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Review article

What we have learnt from *Drosophila* model organism: the coordination between insulin signaling pathway and tumor cells

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ABSTRACT

Cancer development is related to a variety of signaling pathways which mediate various cellular processes including growth, survival, division and competition of cells, as well as cell-cell interaction. The insulin signaling pathway interacts with different pathways and plays a core role in the regulations of all these processes. In this study, we reviewed recent studies on the relationship between the insulin signaling pathway and tumors using the *Drosophila melanogaster* model. We found that on one hand, the insulin pathway is normally hyperactive in tumor cells, which promotes tumor growth, and on the other hand, tumor cells can suppress the growth of healthy tissues via inhibition of their insulin pathway. Moreover, systematic disruption in glucose homeostasis also facilitates cancer development by different mechanisms. The studies on how the insulin network regulates the behaviors of cancer cells may help to discover new therapeutic treatments for cancer.

1. Introduction

Cancer is a disease in which abnormal cells proliferate uncontrollably (tumor) and migrate to other parts of the body (metastasis). It is initiated by a series of mutations in oncogenes and anti-oncogenes and develops as additional mutations continuously occur. A variety of signaling pathways mediate various cellular processes, including cell growth, cell survival, cell division, cell competition, and cell-cell interaction, which were related to tumor formation and migration (Hanahan and Weinberg 2011; Ma et al. 2021). For example, both the Hippo pathway and Wnt pathway were first discovered in *Drosophila melanogaster* (fruit fly, as its common name), and they were found to be able to regulate cell proliferation and organ size (Harvey et al. 2003; Udan et al. 2003; Huang et al. 2005). The Jun N-terminal kinase (JNK) pathway responds to internal and external stressors and regulates cell migration and apoptosis (Uhlirova and Bohmann 2006; Shen et al., 2009; Zhang et al., 2017). Meanwhile, the JNK pathway interacts with Janus kinase/signal transducer, activator of transcription (JAK/STAT) and nuclear factor-kappa B (NF-κB) pathways to support cell survival, thus establishing a cell-cell competition system (Wu et al., 2019).

The insulin signaling pathway senses the nutrient levels and directs cell metabolism, growth, and proliferation (Raman et al., 2007; Sagatys et al., 2007). It interacts with all other pathways mentioned above, thus playing a core role in the regulations of all the cell processes related to cancer development.

The insulin pathway is an evolutionarily conserved pathway existing in almost all metazoan animals (Junger et al., 2003). *Drosophila. melanogaster* is a classical genetic model, whose genome carries orthologs of at least 70% of human disease-related genes. UAS/Gal 4 system, mosaic and MARCM system, RNA interference and CRISPR/Cas9 system serve as great genetic tools for tumor-related genetic manipulation (Figure 1). And the fact that fruit flies have no acquired immunity makes them ideal models for tumor transplantation experiments (Ji et al. 2014; Markstein et al. 2014). Various tumor or cancer models were successfully established based on *D. melanogaster* (Table 1). Besides, the insulin pathway in *D. melanogaster* is not quite different from the pathway in humans. The *Drosophila* insulin-like peptides (DILPs) are secreted by special insulin producer cells after the meal and recognized by insulin receptors on peripheral tissues and organs, thus activating the downstream signaling by phosphorylation cascade (Myers et al., 1994; Robertson et al., 1999). PI3K, Akt, and Rheb are conserved components for the insulin signaling transduction (Weinkove and Leevers 2000). Rheb activates the TOR pathway, and Akt activates the FOXO pathway, simultaneously affecting cell cycle

