysfunctions contribute to tumor-induced mortality? In this chapter, we summarize current knowledge regarding how fly tumors interact with host organs or tissues through the production of cachectic secreted proteins, and how they influence disease progression. We also discuss the power of *Drosophila* models in uncovering the mechanisms and principles of tumor-induced wasting and mortality and exploring therapeutic opportunities using various leading technologies.

Keywords

Cancer cachexia · Tumor · Host interaction · Tumor-secreted proteins · Host wasting · Mortality · Muscle atrophy · Lipid loss · Excessive hepatic gluconeogenesis · Kidney injury · Blood-brain barrier disruption ·

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Coagulopathy · Pathogenic organs · Signaling pathways

5.1 Introduction

Cancer cachexia is a debilitating condition characterized by significant weight loss and contributes to over 30% of cancer-related deaths. It frequently afflicts patients, particularly in advanced stages of the disease (Tisdale 2009). The primary features of cancer cachexia are loss of muscle and loss of fat tissues; hence, it is alternatively named tumor-induced wasting. Recent findings suggest that in cachexic conditions, anorexia, asthenia, and insulin resistance mobilize protein, lipid, and glycogen from muscle and fat, resulting in the depletion of systemic energy reserves (Argiles et al. 2007; Giordano and Jatoi 2005). Furthermore, numerous studies highlight the critical interplay between tumor and host factors in disease progression. For instance, several tumor- and host-secreted proteins, including tumor necrosis factor α (TNF-α), Interleukin 6 (IL-6), Growth Differentiation Factor 15 (GDF15), Activin A or transforming growth factor-β (TGF-β) ligands, leukemia inhibitory factor (LIF), insulin-like growth factor binding protein 2 (IGFBP-2), parathyroid hormone-related protein (PTHrP), and ectodysplasin (EDA), directly target muscle and fat tissues (Oliff et al. 1987; Baltgalvis et al. 2008; Lerner et al. 2016; Zhou et al. 2010; Kandarian et al. 2018; Kir et al. 2014; Bilgic et al. 2023; Dong et al. 2021; Waning et al. 2015), initiating downstream signaling pathways and metabolic processes that lead to imbalance of anabolism/catabolism and energy wasting.

These findings suggested that interventions that disrupt the signals that lead to energy wasting could be therapeutic. However, accumulating evidence suggests that blocking energy wasting through genetic or pharmaceutical targeting of metabolic regulators fails to improve or may even hasten death. For example, restoring exocrine pancreatic function significantly reduces peripheral tissue wasting but worsens the rate of survival of mice with pancreatic cancers (Danai et al. 2018). Moreover, both clinical observations and animal model studies reveal dysfunction of other tissues and organs, including the liver, heart, lungs, kidneys, veins, and nervous system, in response to tumors (Ferrer et al. 2023; Ferrara et al. 2022; Argiles et al. 2015). These findings suggest the multifaceted nature of cancer cachexia or tumor-induced wasting, involving complex interplay between tumors and multiple host organs. It is imperative to investigate the contributions of host organs other than muscle or fat to survival and determine the underlying mechanisms by which tumors compromise their function.

Drosophila is a widely used model organism in metabolism and cancer research, especially given that over 80% of human-disease-associated genes are conserved in the fly (Bier 2005). As a model organism with a century-long history, *Drosophila* boasts a rich array of genetic tools and cutting-edge technologies (Li 2021; Sato and Suzuki 2022; Bosch et al. 2021). In recent years, *Drosophila* has emerged as a powerful model for identifying tumor-derived factors that trigger systemic organ wasting (Liu et al. 2022; Bilder et al. 2021). In addition to validating known mechanisms associated with secreted proteins in mammals (IGFBP/ImpL2, IL/Upd, TGF/Gbb, TNF/Egr) (Kwon et al. 2015; Figueroa-Clarevega and Bilder 2015; Ding et al. 2021; Lodge et al. 2021; Hodgson et al. 2021), these studies also identified novel organ wasting factors (PDGF/Pvf1, Mmp1, Fibrin/Fon, PGLYRP/PGRP-SC2, ITP) and explored the involvement of additional host organs (pancreas, kidney, brain, and blood cells) (Lodge et al. 2021; Xu et al. 2024; Chen et al. 2022; Xu et al. 2023; Hsi et al. 2023; Ding et al. 2025). Furthermore, these studies revealed that functional restoration in the liver (carbohydrate and lipid metabolism), kidney (immune balance and uric acid metabolism), blood cells (clotting or coagulation), or the blood-brain barrier (BBB disruption) increased lifespan regardless of tumor growth. Perturbation of certain secreted proteins associated with tumors, such as PGRP-SC2, Fon, and Upd, also extended lifespan (Chen et al. 2022; Hsi et al. 2023; Kim et al. 2021). These findings provide valuable insights into the molecular underpinnings of tumor-host interactions. In this chapter, we focus on the interplay between

tumor-host interactions and highlight recent advances that make *Drosophila* a powerful model for investigating cancer cachexia or tumor-induced wasting and mortality.

5.2 *Drosophila* as a Model of Organ Wasting Induced by Tumors

Drosophila tumor models used to study cancer cachexia include gut tumors, ovarian tumors, eye tumors, and tumors transplanted into adult flies (Fig. 5.1). Consistent with the heterogeneous nature of cancer cachexia in mammals, these fly tumor models lead to varying cachectic effects.

Adult Gut Tumors Tumors in the adult gut can be generated by expressing the active form of the oncogene *yorkie* (*yki*), yki^{3SA}, in adult fly intestinal stem cells (ISCs) using the temperature-controlled *esg-GAL4* driver. This model induces aberrant proliferation of ISCs in adult flies and subsequently leads to several wasting phenotypes and metabolic abnormalities, including triglyceride (TAG) and glycogen depletion, muscle wasting, ovary degeneration, hyperglycemia, and shortened lifespan (Kwon et al. 2015; Ding et al. 2021; Song et al. 2019). Notably, flies with yki^{3SA} gut tumors also display abdominal bloating and disrupted renal excretion, systemic immune hyperactivation, and uric acid accumulation (Chen et al. 2022; Xu et al. 2023). Similar wasting phenotypes were observed in adult flies bearing N^{DN} Ras^{V12} gut tumors (Xu et al. 2023; Lee et al. 2021). In addition to yki^{3SA} and N^{DN} Ras^{V12}, overexpression of activated Ras (Ras^{1A}) or activated Raf (Raf^{F179}) also results in gut tumors, but with less severe wasting phenotypes (Xu et al. 2023).

