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Review

Fruit fly research in China

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ABSTRACT

Served as a model organism over a century, fruit fly has significantly pushed forward the development of global scientific research, including in China. The high similarity in genomic features between fruit fly and human enables this tiny insect to benefit the biomedical studies of human diseases. In the past decades, Chinese biologists have used fruit fly to make numerous achievements on understanding the fundamental questions in many diverse areas of biology. Here, we review some of the recent fruit fly studies in China, and mainly focus on those studies in the fields of stem cell biology, cancer therapy and regeneration medicine, neurological disorders and epigenetics.

1. Introduction

Drosophila melanogaster (known as fruit fly) is a fascinating model organism and has been extensively used in scientific research for over one hundred years (Bellen et al., 2010). Fruit fly has several practical features that are suitable for laboratory study, including a short life cycle, readily culture and maintenance, and a low number of chromosomes, which enable fruit fly a commonly used model organism in biological research, particularly in genetics and developmental biology. Notably, the genome sequencing of fruit fly reveals that approximately 75% of known human disease genes have orthologs in fruit fly (Adams et al., 2000; Reiter et al., 2001). Thereafter, fruit fly has been greatly benefited the biomedical studies in cancer, immunity and neurological diseases (Bellen et al., 2010; Gonzalez, 2013; Buchon et al., 2014).

After rediscovering Mendelian inheritance in 1900, Professor Thomas Hunt Morgan (1866—1945), an American evolutionary biologist and geneticist who won the Nobel Prize in Physiology or Medicine in 1933, started to use the fruit fly for genetic researches and demonstrated that genes are located on chromosomes, which laid the fundamental basis of the modern genetics. Some of Morgan's Chinese students performed excellent research and are later known in China as the founders of their fields. Among them, Professor Ju-Chi (Ruqi) Li (1895—1991) and Professor Chia-Chen (Jiazhen) Tan (1909—2008) significantly contributed to the genetic research and acted as the pioneers and founders of modern genetics in China. Professor Ruqi Li was the first Chinese PhD graduate from Morgan's lab and published his first fly paper showing how chromosomal mutation influences fruit fly developments in Genetics (Li, 1927). Until now, this research article is still recognized as a classic work in developmental genetics. Professor Jiazhen Tan was trained by Professor Li in China and then in Morgan's lab, conducting many influential works using fruit flies and lady-bird (Tan, 1942; Tan, 1946). Professor Jiazhen Tan was later called "the Chinese Morgan."

Inspired by the pioneers in the field of genetics, in the past decades, the younger generation of Chinese biologists have used fruit fly to make numerous achievements on understanding the fundamental questions in many diverse areas of biology, from developmental biology to neuroscience. In this review, we cover some of the recent fruit fly studies in China, and mainly focus on those studies in the fields of stem cell biology, cancer therapy and regeneration medicine, neurological disorders and epigenetics.

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2. Stem cell biology

2.1. Germline stem cells

Drosophila ovary provides an excellent model system for studying a variety of fascinating biological processes, such as stem cell regulation, germline-soma interaction and meiosis regulation. *Drosophila* oogenesis initiates at the tip of the germarium, where a germline stem cell (GSC) divides asymmetrically to produce a daughter GSC and a cystoblast (CB). CBs eventually develop into mature eggs and sustain oogenesis. Thus, the balance between self-renewal and differentiation of GSCs is the critical regulatory step for germline development. Over the last ten years, several Chinese research groups have used the *Drosophila* ovary as model to study the molecular mechanisms underlying GSC fate determination, and characterized a number of factors that cell-autonomously regulate self-renewal and differentiation of GSCs (Yang et al., 2007; Jiang et al., 2008; Zhao et al., 2008; Chen et al., 2009; Yang et al., 2009; Sun et al., 2010; Li et al., 2015a; Sun et al., 2015; Ji et al., 2017; Li et al., 2017b; Liu et al., 2017c; Chen et al., 2018a). These studies suggest that the miRNA pathway, ubiquitin-mediated cell-cycle program, TSC1/2 tumor suppressor complex and others are cell-autonomously required for GSC maintenance. In addition to intrinsic factors, the maintenance and differentiation of GSCs also require factors involved in the interaction between GSCs and their surrounding stromal cells (also called stem cell niches). Zhaohui Wang's group found glypican Dally functions as the co-factor of Dpp to establish short-range BMP (bone morphogenetic protein) signaling in GSC, thus maintaining GSC identity (Guo and Wang, 2009). Dahua Chen's group showed that GSCs and CBs can differentially respond to niche BMP signal, thus forming a steep gradient of BMP signaling response that controls the GSC fate (Xia et al., 2010). Moreover, Dahua Chen and Yi Tao's groups performed mathematic modeling analyses and revealed a bistable behavior of the feedback-loop system in controlling fate determination of GSCs (Xia et al., 2012). It is worth to note that the Bam protein has been demonstrated to play a critical role in promoting early germ cell differentiation in the *Drosophila* ovary; however, its biochemical nature has long been a mystery. Dahua Chen's group recently showed that Bam functions as an ubiquitin-associated protein, and cooperates with Otu (ovarian tumor) to deubiquitinate and stabilize Cyclin A (CycA), thereby balancing GSC self-renewal and differentiation (Ji et al., 2017).