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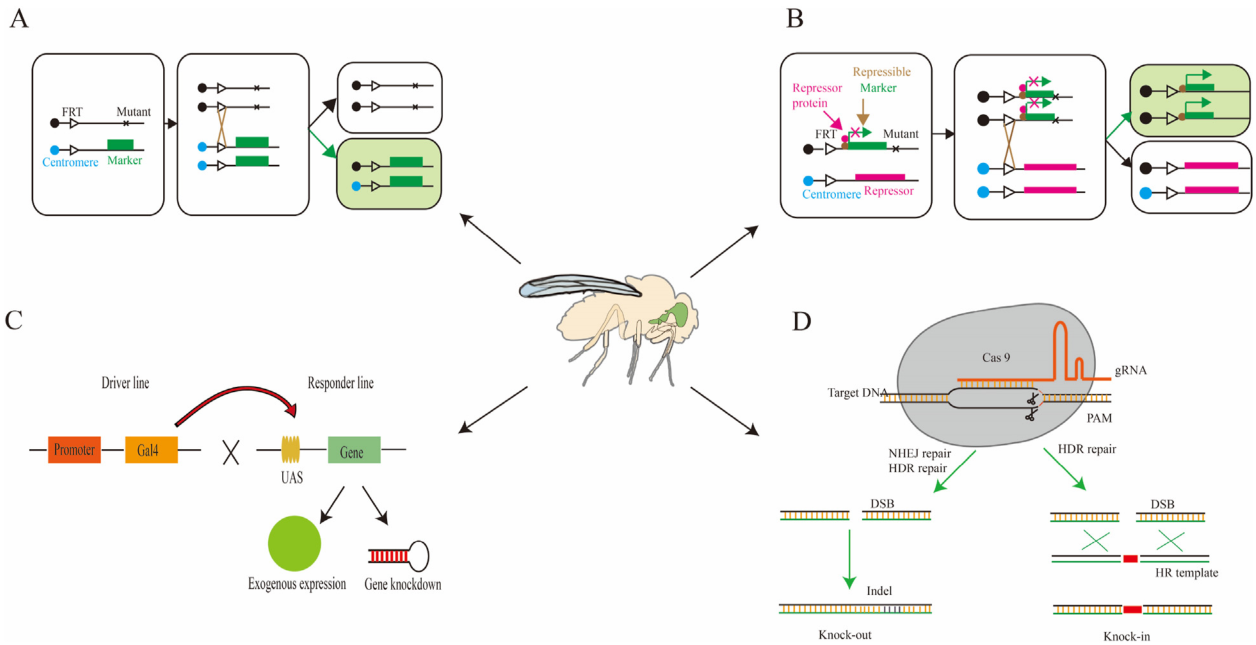

Figure 1. A In traditional mosaic analysis, homozygous mutant cells were identified as unstained cells if the marker gene was trans-placed into the mutant gene at the distal end of the FRT site on the homologous chromosome arm. B In the MARCM system, the transgene encoding the suppressor of gene expression is placed at the distal end of the FRT site on the homologous chromosome arm of the mutant gene. Only in homozygous mutant cells can the marker genes be expressed due to the deletion of suppressor genes. C UAS (Upstream Activation Sequence), is a sequence to which GAL4 (a transcriptional activator placed next to the desired tissue promoter) binds to drive gene expression in a specific tissue. Moreover, gene knockdown/silencing is achieved using UAS-RNAi flies, resulting in hairpin expression and RNAi-mediated gene knockdown in a tissue-specific manner. D CRISPR/Cas9 is a complex composed of Cas9 protein with endonuclease activity and specific sgRNA (single guide RNA). SgRNA first recognizes the particular sequence in the genes causing a series of changes that make itself and the target DNA pair with each other and form a heteroduplex of RNA-DNA. At the same time, sgRNA and Cas9 nuclease form a complex that binds to the target sequence, cleaves, and produces double-strand breaks. This breakage can induce DNA's response to damage and stimulate DNA repair through various endogenous mechanisms, thus editing the genes.

regulation and promoting cell growth and proliferation (McGonnell et al., 2012). The insulin pathway activity is not only determined by blood sugar level but also modulated by the JNK pathway and JAK/STAT pathway (Zhang et al. 2017; Wu et al. 2019; Ding et al. 2021).

The insulin pathway is a hotspot in cancer research. This paper reviewed the recent findings of the relationship between the insulin pathway and cancer development in research using *D. melanogaster* models. We found that the insulin pathway plays different roles in different positions during cancer development. The hyperactivity of the insulin pathway promotes tumorigenesis inside tumors, whereas tumor tissues may induce atrophy of healthy organs and tissues (cachexia) by suppressing their insulin pathway, which is mediated by JNK and JAK/STAT pathway (Figure 2A). Additionally, the disruption of glucose homeostasis caused by the insulin pathway disorder may affect genome stability, thus accelerating the micro-evolution of cancer cells. Generally, *D. melanogaster* is a powerful model for studying the association of insulin signaling pathway with tumors, which has showcased abundant mechanisms behind this association, and will further expand our knowledge in this direction in the future.

2. The hyperactivation of insulin signaling pathway promotes tumorigenesis inside tumors

2.1. The Ras signaling pathway and PI3K signaling pathway

Linked by insulin receptors (InRs) and insulin receptor substrates (IRSs), the insulin/insulin-like growth factors (IGFs) actively direct two signaling pathways, phosphatidylinositol-3-kinase (PI3K) signaling pathway and rat sarcoma (Ras) signaling pathway (Clancy et al. 2001; Weng et al. 2001; Oldham et al. 2002). The Ras signaling pathway stimulates cell proliferation, while the PI3K signaling pathway controls the cell metabolism, growth and survival (Oldham et al. 2002; D'Oria et al. 2017). Mutated Ras proteins are found in 20–30% of human tumors and are often associated with mutations in other genes (such as Myc, tp53, SMAD4), suggesting that mutated Ras alone might not be able to fully support malignant transformation (Kortlever et al. 2017; Kim et al. 2021). The engineered *Drosophila* Ras^{V12} allele is a constitutively active form of Ras. Ras^{V12} MARCM clones in the eye antennal disc grow moderately and proliferate overly to form classical hyperplastic tumors (Pagliarini and Xu 2003), indicated that the Ras was an important linkage between the

Table 1. *Drosophila* cancer models.