Adult Ovarian Tumors To address the potential confounding effects of tumors in essential metabolic organs like the gut, an ovarian tumor model was established, whereby tumorigenesis is driven by the expression of two oncogenes (Ras^{V12} $aPKC^{\Delta N}$) in the follicular epithelium in adult females using the *tj-GAL4* driver. This model exhibits abdominal bloating, fat loss, shortened lifespan, and hypercoagulation or blood clotting (Hsi et al. 2023).

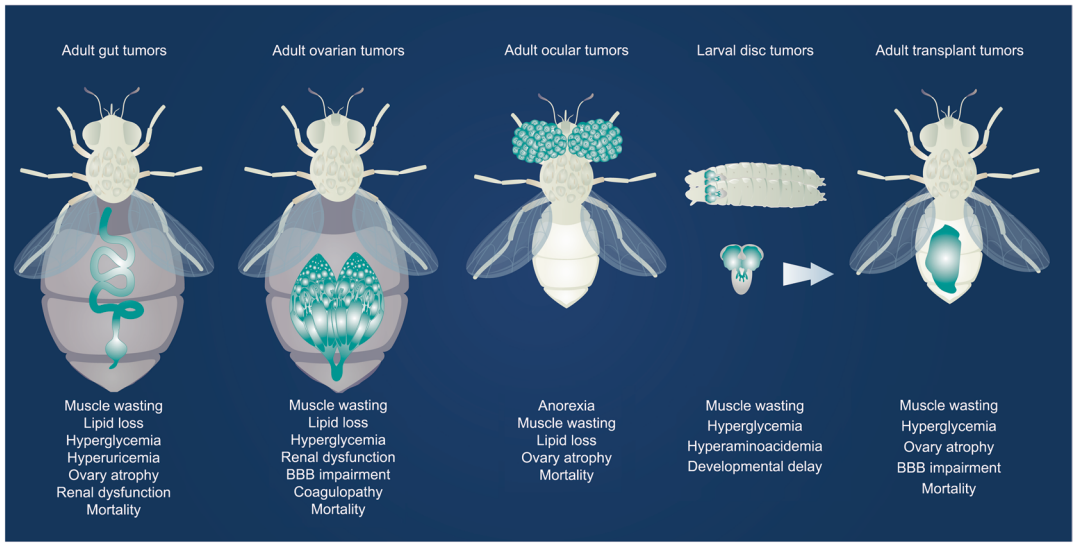

Fig. 5.1 *Drosophila* malignant tumor models associated with cachexia. Schematics show *Drosophila* tumor models and their differential cachexia-related phenotypes of adult gut tumors (yki^{3SA}, N^{DN} Ras^{V12}, Raf^{F179}, or Ras^{1A}); adult ovarian tumors (Ras^{V12} $aPKC^{\Delta N}$); adult ocular tumors (yki^{1SA}); larval imaginal disc tumors (Ras^{V12} $scrib^{-/-}$, Ras^{V12} $Csk^{-/-}$, Ras^{V12} dlg^{RNAi}, Ras^{V12} $lgl^{-/-}$, or Pvr^{AC}); and adult transplant tumors (Ras^{V12} $scrib^{-/-}$, Ras^{V12} dlg^{RNAi}, or Ras^{V12} $aPKC^{\Delta N}$)

Adult Eye Tumors Similar to the *yki*^{3SA} gut tumor model, a *Drosophila* eye tumor model was established by overexpressing *yki*^{1SA} in adult eyes using the *GMR-GAL4* driver. This model led to a significant decrease in appetite and associated lipid loss, ovarian atrophy, and abnormal muscle structure at a late stage (Yeom et al. 2021). While this model exhibited a relatively mild cachectic phenotype at an early stage, it effectively mimics the common anorexia observed in cancer cachexia patients. It is noteworthy that in this model, expression of *yki*^{1SA} was driven in both larval and adult stages.

Larval Disc Tumors A larval tumor model was established by expressing the oncogene *Ras*^{V12} in a *scribble* (*scrib*) tumor suppressor mutant background, *Ras*^{V12} *scrib*$^{-/-}$, resulting in overgrowth tumors in eye-antennal discs (Pagliarini and Xu 2003). Other studies also combined other changes with expression *of RasV12* to generate tumors associated with different genotypes, such as *Ras*^{V12} *dlg*^{RNAi}, *Ras*^{V12} *Csk*$^{-/-}$, *Ras*^{V12} *lgl*$^{-/-}$, and *Pvr*$^{\lambda C}$. These models commonly manifest muscle wasting, hyperglycemia, hyperaminoacidemia, developmental delay, and eventual death during the larval stage (Lodge et al. 2021; Xu et al. 2023; Newton et al. 2020; Khezri et al. 2021).

Tumor Transplant into Adult Abdomen Larval imaginal discs transplanted into host larvae or adult abdomens were originally developed to investigate tissue or tumor growth in vivo (Rossi and Gonzalez 2015). This approach demonstrated that *Ras*^{V12} *scrib*$^{-/-}$, *Ras*^{V12} *dlg*^{RNAi}, or *Ras*^{V12} *aPKC*$^{\Delta N}$ larval disc tumors transplanted into the abdominal cavity of adult flies lead to lipid loss, muscle dysfunction, ovary wasting, abdomen bloating, and death of the flies (Figueroa-Clarevega and Bilder 2015; Kim et al. 2021).

5.3 *Drosophila* as a Model of Tumor-Induced Multiorgan Dysfunction

While extensive studies have explored how tumors disrupt metabolic processes in key energy storage and transport organs, e.g., muscle and fat, emerging evidence suggests that other host organs also contribute significantly to energy imbalance and host mortality. *Drosophila* possesses conserved organ/tissue functions, including muscle, fat, liver (fat body and oenocytes), pancreatic α- and β-cells (Akh- and insulin-producing cells), kidney glomerular podocytes (nephrocytes) and renal tubules, blood cells, neurons, and heart (Bilder et al. 2021). Leveraging powerful genetic tools and convenient tissue-specific sequencing methods (Li et al. 2022), recent studies of cancer cachexia fly models have confirmed the widespread wasting effects of tumors on muscle, fat, and other host organs and further uncovered previously unidentified pathologies, reinforcing the idea that cachexia is a systemic disease (Fig. 5.2).