In addition to ovary, Chinese biologists have used *Drosophila* testis as a model to study germline development, stem cell maintenance and proliferation, and identified a number of RNA-binding proteins, noncoding RNAs and enzymes that regulate *Drosophila* spermatogenesis (Zhang et al., 2009; Zhao et al., 2013; Chen et al., 2014; Wen et al., 2016; Wu et al., 2016; Yu et al., 2016; Shan et al., 2017). These studies made significant contributions to the field of germline development.

2.2. Intestinal stem cells

Intestinal stem cells (ISCs) in the *Drosophila* midgut provide a simple and genetically tractable system to understand the basic principles that control adult stem cell. Each ISC periodically divides to generate a daughter enteroblast (EB), which then differentiates further into one of the two cell types: enterocyte and enteroendocrine cells. Rongwen Xi's group made important progress on the mechanisms underlying cell fate decision during ISC differentiation. They showed that the visceral muscle cells surrounding the intestinal epithelium constitute a regulatory niche for ISCs by producing multiple secreted signal molecules, including Wingless (Wg) and epideraml growth factor (EGF)-like factors, which act on ISCs to promote ISC maintenance and proliferation (Lin et al., 2008, 2010; Xu et al., 2011). Moreover, they identified Ttk69 as a master repressor of enteroendocrine cell fate (Wang et al., 2015a). By studying the regulation of a cell fate inducer Scute, Rongwen Xi's group found that transient induction of Scute in ISCs by feedback regulations directs the generation of enteroendocrine cells from ISCs, indicating that transcription factor oscillation in stem cells may act as a timer for cell fate decision of multipotent stem cells (Chen et al., 2018b).

ISCs are very resistant to apoptotic inducers, but are not able to be regenerated after all the progenitors are ablated (Zhang et al., 2015; Ma et al., 2016). To ensure tissue homeostasis, the proliferation and differentiation of ISCs are tightly regulated by extrinsic and intrinsic factors at multiple levels. Xinhua Lin's group showed that the respiratory organ, trachea, produces Dpp (Decapentaplegic, homolog of BMP) ligands, which activate Dpp signaling in enterocytes (ECs) to restrict ISCs from excessive proliferation (Li et al., 2013b). They found that Dpp signaling in ECs protects ECs from cell death and/or environmental stresses. In the absence of Dpp signaling in ECs or Dpp production in tracheal cells, ISCs undergo unrestricted proliferation and produce excessive amount of ISC-like cells and progeny, resembling human juvenile polyposis (JP) syndrome (Haramis, 2004; Li et al., 2013b). These findings demonstrate the significance of inter-organ communication in tissue homeostasis maintenance.

Moreover, Xinhua Lin's group found that Debra (Dbr), an intrinsic factor, maintains midgut homeostasis by negatively regulating Hedgehog (Hh) signaling in ISCs (Li et al., 2014b). Dbr mediates the degradation of Cubitus interruptus (Ci), the transcription activator in the Hh signaling pathway, thereby restricting Hh signaling from excessive activation in ISCs (Dai et al., 2003; Li et al., 2014b). Additionally, they found that another intrinsic factor, Windpipe (Wdp), maintains midgut homeostasis (Ren et al., 2015). Wdp interacts with the receptor Domeless and promotes its internalization for subsequent lysosomal degradation, forming a negative feedback loop to regulate the duration of Janus kinase/signal transducers and activators of transcription (JAK/STAT) signaling activation, thereby maintaining midgut homeostasis (Ren et al., 2015).