Tumor model	Mutations	Human cancer	Mechanism/Pathway	References
Gliomas model	*dEGFR, dRaf, dp110, dPTEN, dAkt*	Gliomas	EGFR-Ras and PI3K signaling	(Read et al. 2009)
Alveolar rhabdomyosarc-oma model	*PAX-FKHR*	Alveolar rhabdomyos-arcoma	Ras is a genetic modifier of PAX7-FKHR	(Giovannucci et al., 2010)
MEN2 model	*dRet*	Medullary thyroid carcinoma	Ret, Raf, Src, Tor, and S6K kinases	(D'Oria et al., 2017)
Lung cancer model	*Ras* 1^{G12V}, *pten*	Lung cancer	Ras and PI3K pathway	(Levine and Cagan 2016)
Colorectal cancer model	*Ras, p53, pten, apc*	Colorectal cancer	PI3K/Tor, Akt and TORC1	(Levine and Cagan 2016)

Table 2. Clinical anti-tumor drugs targeting the Insulin signaling pathway.

Drugs	Targets	Pathways and biological processes	Tumor types	Reference
Trichostatin A (TSA)	HDAC	Epigenetic	non-small-cell lung cancer, malignant melanoma cells	(Florenes et al., 2004; Mukhopadhyay et al., 2006)
Suberoyl anilide hydroxamic acid (SAHA)	HDAC	Epigenetic	glioblastoma multiforme	(Yin et al., 2007)
LAQ-824/LBH 589	HDAC	Epigenetic	non-small cell lung cancer, ovarian cancer and leukemia cells	(Yu et al., 2007)
Depsipeptide (FK-228)	HDAC	Epigenetic	non-small-cell lung cancer, colon cancer, and chronic myelogenous leukemia	(Choudhary and Wang, 2007; Vinodhkumar et al., 2008; Yu et al., 2007)
MS-275	HDAC	Epigenetic	B-chronic lymphocytic leukemia cells, Jurkat lymphoblastic T cells and prostate cancer cells	(Lucas et al., 2004; Maggio et al., 2004; Qian et al., 2007)
MGCD0103	HDAC	Epigenetic	B-chronic lymphocytic leukemia cells, Jurkat lymphoblastic T cells and prostate cancer cells	(Lucas et al., 2004; Maggio et al., 2004; Qian et al., 2007)
LBH589	HDAC	Epigenetic	leukemia cells	(Fiskus et al., 2006)
AMN107	HDAC	Epigenetic	leukemia cells	(Fiskus et al., 2006)
Axitinib	SHPRH	Wnt/β-Catenin Signaling	colon cancer	(Qu et al., 2016)
Nitazoxanide	BAX, P53, caspase, and BCL-2	Wnt/β-Catenin Signaling	colon cancer, glioblastoma, ovarian Cancer	(Abd et al., 2021)
Vitamin D	β-catenin	Wnt/β-Catenin Signaling	colorectal cancer	(Sherman et al., 2014)
Curcumin	Tcf/β-catenin	Wnt/β-Catenin Signaling	colorectal cancer	(Patel et al., 2008)
Genistein	GSK3β	Wnt/β-Catenin Signaling	colorectal cancer	(Huang et al., 2017)
Resveratrol	PDE4	Wnt/β-Catenin Signaling	colorectal cancer	(Lev-Ari et al., 2005)
Aspirin	β-catenin	Wnt/β-Catenin Signaling	colorectal cancer	(Patel et al., 2010)
Celecoxib	TCF	Wnt/β-Catenin Signaling	colorectal cancer	(Holcombe et al., 2015)
Sulindac	β-catenin	Wnt/β-Catenin Signaling	colorectal cancer	(Gray et al., 2017)
IWPs	Porcupine	Wnt/β-Catenin Signaling	colorectal cancer	(Dihlmann et al., 2001)
ETC-159	Porcupine	Wnt/β-Catenin Signaling	colorectal cancer	(Chen et al., 2009)
LGK 974	Porcupine	Wnt/β-Catenin Signaling	colorectal cancer	(Madan et al., 2016)
LMO2	Dvl	Wnt/β-Catenin Signaling	colorectal cancer	(Wickstrom et al., 2015)
NSC668036	Dvl	Wnt/β-Catenin Signaling	colorectal cancer	(Liu et al., 2016)
XAV939	Axin	Wnt/β-Catenin Signaling	colorectal cancer	(Wang et al., 2015)
IWR	Axin	Wnt/β-Catenin Signaling	colorectal cancer	(Fan et al., 2014)
G007-LK	Axin	Wnt/β-Catenin Signaling	colorectal cancer	(Kulak et al., 2015)
G244-LM	Axin	Wnt/β-Catenin Signaling	colorectal cancer	(Lau et al., 2013)
Pyrvinium	CK1	Wnt/β-Catenin Signaling	colorectal cancer	(Thorne et al., 2010)
PKF115-584 CGP049090 PKF222-815	Tcf/β-catenin	Wnt/β-Catenin Signaling	colorectal cancer	(Lepourcelet et al., 2004)
iCRT3/5/14	Tcf/β-catenin	Wnt/β-Catenin Signaling	colorectal cancer	(Gonsalves et al., 2011)
HI–B1	Tcf/β-catenin	Wnt/β-Catenin Signaling	colorectal cancer	(Shin et al., 2017)
MSAB	Tcf/β-catenin	Wnt/β-Catenin Signaling	colorectal cancer	(Hwang et al., 2016)
PNU-74654	Tcf/β-catenin	Wnt/β-Catenin Signaling	colorectal cancer	(Leal et al., 2015)
LF3	Tcf/β-catenin	Wnt/β-Catenin Signaling	colorectal cancer	(Fang et al., 2016)
CWP232228	Tcf/β-catenin	Wnt/β-Catenin Signaling	colorectal cancer	(Kim et al., 2016)
Rapamycin	mTOR	PI3K/mTOR pathway, Autophagy	rhabdomyosarcoma, glioblastoma, small cell lung cancer, osteosarcoma, pancreatic cancer, breast cancer, prostate cancer, and B-cell lymphoma	(Ballou and Lin, 2008)
Everolimus	mTOR	PI4K/mTOR pathway, Autophagy	Hodgkin lymphoma, non-Hodgkin's lymphoma and breast cance	(Ballou and Lin, 2008)
Temsirolimus	mTOR	PI5K/mTOR pathway, Autophagy	endometrial cancer and mantle-cell lymphoma	(Ballou and Lin, 2008)
AZD8055	mTOR	PI3K/mTOR pathway	advanced solid malignancies	(Chresta et al., 2010)
PP242	mTOR	PI3K/mTOR pathway	acute leukemia, hepatocellular carcinoma cells	(Feldman et al., 2009)
Torin 1	mTOR	PI3K/mTOR pathway	lung tumors, gliomas	(Thoreen et al., 2009)
NVP-BEZ235	mTOR, PI3K	PI3K/mTOR pathway	advanced solid tumours and metastatic breast cancer	(Liu et al., 2009)
PI-103	mTOR, PI3K	PI3K/mTOR pathway	advanced solid tumours and metastatic breast cancer	(Raynaud et al., 2007)