Muscle The most prominent symptom of cachexia in advanced cancer patients is muscle wasting, characterized by a significant reduction in skeletal muscle mass and strength, and contributing to weight loss. Several mechanisms have been identified: (i) increased muscle protein breakdown via the ubiquitin-proteasome pathway, regulated by two key ubiquitin E3 ligases, muscle ring finger-1 (MuRF1) and muscle atrophy F-box (MAFbx/Atrogin-1) (Bodine et al. 2001; Gomes et al. 2001); (ii) enhanced autophagy-lysosome pathways, mediated by Bcl-2 interacting protein 3 (Bnip3) to promote protein degradation (Asp et al. 2010); and (iii) alterations in muscle mitochondrial quantity and quality, including decreased biogenesis, increased mitophagy, altered dynamics (fusion and fission), leading to impaired energy metabolism (Beltra et al. 2021). These wasting effects have been observed in the muscle of both adult and larval tumor-bearing flies (Kwon et al. 2015; Figueroa-Clarevega and Bilder 2015; Lodge et al. 2021; Newton et al. 2020), with similar transcriptional

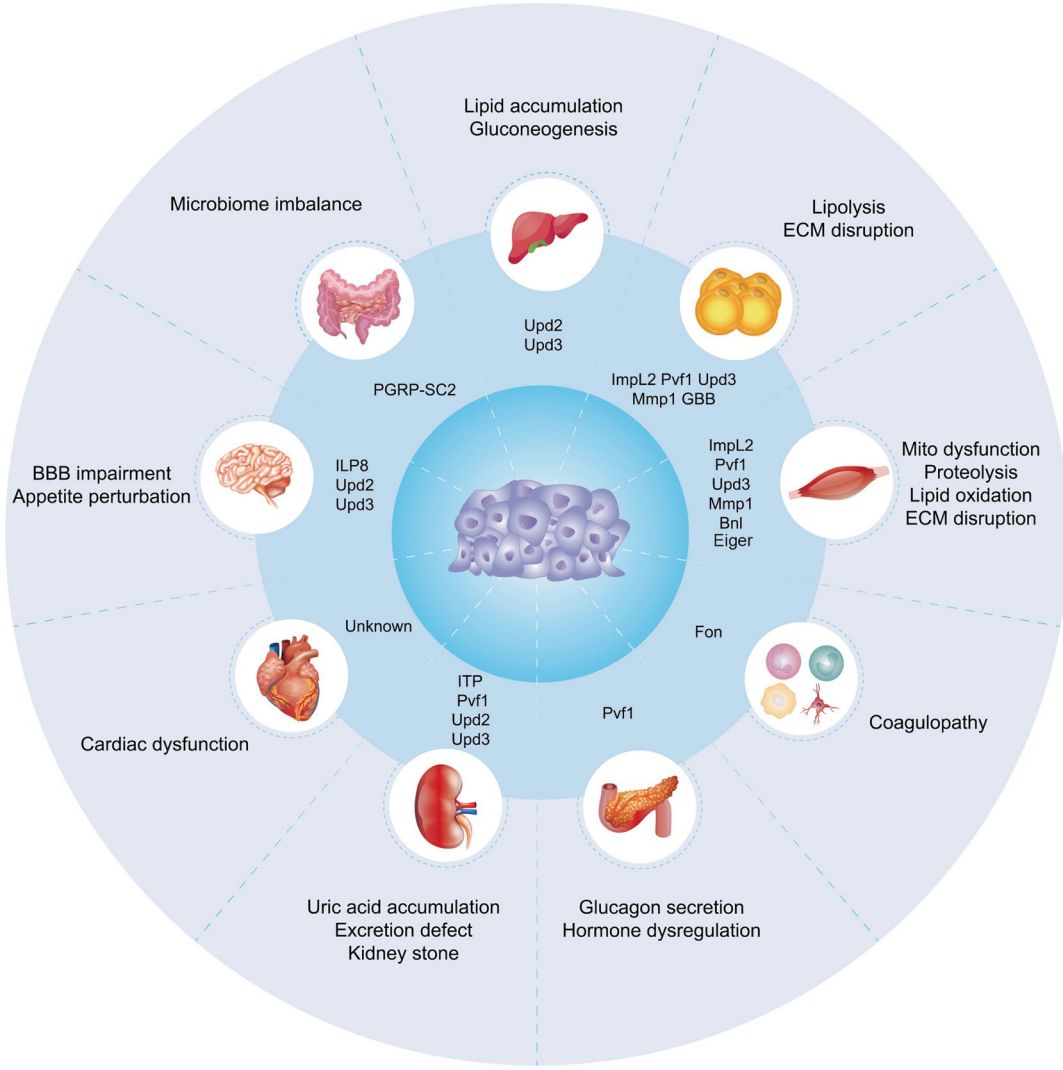

Fig. 5.2 The impact of tumor-associated cachectic secreted proteins on host organs. A schematic showing *Drosophila* cachectic secreted proteins that are derived from both tumors and host to impair the functions of liver (equivalent to oenocytes and fat body) (lipid accumulation, gluconeogenesis), fat tissues (lipolysis, ECM disruption), muscle (mito dysfunction, proteolysis, lipid oxidation, ECM disruption), blood cells (coagulopathy), pancreas α-cells (equivalent to APCs) (glucagon/Akh secretion, hormone dysregulation), kidney (equivalent to Malpighian tubules) (uric acid accumulation, excretion defect, kidney stone), heart (cardiac dysfunction), brain (BBB impairment, appetite perturbation), and intestine (microbiome imbalance). ECM, extracellular matrix; mito, mitochondria; APCs, Akh-producing cells; BBB, blood-brain barrier

changes in key pathogenic genes, including *CG11658* (the homolog of Atrogin-1/MAFbx), *BNIP3*, and mitochondrial genes (Kwon et al. 2015). Importantly, a recent study further revealed that fly disc tumors remotely impair components of basement membrane (BM) and extracellular matrix (ECM) of skeletal muscle via production of matrix metalloproteinases (MMPs), resulting in muscle detachment and weakness (Lodge et al. 2021).