Given the similarities in ISC regulation between flies and mammals, the fly midgut system can also be used to model human diseases, such as intestinal tumorigenesis. Rongwen Xi's group has demonstrated the parallel and cooperative roles for Wnt and EGFR signaling during loss of adenomatous polyposis coli-induced intestinal tumors (Wang et al., 2013). They also identified a Sox21a-mediated feedback amplification loop between ISCs and their immediate daughter progenitor cells, which is essential for intestinal regeneration and tumorigenesis (Chen et al., 2016). These new findings may help to understand tissue regeneration and the disease mechanisms in mammals, including human.

2.3. Renal and nephric stem cells

The malpighian tubules (MTs or fly kidney) of adult *Drosophila* are maintained by renal and nephric stem cells (RNSCs) through self-renewing divisions; however, the underlying mechanisms of how RNSC proliferation and differentiation are regulated remain unclear. Zhouhua Li and Xinhua Lin's groups showed that EGFR/MAPK signaling is dispensable for the maintenance of RNSCs, but required for the proliferation of RNSCs *in vivo* (Li et al., 2015c). EGFR/MAPK (mitogen-activated protein kinases) signaling functions independently of JAK/STAT signaling to regulate RNSC proliferation. Meanwhile, dMyc and CycE are found to partially mediate EGFR/MAPK signaling activity in RNSCs (Li et al., 2015c). They have further revealed that Notch signaling is essential for

RNSC self-renewal and differentiation (Li et al., 2014a). Notch receptor is expressed in both RNSCs and renalblasts (RBs), the immediate daughters of RNSC divisions, while the ligand Delta is expressed at high levels in RNSCs, which serves as a RNSC marker. RNSC-expressed Delta initiates Notch signal activation in RBs to promote cell cycle exit and differentiation, similar to its function in the midgut. Surprisingly, Delta is also required autonomously in RNSCs to maintain stem cell fate. Mechanistically, RNSC-expressed Delta inhibits Notch signal activation in RNSCs via the "*cis*-inhibition" process (Li et al., 2014a). These data demonstrate that differential Notch activity is required in RNSCs and RBs for their maintenance and differentiation, respectively (Li et al., 2014a).

2.4. Neural stem cell

Asymmetric division of a neural stem cell distinguishes a stem cell and its differentiating sibling, and thus plays vital roles in maintaining homeostasis and preventing carcinogenesis. So far, however, the mechanisms that consolidate and lock in such initial fate bias remain obscure. Conceivably, a signaling amplification mechanism could be employed in the stem cells or progenitors to accelerate the transition phase between the initial cell fate decision and the ultimate cell fate commitment. Yan Song's group has recently implicated the Super Elongation Complex (SEC), which controls transcription elongation checkpoint, in driving fly neural stem cell fate commitment (Liu et al., 2017a). SEC is highly enriched in the neural stem cells, where it interacts directly and intimately with the Notch signaling pathway in a self-reinforcing feedback loop for timely stem cell fate lock-in. Their studies revealed an SEC-mediated intracellular amplifier mechanism in ensuring robustness and precision in stem cell fate commitment, which explains the highly frequent association of SEC over-activation with human cancers. More recently, Yan Song's group also showed that the retromer complex could directly regulate Notch receptor retrograde trafficking in neuroblast lineages, and ensure the unidirectional Notch signaling from neural progenitors to neuroblasts. Their results unveil a safeguard mechanism of retromer, where it can act as a bomb squad to specifically retrieve and disarm potentially harmful Notch receptors in a timely manner to prevent abnormal Notch activation-induced neural progenitor dedifferentiation and brain tumor formation (Li et al., 2018).