(*continued on next page*)

Table 2 (*continued*)

Drugs	Targets	Pathways and biological processes	Tumor types	Reference
XL765	mTOR, PI3K	PI3K/mTOR pathway	solid tumours and gliomas	(Molckovsky and Siu, 2008)
chloroquine (CQ) + bortezomib	-	Autophagy	Colorectal cancer	(Cloonan and Williams, 2011)
CQ + vorinostat	-	Autophagy	Colorectal cancer	(Chresta et al., 2010)
hydroxychloroquine (HCQ) + XELOX + bevacizumab	-	Autophagy	Colorectal cancer	(Ogata et al., 2006)
CQ + imatinib	-	Autophagy	Gastrointestinal stromal tumor	(Feldman et al., 2009)
CQ + Src kinase inhibitors	-	Autophagy	Prostate cancer	(Shao et al., 2004)
CQ + cetuximab	-	Autophagy	Vulvar cancer	(Stein et al., 2010)
HCQ + imatinib	-	Autophagy	Chronic myelogenous leukemia	(Alexander et al., 2010)
Antidiabetic	AMPK	Autophagy	colorectal cancer	(Ben et al., 2010)
Arsenic trioxide	BNIP3	Autophagy	leukemia and glioma	(Goussetis et al., 2010; Kanzawa et al., 2005)

hyperactivity of insulin signaling pathway and tumor. The hyperactivation of the PI3K pathway is also known to be associated with many types of human cancers. Activated mutations in PIK3CA, which encodes the p110α catalytic subunit of PI3K, are also found in many tumors (Maher et al. 2001; Furnari et al. 2007). Gliomas often show constitutively hyperactivity of Akt, a major PI3K effector (Maher et al. 2001; Furnari et al. 2007). As the lipid phosphatase antagonizes the PI3K signaling, Phosphatase and tensin homolog (PTEN) is a typical genetic lesion in tumor cells.