Liver and Adipose Tissues In mammals, loss of adipose tissues, another established feature of cancer cachexia, is caused by excessive lipolysis in white adipose tissues, which is regulated by

key lipases like adipose triglyceride lipase (ATGL) and others (Das et al. 2011; Tambaro et al. 2024), to break down triglyceride in lipid droplets (LDs) into free fatty acid and glycerol. Additionally, the browning of beige fat adipocytes contributes to tumor-induced fat loss. This process is modulated by uncoupling protein 1 (Ucp-1) induction within mitochondria, leading to depletion of lipid and carbohydrate reserves and an increase in thermogenesis (Kir et al. 2014; Liu et al. 2024). Multiple *Drosophila* cancer cachexia models are associated with fat loss, which is primarily controlled by enhanced lipolysis and autophagy (Kwon et al. 2015; Ding et al. 2021; Hsi et al. 2023; Song et al. 2019; Katheder et al. 2017). We note that, similar to mammals, cold-blooded *Drosophila* also undergo mitochondrial uncoupling through *Ucp4B/4C* upregulation in the fat cells to balance energy consumption and thermogenesis (Da-Re et al. 2014; Ulgherait et al. 2020; Chatterjee et al. 2022). It would be interesting to explore the pathological roles of mitochondrial uncoupling in tumor-bearing flies.

Alterations in the physiology of the liver, which functions as the central node of energy supply and utilization in mammals, have been reported to mediate cancer-associated wasting (Argiles et al. 2015; Argiles et al. 2018). These alterations include glycogen decline and increased gluconeogenesis, decreased mitochondrial activity and oxidative capacity, impaired fatty acid mobilization and lipogenesis, decreased albumin production and increased amino acid catabolism, as well as increased production of acute-phase proteins and inflammatory response (Rosa-Caldwell et al. 2020; Narsale et al. 2015). Hepatic gluconeogenesis, which converts circulating amino acids and lipids into glucose via the activities of rate-limit enzymes, causes muscle atrophy and lipid loss in both cachectic and non-cachectic mice (Narsale et al. 2015; Just et al. 2020; Okun et al. 2021), indicating a pathogenic role for hepatic gluconeogenesis in cancer cachexia. In *Drosophila*, the fat body and oenocytes function as analogs to the human liver, playing crucial roles in maintaining carbohydrate and lipid metabolic balance, detoxification, and immune responses (Li et al. 2023a; Gutierrez et al. 2007; Huang et al. 2022; Huang et al. 2019; Ghosh et al. 2020). Studies have revealed enhanced glycogen breakdown and gluconeogenesis in the fat body, along with lipid accumulation in the oenocytes of tumor-bearing adult flies and larvae (Kwon et al. 2015; Lodge et al. 2021; Liu et al. 2025), mimicking the liver dysfunction in tumor-bearing mammals.

Brain Anorexia represents a key risk factor for cachexia development. Brain mediators that control food intake, appetite, satiation, taste, and smell, as well as systemic inflammation, contribute to the anorexia of the cancer patients, highlighting important impacts of the brain on energy wasting (Molfino et al. 2010). Tumor-bearing adult flies reassemble the food intake decline and taste valence shift, mediated by orexigenic short neuropeptide F (sNPF)-expressing and bitter-sensing neurons, respectively (Yeom et al. 2021; Leung et al. 2024). These changes occur before the onset of fatal organ wasting effects. Furthermore, another study uncovered disruption of the blood-brain barrier (BBB) as a phenotype common to tumor-bearing flies and mice (Kim et al. 2021). BBB restoration, achieved through genetic manipulation, extends survival of tumor-bearing flies without affecting organ wasting (Kim et al. 2021), suggesting that regulation of organ wasting and host death in the context of tumors can be uncoupled.

Pancreas In addition to producing digestive enzymes important for maintaining fat and muscle in pancreatic ductal adenocarcinoma (PDAC) patients, the pancreas also plays a central role in modulating systemic energy absorption and distribution. This is achieved through the endocrine release of regulatory peptide hormones, such as glucagon and insulin, from pancreatic α-cells and β-cells, respectively (Valente et al. 2024).

Importantly, *Drosophila* insulin-like peptides (ILPs), the homologs of insulin and insulin-like growth factors (IGFs), are majorly produced in brain endocrine cells to promote systemic growth and anabolism (Nassel et al. 2015). *Drosophila* also produces adipokinetic hormone (Akh), the homolog of glucagon, in endocrine cells of the corpora cardiaca (CC). Akh targets fat body and certain neurons, leading to major systemic catabolism in response to starvation and other stress conditions (Ahmad et al. 2020). Akh production is regulated by multiple peptide hormones from distal tissues and neurotransmitters from upstream innervating neurons. Excessive Akh production results in energy wasting in both sleep-deprived and tumor-bearing flies (Li et al. 2023b). Notably, genetic removal of Akh and glucagon abolish muscle and fat wasting, respectively, in tumor-bearing flies and mice (Ding et al. 2025). These findings highlight the importance of the pancreas, a key organ modulating systemic energy mobilization, for understanding the pathogenic mechanisms of organ wasting.

Kidney The kidney functions as a filtration organ, removing circulating wastes or toxins and maintaining the internal balance of fluids and ions. Kidney dysfunction, including impairment of either filtration in the glomerulus or fluid excretion in the renal tubules, is frequently observed in advanced cancer patients (Malyszko et al. 2020). Interestingly, kidney dysfunction has been found to trigger a cascade of systemic effects, including uremic toxin accumulation, neurohormonal perturbation, immune and inflammatory responses, hemodynamic modification, as well as metabolic alterations (Lee et al. 2018). These factors are believed to lead to widespread organ damages and aggravate mortality and host wasting in tumor-bearing subjects (Wang et al. 2022a; Zoccali et al. 2017). *Drosophila* Malpighian tubules (MTs) are the functional equivalent of renal tubules, regulating fluid balance, metabolic waste excretion, lipid transport, and uric acid metabolism (Dow et al. 2022; Cohen et al. 2020). MTs primarily consist of two cell types: principal cells (PCs) that use proton pumps/V-ATPases on their apical membranes to drive cation transport, establishing an electrochemical proton gradient that facilitates H+/K+ exchange (Chintapalli et al. 2015; Day et al. 2008), and stellate cells (SCs) that express chloride and water channel proteins, which are responsible for chloride transport and osmotic water flow (Cabrero et al. 2020). Several groups found that tumors can remotely impair MT functions. For instance, abdominal bloating in tumor-bearing larvae is a manifestation of renal failure caused by disruption of fluid excretion and changes to the morphology of renal SCs (Xu et al. 2023; Kwok et al. 2024). Additionally, adult gut tumors remotely impair uric acid and phosphate metabolism and promote apoptosis in renal PCs, leading to uric acid accumulation and ultimately host death (Xu et al. 2024; Chen et al. 2022; Oi et al. 2024). Furthermore, the homologs of purine metabolic enzymes, phosphate transporters, and aquaporins in MTs are transcriptionally regulated by tumors (Xu et al. 2024; Chen et al. 2022; Xu et al. 2023). Interestingly, genetic restoration of uric acid metabolism in PCs or pharmaceutic inhibition of uric acid synthesis significantly increases the survival of tumor-bearing flies without affecting muscle or fat wasting (Chen et al. 2022), consistent with the clinical observation that hyperuricemia is positively associated with general cancer-induced mortality (Shin et al. 2006). In addition to renal tubule-like MTs, *Drosophila* also have nephrocytes, which correspond to mammalian glomerular podocytes which have a role in filtration and degradation (Weavers et al. 2009; van de Leemput et al. 2022). A recent study indicated that chronic nephrocyte dysfunction nonautonomously causes muscle wasting, neurodegeneration, and mortality in flies (Feng et al. 2021), raising the possibility of nephrocyte participation in tumor-induced organ wasting and mortality. Collectively, the findings from *Drosophila* models not only confirm the role of renal dysfunction in cancer cachexia but also reveal previously uncharacterized pathologies associated with this condition.