3. Developmental signaling, cancer therapy and regeneration

3.1. Hippo signaling pathway

The Hippo signaling pathway controls the organ size, tissue homeostasis, repair and regeneration by inhibiting cell proliferation, promoting apoptosis and stem cell maintenance. Malfunction of the Hippo pathway results in various diseases including cancers, it is thus a potential target for cancer therapy and regeneration medicine. Lei Zhang's group has being focused on identifying novel regulators and studying molecular actions of the Hippo pathway. They identified proteinase-activated receptor 1 (Par-1) (Huang et al., 2013a) and activated cdc42 kinase (Ack) (Hu et al., 2016) as novel components regulating upstream core kinase complex. Ack can interact with Expanded (Ex) and phosphorylate Ex on multiple sites, especially Y679 and Y766 residues, to promote tissue growth (Hu et al., 2016). When Hippo signaling is off, Yorkie (Yki) translocates into the nucleus and binds to the transcription factor Scalloped (Sd) to promote downstream target gene expression. Moreover, Lei Zhang's group identified another novel component of the Hippo pathway, Sd-Binding-Protein (Sdbp) (Guo et al., 2013)/Tgi (Koontz et al., 2013) which competes with Yki for Sd binding through its TDU domain to inhibit the transcriptional activity of Sd-

Yki complex. Shian Wu's group identified that hypoxia condition regulates Hippo signaling through ubiquitin E3 ligase seven in absentia homolog 2 (SIAH2)-mediated turnover of Wts (Lats1/2 in mammal), uncovering that oxygen availability involves in development and tumorigenesis via both the hypoxia and Hippo pathways (Ma et al., 2015a). Shian Wu's lab also found that E3 ligase dSmurf is essential for proteostasis of Wts and Hippo signaling (Cao et al., 2014). Pez has been identified as a negative upstream regulator of Yki and to restrict ISC proliferation. Lei Zhang's group showed that an E3 ubiquitin ligase Su(dx) targets Pez for degradation, revealing a new mechanism of Pez in maintaining the homeostasis of *Drosophila* midgut (Wang et al., 2015b). They also demonstrate that Brahma (Brm) chromatin remodeling complex interacts with Yki-Sd to maintain ISC proliferation ability for midgut regeneration. Hippo signaling tightly controls the Brm protein levels by inducing caspase-dependent cleavage (Jin et al., 2013).

3.2. Hedgehog, Wnt and Dpp signaling pathways

Hedgehog (Hh) signaling pathway plays vital roles in regulating embryonic tissue patterning and adult tissue maintenance and repair in metazoan. Dysregulation of Hh signaling is linked to numerous human disorders, including congenital malformations and cancers. Understanding the biological functions and deciphering the underlying mechanisms of Hh signaling provide translational potential of various Hh-related diseases (Xiong et al., 2015). Two transmembrane proteins, Patched (Ptc) receptor and Smoothened (Smo) signal transducer, are involved in an unusual reception system of Hh signaling. A large number of studies have been focusing on investigating the activation of Smoothened and its downstream signal transduction; however, little is known about the regulation of Patched receptor. Dahua Chen's group showed that ubiquitin E3 ligase Smurf directly targets Patched for ubiquitination to regulate Hh signaling. Mathematic modeling analysis suggests that a bidirectional control involving Smurf and Patched is important for signal-receiving cells to precisely interpret external signals, thereby maintaining Hh signaling reliability (Huang et al., 2013b).

The Cubitus interruptus (Ci)/Gli transcription factors can be degraded either completely or partially from a full-length form (Ci155/Gli^{FL}) to a truncated repressor (Ci75/Gli^{R}). Yun Zhao's group has identified Ter94 (*Drosophila* valosin-containing protein) ATPase as a novel stability regulator of Ci by targeting K11-linked ubiquitinated Ci for the selective partial degradation (Zhang et al., 2013e). They also identified ubiquitin specific peptidase 7 (Usp7) as a novel deubiquitinase of Ci to remove ubiquitin and stabilize Ci in the presence of Hh (Zhou et al., 2015). They confirmed that Ter94-mediated Ci selective degradation and Usp7-Ci regulation axis is conserved in mammals. Moreover, they identified Atrophin as a novel repressor of the Hh signaling pathway by interacting with the N terminus of Ci repressor (Ci^{R}) and enhancing the repression effects in a Ci^{R} dependent manner. They demonstrated that Atrophin can interact with a histone deacetylase, Rpd3 (*Drosophila* homolog of histone deacetylase 1) and recruit it to the Ci^{R} binding sites resulting in local histone H3 deacetylation, which experimentally clarifies how Ci regulates its downstream target genes (Zhang et al., 2013d). In addition, Yun Zhao's group has explored the biological functions of Hh signaling pathway: they demonstrated that sumoylation of Ci is required for Hh signaling-mediated cyst stem cell proliferation in the testis (Lv et al., 2016), and neuronal Hh ligands are important for ISC differentiating toward ECs (Han et al., 2015).