The activations of Ras and PI3K signaling pathways were often found to be associated with each other in tumorigenesis (The Cancer Genome Atlas Research Network, 2012; Kandoth et al. 2013). Renee D. Read et al. established a glioma model by constitutively coactivating the epidermal growth factor receptor (EGFR)-Ras and PI3K pathways in *D. melanogaster* glial cells and glial precursor cells. This model produces highly proliferative and invasive neoplastic cells that promote transplantable tumor-like growths, mimicking human glioma. They also found that at least four pathway circuits are necessary for glial neoplasia initiated by EGFR-Ras and PI3K signaling. Tor-eIF4E-S6K pathway, which provides protein translation essential for proliferation and growth, is one of the four pathways for the glial neoplasia (Read et al. 2009). Ras/PI3K pathway is one of the most investigated pathways for cancer therapy, with a large number of therapeutic agents under clinical development. The mitogen-activated extracellular signal-regulated kinase (MEK) inhibitor trametinib and HMG-CoA reductase inhibitor fluvastatin were also found to be able to synergistically reduce the activation of the Ras/PI3K pathway, thus correcting tracheal development and reducing excessive proliferation in a *Drosophila* lung cancer model (Levine and Cagan 2016). PI3K pathway inhibitors, such as BEZ235, were effective for multiple PI3K mutant tumor types (Rodon et al. 2013; Dienstmann et al. 2014). Erdem Bangi et al. found that the resistance to PI3K pathway inhibitors was an emergent property of colorectal cancer caused by Ras activation accompanied with Pten loss in the fruit fly model (Bangi et al. 2016) (Figure 2B).

In conclusion, hyperactivity of the insulin signaling pathway activates both Ras and PI3K pathways, which promoting the cell proliferation, growth, and survival in tumor tissues, and finally benefiting the tumor development.

2.2. The insulin and wingless/wnt mitogenic signaling pathway

Insulin signaling can activate the wingless/Wnt mitogenic signaling pathway mediated by Ras (Hall and Verheyen 2015). Wnt activation has been frequently observed in many tumor types, including those with a strong association with diabetes, such as hepatocellular carcinomas and colorectal cancers (Fodde et al. 2001; Laurent-Puig and Zucman-Rossi 2006). Hirabayashi et al. showed evidence that the insulin signaling pathway could promote tumor development via the Wnt signaling pathway in *D. melanogaster*. They also found that Ras/Src-activated cells could increase the sensitivity of the insulin pathway, thereby taking advantage of high circulating glucose levels, and resulting in a Wg- and JNK-dependent enhancement of tumor progression. Further studies demonstrated that the increased insulin/PI3K signaling could prevent apoptosis and promote canonical Wingless/Wnt mitogenic signaling in Ras/Src tumors, thus inducing malignant tumors (Hirabayashi et al. 2013) (Figure 2B). In conclusion, the wingless/Wnt mitogenic signaling pathway is one important downstream pathway of the Ras/PI3K pathway to promote tumor development.

2.3. The insulin signaling pathway and autophagy

It was found that the insulin signaling pathway promotes tumorigenesis also via autophagy-related factors. Beclin 1 is the core factor for autophagy and plays an important role in mammalian autophagy and phagocytosis (Shravage et al. 2013). Beclin1 has been reported as a tumor suppressing gene (Yue et al. 2003). The deletion of Beclin 1 was shown to occur with a high frequency in breast, ovarian, and prostate cancers (Liang et al. 2006; Li et al. 2013). It has also been reported that knockdown of Atg 6, the homolog of Beclin1 in *D. melanogaster*, could induce hyperproliferation, centrosome amplification, and DNA damage accumulation in *D. melanogaster* intestinal stem cell (ISC) (Na et al. 2018). Atg6 and other autophagy-related genes have been reported to be negatively regulated by AKT/TOR pathway (Jung et al. 2010). In further research, metformin, a drug for type 2 diabetes, was found to inhibit the proliferation of ISC in an Atg6-dependent manner (Liu and Rando 2011). Richard C. Wang et al. found that Beclin1 mutants are resistant to Akt-mediated phosphorylation and can inhibit Akt-driven tumorigenesis (Wang et al. 2012). This suggests that insulin signaling may regulate Atg6 via AKT/TOR in the process of carcinogenesis (Figure 2B).