Blood Cells Consistent with what is observed in mammals, *Drosophila* blood cells or hemocytes are recruited to the tumor microenvironment to activate both local and systemic immune responses via production of inflammatory cytokines (Pastor-Pareja et al. 2008; Parisi et al. 2014; Kinoshita et al. 2022; Voutyraki et al. 2023; Xu et al. 2022; Chen et al. 2021), leading to tumor growth suppression and systemic energy consumption. *Drosophila* hemocytes are classified into crystal cells (platelet-like cells involved in melanization), lamellocytes (stress-induced cell types encapsulating giant foreign bodies), and plasmatocytes (equivalent to monocytes or macrophages with phagocytic activity), based on their gene expression and cell morphology (Tattikota et al. 2020; Vlisidou and Wood 2015). The results of recent study indicated that fly ovarian tumors upregulate clotting factors to increase coagulation of crystal cells, ultimately causing host death (Hsi et al. 2023). Given the lack of vasculature in *Drosophila*, this finding facilitates exploration of non-thrombotic mechanisms of cancer mortality associated with coagulopathy.

Gut The gut plays a critical role in regulating systemic energy homeostasis through direct nutrient absorption and transport, metabolic regulatory peptide hormone production, and microbiome maintenance, in both *Drosophila* and mammals (Miguel-Aliaga et al. 2018; Zhou et al. 2020). While non-gut-derived tumors in *Drosophila* might not directly cause defects in nutrient uptake or gut integrity (Figueroa-Clarevega and Bilder 2015; Lodge et al. 2021; Hsi et al. 2023), yki^{3SA} adult gut tumors significantly perturb gut peptide hormone production and microbiome balance (Chen et al. 2022; Song et al. 2019): two events commonly observed in in tumor-bearing patients and mice (Ferrara et al. 2022; Panebianco et al. 2023). The disruption of microbiome balance further activates systemic NF-κB immune signaling, leading to hyperuricemia and lethality in *Drosophila* (Chen et al. 2022).

Other Organs/Tissues In addition to causing wasting of skeletal muscles, cancer cachexia can also impact the heart muscle. Heart weight declines and functional impairment have been observed in both cachexic tumor models and clinical samples (Zhou et al. 2010; Argiles et al. 2018; Olivan et al. 2012; Barkhudaryan et al. 2017). Recent studies indicate the remarkable effectiveness of cardio workout-associated exercise in body fat loss and metabolic boost, regardless of the amount of calories burned (Kolnes et al. 2021), highlighting the essential roles of the heart in modulating systemic energy homeostasis. Given this, the cardiovascular system and endothelial cells also likely play as-of-yet undetected roles in cancer cachexia. Lung dysfunction and respiratory failure, potentially associated with diaphragm or respiratory muscle wasting, have been reported in cancer cachexia as well (Murphy et al. 2022). While chronic obstructive pulmonary disease (COPD) is a well-established cause of cachexia (Sanders et al. 2016), the specific mechanisms by which lung system dysfunction promotes organ wasting and mortality in the context of cancer still remain a puzzle. *Drosophila* cardiac tube and trachea, which closely mimic the functions of heart, vascular, and lung system (Zhao et al. 2023; Scholl et al. 2021), offer a simple model for future studies that explore the physiology of these organs/tissues in the context of tumors and their contributions to development of cancer cachexia.

5.4 Tumor-Associated Secreted Proteins and Signaling Pathways

As the multifaceted nature of cancer cachexia, tumors nonautonomously induce various organ failure. A number of studies have focused on identifying hormonal changes. Here we summarize the findings of tumor-associated cachectic secreted proteins and signaling pathways in *Drosophila* models (Fig. 5.2).

IGFBP/ImpL2 Insulin resistance or suppression of insulin/IGF signaling is known to block sys-

temic anabolism and trigger organ wasting. Multiple *Drosophila* tumors, including yki^{3SA} gut tumors, Ras^{V12} $scrib^{-/-}$ disc tumors, and Ras^{V12} $aPKC^{\Delta N}$ ovarian tumors (Kwon et al. 2015; Figueroa-Clarevega and Bilder 2015; Hsi et al. 2023), produce Imaginal morphogenesis protein-Late 2 (ImpL2), a secreted protein that robustly binds to ILPs in the hemolymph and restricts their bioavailability, to antagonize insulin/IGF signaling pathways in various tissues (Honegger et al. 2008), leading to muscle wasting, lipid loss, hyperglycemia, and ovary atrophy in the context of tumors. The insulin/IGF pathway regulates protein, carbohydrate, and lipid metabolic homeostasis via downstream components such as protein kinase B (PKB/Akt) and transcriptional factor forkhead box, sub-group O (FoxO) (Teleman 2010). For example, FoxO directly promotes transcription of the ATGL homolog *brummer* (*bmm*), which is involved in lipolysis, and of *Pepck*, which is involved in gluconeogenesis, while Akt stimulates mTORC1 complex via phosphorylation to regulate protein synthesis (Teleman 2010). ImpL2 functions similarly to the human IGFBP family proteins (IGFBP1–7) (Roed et al. 2018), some of which have been reported to be involved in cancer cachexia (Dong et al. 2021).