The heart is one of the first functional embryonic organs occurring during development (Wu, 2010). Although the

mechanisms that control heart development after the initial heart tube formation of fly are different from mammals, mechanisms that control the heart tube creation appear to be conserved in both fly and vertebrates. Xiushan Wu and his colleagues first identified the wingless (wg) as an important regulator in fly heart development (Wu et al., 1995; Park et al., 1996). Their subsequent studies further suggest the importance of Wg/Wnt signaling in fly heart development (Tang et al., 2013).

Dpp signaling is essential for patterning the wing. Jie Shen's group has explored the role of Dpp signaling on cell morphogenesis and proliferation control. The Dpp target genes optomotor-blind (omb) and spalt (sal) mainly mediate the Dpp's functions. Discontinuities in Omb and Sal activity lead to a re-organization of the epithelial cytoskeleton and basal retraction of cells (Tang et al., 2016). Sal activity promotes cell proliferation without regional manner in the wing disc (Wang et al., 2017). Omb regulates proliferation in a region-specific manner by control of the proliferation-promoting microRNA bantam (ban) expression. Dpp-Omb signaling inhibits proliferation in the medial wing disc by suppression of ban and promotes proliferation in the lateral wing disc by activation of ban (Zhang et al., 2013b). Omb orthologous human TBX2 (T-box transcription factor 2) and TBX3 are overexpressed in various cancers. Overexpressing Omb and TBX2 in the wing epithelium induces two types of cell motility, long distance migration within the plane of the epithelium and cell invasion across the basal lamina without degradation of extracellular matrix (Shen et al., 2014).

3.3. JNK signaling pathway

The JNK pathway plays crucial roles in animal development. Dysregulation of JNK signaling has been implicated in various types of human diseases including cancers, neurodegenerative diseases, immunity defects and metabolic syndromes. Lei Xue's group identified a number components and modulators of JNK pathway. They showed that forkhead boxO (FoxO) is a downstream target of JNK, and the Pelle kinase can promote cell death by directly phosphorylating FoxO (Wu et al., 2015). Moreover, they found that impaired Hippo signaling promotes Rho1-JNK-dependent growth (Ma et al., 2015b), and that the E3 ubiquitin ligase POSH regulates Hippo signaling through ubiquitin-mediated expanded degradation (Ma et al., 2018). On the other hand, they found that the Hippo pathway promotes JNK-dependent cell migration through miRNA ban-mediated Rox8 stability. Furthermore, Myc suppresses tumor invasion and cell migration by inhibiting JNK signaling (Ma et al., 2017).

3.4. Natural lineage reprogramming

Recently, a promising regenerative strategy has been suggested by converting a highly specialized cell into the desired cell identity in a living body. Although very rare, natural lineage reprogramming can occur with high efficiency and temporo-spatial precision. However, it is still unclear about the molecular mechanisms underlying in vivo lineage conversion. Yan Song's group has recently revealed a natural midgut-to-renal lineage reprogramming event during fruit fly metamorphosis. Moreover, they also identified a highly conserved protein called Cut as a crucial cell identity switch in this process. By intersecting with a pulse of steroid hormone, a steep gradient of a spatial molecule (Wingless/Wg) induces Cut to specifically express in a small subset of fly midgut progenitors and precursors that produce functional midgut cells, which are later converted into renal identity. These reprogrammed progenitors in turn migrate across organ boundary and onto renal tubules, and give rise to functional renal cells. Notably, although midgut

progenitors depleted of Cut migrate normally onto renal tubules, they could not complete switching their cell identity and fail to give rise to midgut cells along renal tubules, causing renal identity crisis (Xu et al., 2018).