2.4. The insulin signaling pathway and epigenetic regulation

It was reported that the activity of the insulin signaling and the activity of histone deacetylase (HDAC) often interact with each other, suggesting that the insulin signal is also involved in epigenetic regulation. A number of histone deacetylase (HDAC) inhibitors have been developed and applied in clinical trials to inhibit tumor growth (Witt et al. 2009). The depletion of histone deacetylase 3 (Hdac3) results in a reduction in body size in *D. melanogaster*. Further studies showed that Hdac3 could counteract the organ overgrowth induced by overexpression of InR, PI3K, or S6K. Increasing the level of H4K16ac can effectively reverse the PI3K-induced tissue overgrowth (Lv et al. 2012). The interaction between the insulin signaling pathway and HDAC activity as well as the association of HDAC activity with tumor development have been reported. However, there is no direct evidence of the involvement of HDAC in the promotion of tumors by insulin signaling, and further studies are required to substantiate this possibility (Figure 2B).

2.5. The insulin signaling pathway and cell competition

The hype-activation of the insulin signaling pathway can cell-autonomously promote cell growth and cell survival and advances the competitiveness of these cells against other cells. Cell competition

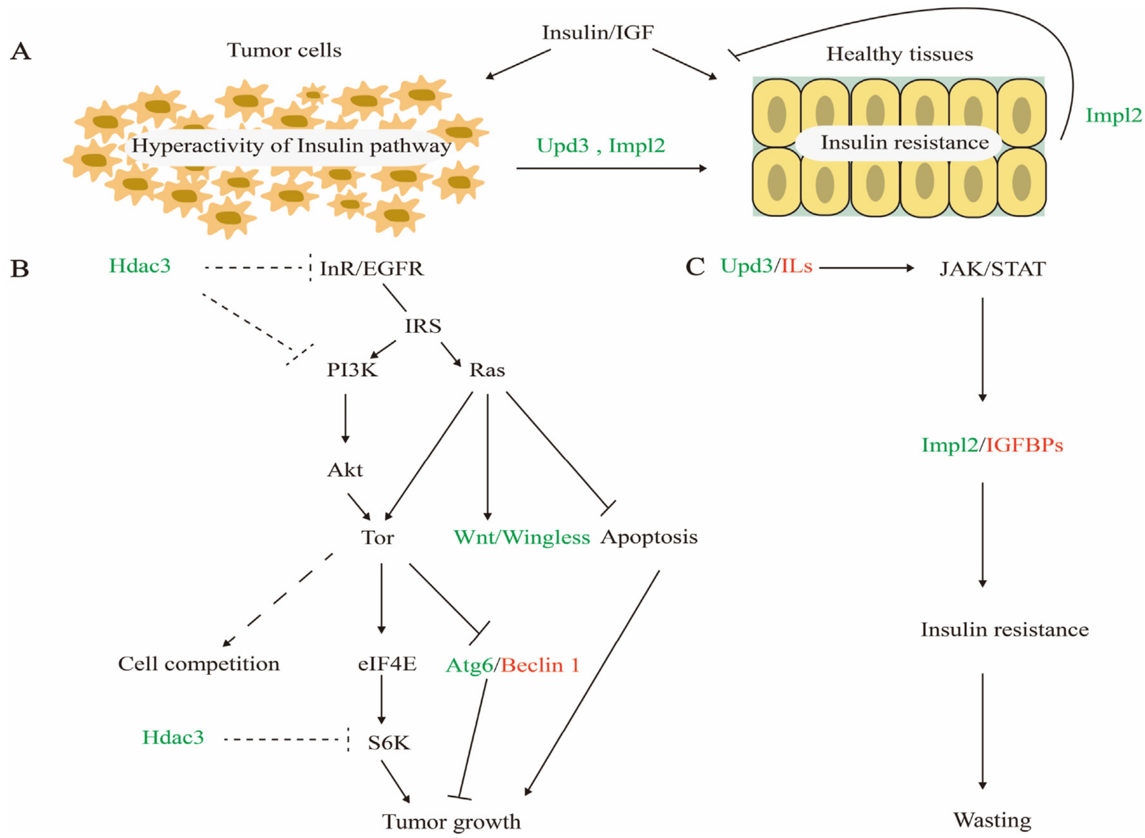

Figure 2. A The relationship between the Insulin pathway and cancers. B The hyperactivation of Insulin signaling promotes tumorigenesis inside tumors. Insulin pathway can promote tumorigenesis by activating the TOR-eIF4E-S6K pathway and enhancing the insulin/PI3K signal, because during the process, tumor cell apoptosis is inhibited, Wingless/Wnt mitotic signal is activated, the expression of autophagy-related factor Atg 6/Beclin 1 and overexpression of InR, PI3K or S6K are promoted, and cell competition is initiated. Epigenetic factor such as Hdac3 may play a role in tumor growth via inhibiting InR or PI3K. C Insulin resistance induces cachexia in the healthy tissues. The IGF/Insulin pathway can be blocked in healthy tissues by tumor cells via Upd 3/JAK/STAT signaling and cytokine Impl2, which may lead to the wasting of cells and organs. The solid line represents a definite regulatory effect, while the dotted line represents a possible regulatory effect. Red refers to the names of certain components in mammals, green refers to the components or the names of the components in the *Drosophila* system, and black refers to the components, which share the same name in both mammals and *Drosophila*.