PDGF/Pvf1 The adult yki^{3SA} gut tumors and larval $scrib^{-/-}$ disc tumors also increase systemic catabolism and orchestrate differential wasting effects in various organs via production of PDGF- and VEGF-related factor 1 (Pvf1) (Song et al. 2019; Parisi et al. 2014), a secreted protein that binds to its PDGF- and VEGF-receptor related (Pvr) receptor and activates downstream MAPK pathways (Song et al. 2019; Parisi et al. 2014). Pvf1/Pvr signaling activates MEK/ERK pathway to increase lipolysis and proteolysis in fat and muscle, respectively (Song et al. 2019). Moreover, Pvf1/Pvr signaling further activates ERK signaling in Akh-producing cells (APCs) to trigger Mmp2-associated ECM degradation and enhances innervation of upstream excitatory neurons, resulting in excessive Akh production and systemic energy depletion (Ding et al. 2025). Pvf1/Pvr signaling also activates the JNK pathway in PCs of renal tubules to regulate gene expression associated with uric acid (*Uro*), phosphate (*MFS2*), and water (*Elgp2*) balance, resulting in tumor-induced renal dysfunction (Xu et al. 2024). Additionally, tumor-secreted Pvf1 activates Pvr in hemocytes to promote proliferation and augment systemic inflammatory responses (Parisi et al. 2014). Interestingly, Pvf1 is equivalent to human-platelet-derived growth factor-BB (PDGF-BB), which is secreted by tumors to promote glucagon secretion in the pancreas and cause systemic wasting (Ding et al. 2025).

IL/Upd In *Drosophila,* three Unpaired ligands (Upd1/2/3), the homologs of interleukins (ILs), activate JAK/STAT signaling via a gp130-like receptor, Domeless (Dome). Upd2/3 are produced in Ras^{V12} $scrib^{-/-}$ larval disc tumors, yki^{3SA} adult gut tumors, and Ras^{V12} $aPKC^{\Delta N}$ adult ovarian tumors (Ding et al. 2021; Kim et al. 2021; Kwok et al. 2024). Notably, tumor-derived Upd3 alone induces tumorigenesis in the gut, muscle wasting, fat loss, and hyperglycemia (Ding et al. 2021; Liu et al. 2025). Upd2/3 from transplanted Ras^{V12} $scrib^{-/-}$ disc tumors remotely target glial cells in the brain to cause BBB disruption via JAK/STAT signaling, eventually causing host death (Kim et al. 2021). These findings are consistent with mammalian studies demonstrating that IL-6, a homolog of Upd2/3, activates JAK/STAT signaling and leads to tumor-associated energy wasting and BBB disruption in a conserved manner (Kim et al. 2021). Tumor-derived Upd2/3 also target SCs in the renal tubules, altering their morphology and impairing their fluid-excreting capacity (Kwok et al. 2024). JAK/STAT signaling in fly peripheral organs induces local ImpL2 expression, exacerbating insulin resistance and contributing to systemic wasting (Ding et al. 2021).

INSL/ILP8 Insulin-like peptide 8 (ILP8) is a *Drosophila* secreted protein in the insulin/relaxin-like protein family that acts through the relaxin receptor (Lgr3) and not the insulin receptor (InR) in brain neurons, initiating cAMP signaling to regulate larval development (Colombani

et al. 2012; Garelli et al. 2012; Vallejo et al. 2015). Interestingly, ILP8 is induced in *yki*^{1SA} adult eye tumors to suppress food intake and cause anorexia, prior to later organ wasting, by upregulating anorexigenic *nucleobinding 1* (*NUCB1*) and downregulating orexigenic *short neuropeptide F* (*sNPF*) and *NPF* expression in the brain (Yeom et al. 2021). A similar regulation was observed in mammals, as mammalian insulin-like peptide 3 (INSL3), the homolog of ILP8, also contributes to tumor-associated anorexia (Yeom et al. 2021).

TGF/Gbb The *Drosophila* genome contains seven transforming growth factor-β (TGF-β) type ligands. Among these, Glass bottom boat (Gbb) signals through Thickveins (Tkv) and Saxophone (Sax) type I receptors, Wishful Thinking (Wit) and Punt (Put) type II receptors, and the downstream transcriptional factor Mad to regulate gene expression (Upadhyay et al. 2017). Gbb is produced by *Ras*^{V12} *dlg*^{RNAi} larval disc tumors and activates TGF-β signaling in both host fat body and muscle, leading to organ wasting (Lodge et al. 2021). Notably, enhanced TGF-β or activin signaling is an established cause of muscle wasting in tumor-bearing patients and mice (Zhou et al. 2010; Waning et al. 2015).

Mmp1 Only two Mmps in *Drosophila*, secreted Mmp1 and membrane-tethered Mmp2 (Jia et al. 2014), are present to regulate ECM homeostasis and tissue integrity in *Drosophila*. *Ras*^{V12} *dlg*^{RNAi} larval disc tumors secrete Mmp1 to remotely target muscle and fat tissues and cause their degeneration. Mmp1 nonautonomously cause the degradation of peripheral BM/ECM components, disrupting muscle and fat tissue integrity. Additionally, Mmp1 autonomously impairs the production of tumor-derived Gbb, another cachectic ligand, probably through tumor ECM disruption (Lodge et al. 2021). Interestingly, transcriptional induction of *Mmp1* has been also observed in *Ras*^{V12} *Csk*$^{-/-}$ larval disc tumors and *yki*^{3SA} adult gut tumors (Song et al. 2019; Hirabayashi et al. 2013), suggesting that Mmp1-associated peripheral ECM disruption might be a common wasting pathogenesis.

Fibrin/Fon *Drosophila* produces a few secreted proteins analogous to human fibrin, such as Fondue (Fon) and (Hml), which regulate hemolymph clotting or coagulation (Scherfer et al. 2004; Scherfer et al. 2006). *Ras*^{V12} *aPKC*$^{\Delta N}$ adult ovarian tumors secrete Fon to directly cause coagulopathy (early hypercoagulation and late hypocoagulation), decreasing fly survival (Hsi et al. 2023). Similar to Mmp1, Fon also plays crucial roles in ECM homeostasis and muscle attachment (Green et al. 2016). Whether Fon is associated with cachectic effects in distinct *Drosophila* tumors is not known.

FGF/Bnl Branchless (Bnl), a homolog of fibroblast growth factors (FGFs), is secreted by *Ras*^{V12} *Csk*$^{-/-}$ larval disc tumors in high-sugar diet conditions. Similar to Upd3, Bnl simultaneously promotes tumor growth and muscle degradation via activating the Breathless (Btl) receptor, the homolog of FGF receptor (Newton et al. 2020). Interestingly, FGF21, one of 18 human FGFs, has been implicated in energy wasting and age-related cachexia (Franz et al. 2019), suggesting a potential role in cancer cachexia as well.