4. Metabolism and physiology

4.1. Metabolism and development

Drosophila shares similar metabolic pathways with mammals, and as an insect, it also has unique features in metabolism and physiology. Sheng Li's group focuses on the functions and interplays of steroid and sesquiterpenoid hormones during developmental transitions. Their study revealed a crosstalk between these two hormones in the regulation of insect metamorphosis (Liu et al., 2018). Besides this, they also identified two distinct roles of the most abundant sesquiterpenoid, methyl farnesoate (MF). MF acts as a hormone directly through two juvenile hormone (JH) receptors, Met and Gce, and as the precursor of JH for maintaining larval juvenile status (Wen et al., 2015). Bing Zhou's group studied iron homeostasis. They identified ZIP13 (also known as Slc39a13) as an iron transporter. Loss of function of ZIP13 results in multiple iron homeostasis defects, including iron decrease in the secretory compartments (Xiao et al., 2014).

Yong Q. Zhang's group together with Zhaohui Wang's group revealed developmental roles of Acyl-CoA synthetase ACSL4, which converts long-chain fatty acids to acyl-CoAs, in particular in synapse homeostasis. Drosophila ACSL4 mutants exhibit numerous defects in axonal transport, synapse development and function at the neuromuscular junction (NMJ) synapses (Zhang et al., 2009; Yao et al., 2011). Mechanistically, dACSL4 mutants show aberrant endosomal recycling and elevated BMP signal. Importantly, reducing the doses of the BMP pathway components can partially suppress the overgrowth of NMJ synapse (Liu et al., 2014b). Consistent with the enzymatic role of ACSL, aACSL4 affects the composition of fatty acids and membrane lipids; lipidomic analysis shows an elevated level of mannosyl glucosylceramide (MacCer) in dACSL4 mutant brain and genetic manipulations of MacCer support the close correlation of MacCer level with NMJ growth (Huang et al., 2016).

By studying genes in peroxisome biogenesis and sterol transport, Xun Huang's group revealed roles of very long chain fatty acid (VLCFA) and sterol in spermatogenesis. Peroxisome is important for the catabolism of VLCFA. Several peroxisome biogenesis defective PEX (peroxins) mutants, where VLCFA was elevated, are male infertile. Notably, the cytokinesis defect is associated with the level of VLCFA and lowing the level of VLCFA rescues the sterility of PEX mutants (Chen et al., 2010). In addition, their study revealed that Osbp (oxysterol-binding protein) mutants with sterol transport defects exhibit individualization defects during spermatogenesis (Ma et al., 2010). However, how sterol homeostasis exactly affects spermatogenesis is not known.

4.2. Lipid metabolism

The eases of genetic manipulation and environmental intervention make Drosophila an excellent model for metabolic diseases such as obesity and diabetes. Xun Huang's group focuses on studying lipid storage regulation in adipose tissue, the fat body, and non-adipose tissue, the salivary gland. By generating the first Drosophila model of the most severe lipid dystrophy disease BSCL2 (Berardinelli-Seip congenital lipodystrophy 2), they revealed distinct and autonomous functional mechanisms of Seipin, the gene mutated in human BSCL2, in both adipose and non-adipose tissues. Similar to mammalian BSCL2 models, Drosophila Seipin (dSeipin)

mutants exhibit opposite phenotypes in adipose and non-adipose tissues: *dSeipin* mutants have ectopic lipid droplet in salivary gland; while in fat body, lipid storage is greatly reduced in *dSeipin* mutants. They further demonstrated that elevated level of phosphatidic acid likely contributes to the ectopic lipid droplet phenotype in salivary gland (Tian et al., 2011). On the other hand, the reduced lipid storage phenotype in the fat body can be explained by the interaction of dSeipin and SERCA, a calcium ATPase in endoplasmic reticulum (ER), which regulates calcium level in the ER. ER calcium level is reduced in *dSeipin* mutant fat cells. Genetically restoring the ER calcium level rescues the lipodystrophy phenotype of *dSeipin* (Bi et al., 2014). Ultimately, the decreased ER calcium affects calcium level in mitochondria, where citrate, the precursor of lipogenesis, is produced through TCA cycle. Restoring mitochondrial calcium or replenishing citrate in the medium restores lipid storage in *dSeipin* mutants (Ding et al., 2018). Their study suggests that a dSeipin-SERCA mediated ER Ca^{2+}-mitochondrial Ca^{2+}-TCA axis contributes to BSCL2 lipodystrophy. Besides BSCL2 models, Xun Huang's group also revealed other mechanisms in regulating lipid storage, including general transcription factor telomeric repeat binding factor 2 (TRF2)-mediated lipid droplet size regulation (Fan et al., 2017), CDP diglyceride synthetase (CdsA)-involved lipid partition for storage and growth (Liu et al., 2014a), and the cooperation of two lipid droplet proteins perilipin 1 and 2 (PLIN1/PLIN2) in regulating the balance of lipid storage and lipolysis (Bi et al., 2012).