functions as a tumor-suppressing mechanism since malignant/oncogenic cells can be removed during the process. In a *Drosophila* tumor model, oncogenic *scribble* (*scrib*) mutant cells, when surrounded by wild-type cells, can be eliminated by cell competition. Yuya Sanaki et al. found that in flies with the low expression levels of the insulin receptor substrate chico, the *scrib* cells can evade cellular competition and develop into tumors. Downregulation of Chico in insulin-producing cells (IPCs) raises the expression of DILP2, which activates insulin-mTOR signaling, thereby promoting protein synthesis in *scrib* cells (Sanaki et al. 2020). The findings of Bowling et al. are consistent with this. They found that insulin-TOR signaling can also control cell competition during mouse embryonic development (Bowling et al. 2018). These studies indicate that the active insulin-TOR signaling pathway systemically abrogates tumor-suppressing cell competition, thus causing tumorigenesis (Figure 2B).

In brief, hyperactivity of the insulin signaling pathway actives both Ras and PI3K pathways and their downstream wingless/Wnt signaling pathway to promote tumor development. The interaction between the insulin signaling pathway and HDAC activity also benefits the tumor development. Besides, insulin-TOR signaling pathway indirectly accelerates tumorigenesis by blocking tumor-suppressing cell competition.

3. Tumors suppress the insulin signaling activation in the peripheral tissues and cause cachexia

Cachexia is a multiorgan, multifactorial and often irreversible wasting syndrome associated with cancer and other severe chronic illnesses. Insulin resistance is a frequent feature of both cachectic patients and rodent cachexia models (Honors and Kinzig 2012; Tisdale, 2009). Studies have shown that ImpL2, an insulin-like growth factor binding protein (IGFBP), can cause the wasting of cells by preventing insulin signaling in the peripheral tissues of tumor in the *D. melanogaster* model. Knocking-out of *ImpL2*, especially in the tumor, ameliorates the wasting of phenotypes (Figueroa-Clarevega and Bilder 2015). Activation of Yorki, the transcriptional coactivator in the *D. melanogaster* gut, leads to proliferation of ISCs and increases *ImpL2* expression. Further studies showed that with the activation of Yorkie in the intestine, the expression of restricted glycolytic enzymes and the central component of the insulin/IGF pathway are up-regulated, which may be the mechanism for tumor tissue's escape from the effects of ImpL2 (Kwon et al. 2015). Guangming Ding et al. found that the secretion of Upd 3 by Yki-gut tumor promotes hyperproliferation and enhances JAK/STAT signaling in host organs. Further studies on the mechanism suggested that Upd3/JAK/STAT signaling could regulate *ImpL2* expression by damaging muscle mitochondrial homeostasis, blocking the insulin/IGF pathway in adipocytes and muscle, and resulting in fat loss and muscle dysfunction. Inhibition of the JAK/STAT pathway in adipocytes and muscle alleviates cachexia phenotypes of Yki-gut tumor (Ding et al. 2021). Thus, tumor cells secrete not only *ImpL2* but also Upd3 to induce *ImpL2* expression in other tissues, which can cause severe cachexia. The *D. melanogaster* ImpL2 is homologous to the mammalian insulin-like growth factor binding proteins (IGFBPs). The IGFBPs can bind with IGFs with high affinities to regulate the activity of IGFs in target tissues (Huang et al. 2016). IGF/PI3K/Akt pathway has been shown to induce hypertrophy and prevent the induction of necessary atrophic mediators (Stitt et al. 2004). Xiu-yan Huang et al. found that a high expression level of IGFBP-3, produced by pancreatic cancer cells, leads to the wasting of muscle by inhibiting IGF/PI3K/AKT signal, damaging myogenesis and promoting myotube protein degradation (Huang et al. 2016). IGFBPs in mammals can antagonize insulin/IGF signal transduction, and these studies showed that the proper control of transduction could prevent the wasting of organs (Figueroa-Clarevega and Bilder 2015) (Figure 2C). All these evidences suggest that the insulin signaling pathway in healthy tissues of cancer patients may play an opposite role to it in tumor cells, which are remotely suppressed by the tumor and induce the wasting.