TNF-α/Egr *Drosophila* Eiger (Egr) is an established homolog of human TNF-α, an evolutionarily ancient mediator of systemic inflammation and organ wasting (Reid and Li 2001). Knockdown of *Wengen* (*Wgn*), the fly TNF-α/Egr receptor, in the muscle of larvae bearing *Ras*^{V12} *scrib*$^{-/-}$ disc tumors attenuates muscle degeneration (Hodgson et al. 2021), indicating conserved roles for the TNF-α/Egr axis and downstream JNK signaling in tumor-induced muscle wasting (Hodgson et al. 2021). However, the source of Egr remains to be verified, although studies have speculated that it is expressed in tumor cells,

tumor-associated hemocytes, or both (Parisi et al. 2014; Cordero et al. 2010; Igaki et al. 2009).

PGLYRP/PGRP-SC2 Both *Drosophila* and mammalian studies have demonstrated that local and distal tumors significantly perturb the gut microbiota, leading to microbial dysbiosis and impacting tumorigenesis and even cachexia progression (VanderVeen et al. 2024; Zhou et al. 2021). Adult yki^{3SA} gut tumors cause a substantial increase in abundance and composition of gut microbiota by disrupting intestinal production of Peptidoglycan Recognition Protein SC2 (PGRP-SC2) (Chen et al. 2022), a homolog of human peptidoglycan recognition proteins (PGLYRPs) (flyrnai.org/diopt), that generally diminishes most commensals and pathogens. The increase of microbiota further triggers systemic hyperactivation of immune deficiency (Imd)-NF-κB pathway and the downstream transcriptional factor Relish (Rel). Notably, Imd-NF-κB-Rel activation in the renal tubules sufficiently perturbs gene expression of uric acid mobilization enzymes and antimicrobial peptides (AMPs), causing hyperuricemia, renal injury, and tumor-induced lethality (Chen et al. 2022; Oi et al. 2024). Interestingly, this immune and mortality regulation is independent of tumor-induced organ wasting (Chen et al. 2022). Given the Imd-NF-κB hyperactivation observed in many tissues in yki^{3SA}-tumor bearing flies, investigating immune-associated functional changes in other tissues, such as neurons, heart, trachea, and oenocytes, could provide valuable insights into what mechanisms contribute to cancer cachexia or mortality.

ITP Abdominal bloating due to fluid accumulation has been observed in flies bearing various tumors, including yki^{3SA} or N^{DN} Ras^{V12} adult gut tumors and Ras^{V12} $lgl^{-/-}$ larval disc tumors, and has been attributed to renal dysfunction (Xu et al. 2023; Lee et al. 2021; Santabarbara-Ruiz and Leopold 2021). Ion transport peptide (ITP) was recently identified as the first antidiuretic peptide hormone in *Drosophila* or insects: this was secreted by distinct tumors to fundamentally block fluid excretion and cause bloating. Mechanistically, isoform F of ITP (ITP_F) activates Tachykinin-like receptor at 99D (TkR99D) in the SCs of renal tubules, initiating cGMP synthesis and associated antidiuretic programs. While a mammalian homolog of ITP has not been unidentified, human NK3R acts as a functional equivalent to TkR99D. In addition, pharmaceutical blockade of NK3R significantly alleviated defects in fluid excretion and renal injury in mice bearing colon or gastric tumors (Xu et al. 2023), suggesting a potential therapeutic target.

5.5 Future Perspectives and Outstanding Questions

Drosophila and mammalian models exhibit similar cancer cachexia phenotypes (Liu et al. 2022). However, many findings using the *Drosophila* models have recently revealed new physiopathological features and advanced our understanding of cancer cachexia. For example, ITP regulation of tumor-induced renal excretion defects sheds light on the critical roles of antidiuretic hormone(s) (Xu et al. 2023). Other studies also identified that coagulation, BBB disruption, and renal uric acid metabolic imbalance independently contribute to cancer mortality (Chen et al. 2022; Hsi et al. 2023; Kim et al. 2021). In addition, the classic hyperglycemic hormones, like fly Akh and human glucagon, have been identified as key cachectic hormones, primarily driving tumor-induced wasting (Ding et al. 2025). Finally, integrating *Drosophila* genetics with mouse pharmacology has pinpointed potential therapeutic targets (TkR99D/NK3R, AkhR/GcgR, ERK, and Jak-Stat pathway) (Xu et al. 2023; Ding et al. 2025; Kim et al. 2021; Li et al. 2023a). Note that mouse studies face limitations and barriers, such as ethical regulations, genetic redundancy, and intratissue cellular heterogeneity. By contrast, the *Drosophila* model does not face the same limitations, and fly studies benefit from other technical

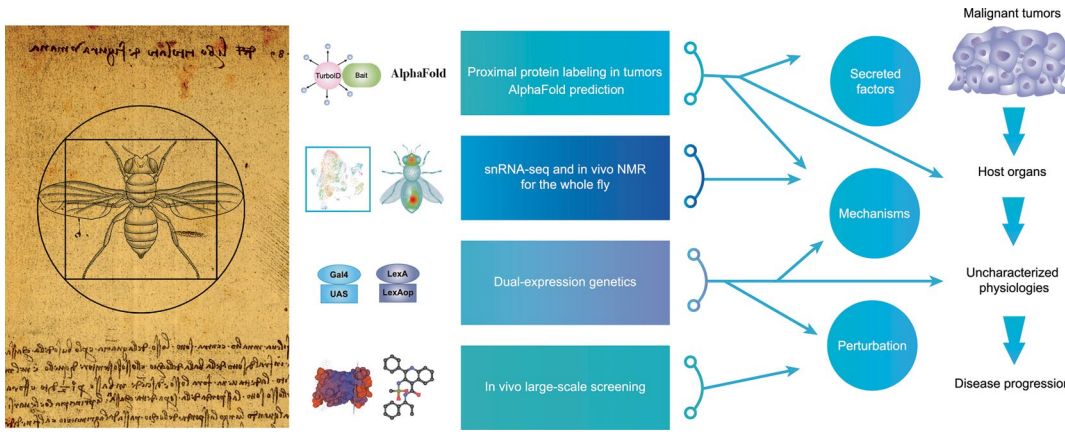

Fig. 5.3 Strategic options for future cancer-cachexia research in *Drosophila*. *Drosophila* model can be leveraged to study human diseases like cancer cachexia. By combining TurboID-induced biotinylation of endogenous proteins and AlphaFold, novel tumor- and host-secreted cachectic proteins can be identified. snRNA-seq and in vivo NMR of whole flies can be employed to investigate the uncharacterized physiology of host organs in the context of tumors. Dual expression genetics can be used to dissect the molecular mechanisms underlying tumor-host interactions. Finally, large-scale in vivo screening can be used to validate both genetic and pharmacological perturbations

advantages. By leveraging these unique advantages, we can further advance our understanding of the following unaddressed fundamental questions about cancer cachexia (Fig. 5.3).