5. Neurological diseases

Wei Xie and Junhai Han's groups used *Drosophila* as the model to investigate the roles of autism-related genes in neural development and neural transmission. They have demonstrated that the well-known autism candidate genes encoding Neurexin and Neuroligins predominantly expess in pre- and post-synaptic terminals, respectively. Both Neurexin and Neuroligins play critical roles in synaptogenesis. Loss of Neurexin and Neuroligins results in reduced bouton numbers, aberrant presynaptic and postsynaptic development at *Drosophila* NMJ (Zeng et al., 2007; Sun et al., 2011). In addition, they have revealed that Neurexin restricts the axonal branches of visual L4 neuron in column through clustering of the classical axon guidance molecule, Ephrin (Liu et al., 2017b). Moreover, they have shown that Neurexin mediates retinoid transport through stabilizing the retinoid transporter apolipoproteins (Tian et al., 2013).

Except for neural development, they have demonstrated that Neurexin and Neuroligins also play critical roles in synaptic transmission. Wei Xie's group has revealed that Neurexin regulates synaptic transmission in several steps. Firstly, Nexurexin interacts with the Scribble-Pix complex to stimulate F-actin assembly and to promote synaptic vesicle clustering (Rui et al., 2017). Secondly, Neurexin interacts with N-ethylmaleimide-sensitive factor (NSF) to regulate synaptic vesicle release (Li et al., 2015b). Thirdly, Neurexin functionally couples with the calcium channel Cac to regulate synaptic transmission. They also revealed that Neuroligin 4 modulates gamma-aminobutyric acid (GABA) transmission in large ventral lateral neurons through recruiting $GABA_A$ receptors resistant to dieldrin. Notably, even though Neurexin and Neurolign4 function in different brain regions, both of their mutant flies show reduced night-time sleep (Li et al., 2013a). Additionally, Junhai Han's group showed that $GABA_A$ receptor could be regulated by the ubiquitin E3 ligase Fbxl4 (F-box and leucine rich repeat protein 4) to control clock output (Li et al., 2017a).

Mutations in Neurexins and Neuroligins lead to autism, while loss of the ubiquitin ligase E3A (UBE3A) results in Angelman syndrome, which is characterized by severe mental retardation, developmental and speech impairment, ataxia, seizures, and happy disposition. Using the *Drosophila* NMJ as a model, Yong Q. Zhang's group showed that the *Drosophila* homolog of UBE3A specifically targets Thickvein for ubiquitin-mediated degradation to downregulate BMP signaling at NMJ synapses (Li et al., 2016). Yong Q. Zhang 's group also showed that the fragile X mental retardation protein FMRP, loss of which results in the most common form of inherited intellectual disability Fragile X syndrome, is required for axonal transport of mitochondria and maintains genome stability (Yao et al., 2011; Liu et al., 2012; Jiang et al., 2016). Dynamical regulation of mitochondria (e.g., mitochondrial fusion, fission and transport) is involved in a variety of biological processes and regulated by a number of factors, including Miro. Lei Liu's group found that the loss of *vimar* (atypical GEF coding gene) strengthened mitochondrial fission under normal physiological conditions. Their genetic analyses suggest that while loss of *vimar* rescues mitochondrial enlargement induced by a gain-of-function *Miro* transgene, a gain-of-function *vimar* transgene enhances Miro function. Thus, their findings identified a novel regulator of mitochondrial fission through Miro and indicated a potential therapetical target for diseases in which mitochondrial fission and fusion are dysfunctional (Ding et al., 2016).

Long non-coding RNAs (lncRNAs) consist of a large proportion of the transcriptome among the species. Li Liu's group identified a novel lncRNA, CASK regulatory gene (*CRG*), expressed in the nervous system of *Drosophila*, which could be involved in the regulation on the movement in adult *Drosophila*, and this effect was mediated by the adjacent protein-coding gene, *CASK* (Ca^{2+}/calmodulin-dependent protein kinase). Moreover, they found that CRG is required for the recruitment of RNA polymerase II to the *CASK* promoter regions, which in turn enhances CASK expression. Their findings reveal new functional roles of lncRNAs and provide insights into understanding the pathogenesis of neurological diseases associated with movement disorders (Li et al., 2012).