4. The relationship between glucose homeostasis and tumor

Epidemiological studies provided strong evidence for the link between cancer and metabolic diseases, including diabetes and obesity. Patients with metabolic disorders have higher morbidity of certain tumor types and higher cancer-related mortality (Calle et al. 2003; Coughlin et al. 2004; Inoue et al. 2006; Barone et al. 2008; Giovannucci et al. 2010). Progesterone receptor-negative breast cancer patients with obesity have a higher risk of lymph node metastasis, suggesting that metabolic dysfunction may promote tumor invasion (Maehle et al. 2004). Increased circulation of insulin has also been found as a risk factor for the development of hepatocellular carcinoma and colorectal cancer (Kaaks et al. 2000; Donadon et al. 2009). In a high dietary sugar model, a high-sugar diet was reported to promote tumor growth and metastasis of fly tumors with elevated Ras and Src signaling. High dietary sugar can increase the activity of the Wingless/Wnt pathway, which promotes insulin sensitivity by upregulating gene expression of the insulin signaling pathway (Hirabayashi et al. 2013). Sanaki et al. showed that *scrib* mutant cells are insulin-insensitive and have lower protein synthesis levels than those in health tissues. Hyperinsulinemia breaks this balance and causes scrib tumorigenesis. This evidence suggested that hyperinsulinemia can promote tumor development and progression. In addition, studies in mice showed that high-fat diet-induced obesity suppresses extrusion of oncogenic Ras^{V12} cells from mice intestine (Sasaki et al. 2018) and that endogenous hyperinsulinemia contributes to pancreatic ductal adenocarcinoma (Zhang et al. 2019). Thus, metabolic dysfunction, especially hyperinsulinemia, plays a role in promoting tumorigenesis. The mechanism by which hyperinsulinemia controls the initial step of tumorigenesis needs further investigation. Chiara Merigliano et al. established two *Drosophila* models of type 2 diabetes: the first by impairing insulin signaling and the second by rearing flies in a high sugar diet. With glucose treatment, deficiency of Pyridoxal 5′ phosphate (PLP), the active form of vitamin B6, causes severe chromosome and DNA damage, suggesting that hyperglycemia combined with lower PLP levels may impair the integrity of DNA, thus leading to the development of cancer. These results suggest that low PLP levels, which can impact the integrity of DNA, may be considered one of the possible reasons for the link between diabetes and cancer (Merigliano et al. 2018). In one sentence, A disruption of glucose homeostasis caused by a problem with insulin signaling pathway can create a dangerous micro-environment, which benefits the tumor development and evolution.

5. Conclusion and outlook

The insulin signaling pathway is a conserved pathway in mammals and *D. melanogaster*. It causes the nutrient signals to be associated with cell growth, and regulates many essential metabolic functions and cell processes. Many studies revealed that people with metabolic dysfunction, including obesity and diabetes, are at increased risk for certain cancers. As mentioned above, cancer is a complicated disease. Its occurrence is related to a variety of signaling pathways and physiological processes that go out of control at the same time. Insulin/IGF signaling pathway can control the cell proliferation, growth and survival by interacting with numerous downstream cancer-related pathways, such as PI3K, Ras, mTor, and Wnt/Wingless pathways, thus forming a network inhibiting cancer formation. Insulin resistance, cachexia, autophagy, epigenetics, and cellular competition are all closely related to the occurrence of tumors, and these processes can be regulated by the insulin signaling pathway. Thus, the insulin signaling pathway is a core factor in cancer development and plays a significant role in tumor therapies.

Studies using the *D. melanogaster* model greatly improved our understanding of the relationship between cancer and the insulin pathway. In general, the insulin pathway plays two roles in cancer development: on one hand, hyperactivity of the insulin pathway strongly enhances cell survival and cell proliferation in tumor tissues; on the other hand, the activity of the insulin pathway can be suppressed in healthy tissues by insulin antagonism cytokines, which are secreted by tumor cells. The promoting role is directly mediated by PI3K, Ras, mTor, and Wnt/Wingless pathways downstream to insulin signaling, and cell-autonomous increases the competitiveness of tumor cells against health cells; while the suppressing role was due to active the JNK and JAK/STAT pathway, which remotely inhibits the insulin signaling of healthy tissues. Besides, systematic problems in glucose homeostasis may affect tumorigenesis in various aspects. A lot of regulatory factors affecting tumor development in the insulin pathway were identified in multiple previous studies. These factors could be potential novel therapeutic targets for cancer treatment. However, the specific mechanism of tumor-insulin signaling pathway interaction via such factors still needs to be elucidated. We also listed the clinical anti-tumor drugs targeting the insulin pathway in Table 2. In future research, the interaction between metabolic diseases and cancer can be further explored, and new drugs may be developed by studying the mechanism of the signal pathway using the *D. melanogaster* model.

Declarations

Author contribution statement

TANG weina, QIAO huan-huan: Analyzed and interpreted the data & Wrote the paper.

LI ying: Analyzed and interpreted the data.

WANG yiwen: Conceived and designed the experiments & Wrote the paper.

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Data availability statement

Data included in article/supp. material/referenced in article.

Declaration of interest's statement

The authors declare no conflict of interest.

Additional information

No additional information is available for this paper.

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