1. *Beyond muscle and fat wasting, what other organ lesions significantly affect quality of life and survival of tumor-bearing subjects?* While muscle and fat wasting are prominent features of cancer cachexia with many established pathogenic mechanisms, other organs may also be affected, such as the pancreas, kidneys, liver, heart, and lungs. Understanding the impact of these organs on final outcomes is crucial. Dual expression tools in *Drosophila* (del Valle Rodriguez et al. 2011), which combine the LexA/LexAop and Gal4/UAS systems, can be used to both generate gut tumors and independently perform genetic manipulations in host organs within a single fly (Chen et al. 2022). The emerging split-GAL4 system that requires the intersection of two independent enhancers to activate transgene expression further allows precise control of gene expression in small groups of cells, like subgroup neurons or gut cells, in the context of tumors (Luan et al. 2020; Ewen-Campen et al. 2023). This makes it possible to efficiently explore the impacts of individual organs in the context of a tumor-bearing fly. For example, Pvf1, secreted by *yki*^{3SA} gut tumors, systemically activates its receptor Pvr to cause host wasting, and use of a dual expression system revealed that Pvr inactivation specifically in Akh-producing cells (APCs), but not muscle or fat tissues, exhibited the greatest improvement in host wasting, including muscle wasting, lipid loss, hyperglycemia, and ovary atrophy (Ding et al. 2025). These findings highlight the uncharacterized pathologies of APCs or pancreatic α-cells in cancer cachexia. Using dual expression genetics to perform tissue cross-screening should help identify additional organs or tissues relevant to cancer cachexia.
2. *What are the molecular mechanisms underlying organ lesions?* Identifying the specific molecular pathways involved in organ dysfunction in cancer cachexia can provide valuable insights into disease pathogenesis and point to potential therapeutic targets. Facilitated by the small size and simple organ composition of *Drosophila*, whole-organism or peripheral single-nucleus RNA-seq (snRNA-seq) and spatial transcriptomics have

emerged as powerful tools to conveniently perform in-depth gene expression analysis in each tissue, revealing changes in cell composition, biological processes, and novel physiological changes (Li et al. 2022; Lu et al. 2023; Wang et al. 2022b). Previous studies have utilized these methods to identify increased gluconeogenesis in fat body or liver, perturbed uric acid metabolism in renal tubules, along with related signaling pathways, in adult flies bearing yki^{3SA} gut tumors (Xu et al. 2024; Liu et al. 2025). In addition, NMR analysis in living flies has also demonstrated its effectiveness in studying the localization and identification of metabolites (Sarou-Kanian et al. 2015), such as renal uric acid and hepatic pyruvate, associated with organ lesions in the context of tumors. All these observations can be rapidly confirmed by genetic manipulation using dual expression systems. Furthermore, drug-target screening can be applied to fly models, as targets of most drugs, like enzymes, transporters, GPCRs, cluster of differentiation (CD) markers, ion channels, as well as nuclear receptors, approved by FDA or in clinical studies have homologs in *Drosophila* (Perrimon et al. 2007; Munnik et al. 2022; Santos et al. 2017). For example, pavinetant targets human NK3R, the homolog of fly TkR99D (Xu et al. 2023). Non-biased in vivo screening through systemic and tissue-specific knockdown of drug-target homologs, followed by drug administration, can validate the effects of these targets in tumor-bearing flies (Xu et al. 2023). These findings can be further translated into rodent models and clinical studies to develop novel therapeutic strategies for cancer cachexia.

3. *Are there novel secreted proteins that coordinate the pathological changes in various tissues/organs as mentioned above to the greatest extent?* Multiple tumors commonly secrete ImpL2 to cause energy wasting, but ImpL2 does not likely affect mortality caused by Ras^{V12} $aPKC^{\Delta N}$ adult ovarian tumors or transplanted Ras^{V12} $aPKC^{\Delta N}$ larval disc tumors (Kwon et al. 2015; Figueroa-Clarevega and Bilder 2015; Lodge et al. 2021; Hsi et al. 2023; Kim et al. 2021). Based on the available data, Pvf1 appears to be a more encompassing tumor-associated cachectic ligand, as its removal significantly diminishes energy wasting, renal dysfunction, and mortality (Xu et al. 2024; Chen et al. 2022; Song et al. 2019). However, induction of Pvf1 is absent in Ras^{V12} $scrib^{-/-}$ larval disc tumors and Ras^{V12} $aPKC^{\Delta N}$ adult ovarian tumors (Hsi et al. 2023; Song et al. 2019). Tumor-associated PGRP-SC2 and ITP modulate renal dysfunction without affecting energy wasting (Chen et al. 2022; Xu et al. 2023). Therefore, identifying critical secreted proteins orchestrating the cachectic effects of distinct organs in different tumor models is essential for developing novel therapeutic interventions, such as insulin for diabetes and TNF-α for inflammation. Note that as the established RNA-seq analysis in *Drosophila* is limited to known and predicted secreted proteins based on putative signal peptide or extracellular domain (Pei et al. 2018; Hu et al. 2015), it fails to capture the full spectrum of secreted proteins, including nonconventional ones that bypass ER like Transglutaminase (Tg-A) (Shibata et al. 2017). TurboID and other variant enzymes, which generate reactive biotin species to promiscuously label the proximal proteins via in situ biotinylation (Wei et al. 2021; Droujinine et al. 2021), has emerged as a powerful approach for identifying novel secreted proteins. For instance, we can discover both conventional and unconventional tumor-secreted proteins by expressing ER-, cytoplasm-, and other organelle-localized TurboIDs in tumors or host organs and detecting biotinylated proteins in the hemolymph using mass spectrometry. Additionally, AlphaFold's ability to accurately predict 3D protein structures could significantly facilitate the identification of novel ligands or membrane receptors by enabling in-depth structural analysis of potential ligand-receptor pairings (Abramson et al. 2024; Yang et al. 2023; Danneskiold-Samsoe et al. 2023). Genetic screening can then be used to assess

the cachectic effects of these newly identified proteins. This approach will allow for a more comprehensive understanding of the molecular mechanisms underlying cancer cachexia and identification of potential therapeutic targets.

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