6. Learning, memory and decision-making

Fruit fly possessing a compact brain and complicated behaviors, serves an excellent model system for uncovering the nature of intelligence. Substantial achievements have been made in cognitive neuroscience field with this small insect, including information coding and processing, the neural circuit of learning and memory, the dynamics of memory, and most intriguingly, decision-making and remaking. Aike Guo's group has made a serial of important contributions in this field. They demonstrated, for the first time, that flies make decisions based on conflicting learning cues (Tang and Guo, 2001), and the dopaminergic system plays a critical role in this advanced cognitive function (Zhang et al., 2007). They further investigated the reversal learning in both olfactory and visual systems, and this unique type of learning shares common circuit mechanisms with decision-remaking (Ren et al., 2012; Wu et al., 2012). Another interesting learning type studied in Aike Guo' group is the cross-modal learning through the interaction between olfactory and visual cues (Guo and Guo, 2005) and his study illustrated potential neural pathway underlying this interaction (Zhang et al., 2013a).

Utilizing the optogenetics approach, Yan Li and Aike Guo' groups together uncovered the novel function of gap junctions in visual learning of flying flies (Liu et al., 2016b) and revealed the neural circuit and molecular mechanisms underlying cross-modal learning (Zhang et al., 2013c), sleep (Yi et al., 2013), and addictive behaviors (Zhang et al., 2016). Yan Li's group also characterized nutrient-specific feeding behavior and identified a protein-specific satiety factor (Liu et al., 2015; Sun et al., 2017). These findings allow in-depth investigation of feeding decision, as well as the neural

network that processes the decision-making.

7. Fly innate behaviors: aggression, courtship and sleep

Animals are born with the instinct to fight and mate. Individuals can still display innate aggression and courtship behavior even when isolated immediately after birth, suggesting that a genetic program specifies the neural circuits governing aggression and courtship. Yi Rao's group has addressed neural mechanisms by which the neurotransmitter octopamine regulates aggression and courtship in *Drosophila*. Loss-of-function or gain-of-function of a gene encoding tyramine beta hydroxylase (TβH) required for synthesizing octopamine reduced or increased aggression, respectively, as did functional inhibition or activation of octopaminergic neurons. Interestingly, resupply of the TβH back to five octopaminergic neurons in the subesophageal region restored the aggression phenotype of flies lacking TβH, suggesting an important role for these five neurons in aggression (Zhou et al., 2008). In a related study, they examined the involvement of octopamine in courtship conditioning behavior, wherein male courtship is depressed by male experience with a previously mated female. They have revealed that octopamine regulates courtship conditioning through the octopamine receptor OAMB, which is preferentially expressed in the mushroom body, the primary site for fly memory (Zhou et al., 2012). These findings have contributed to a mechanistic understanding of how neural circuits are regulated by neuromodulators to generate adaptive behaviors in different social contexts.

Sleep homeostasis is essential from flies to humans. But the molecular mechanisms underlying sleep homeostasis are poorly understood. Yi Rao's group have characterized the roles of neurotransmitter 5-hydroxytryptamine (5-HT) in *Drosophila* sleep (Qian et al., 2017). They found that *Trh* (thyrotropin releasing hormone) and *5HT2b* (5-HT receptor 2B) knock-out mutants displayed decreased sleep time and diminished sleep rebound after sleep deprivation. They also revealed the expression of 5HT2b in a small subset of dorsal fan-shaped body (dFB) neurons is essential for sleep homeostasis. Genetic ablation of 5HT2b neurons in the dFB led to the decreased sleep and impaired sleep homeostasis. Their results suggest that serotonergic signaling in specific neurons is required for the regulation of sleep homeostasis.

Besides, some endocrine hormones and neuropeptides are also important for the regulation of sleep and sleep homeostasis. Zhangwu Zhao's group characterized that sleep deprivation increases transcription of short neuropeptide F (sNPF) and wakefulness at night in control flies but not in the *sNPF* mutant flies, suggesting that sNPF autoregulation plays an important role in sleep homeostasis. They also showed that sNPF could modulate sleep through the sNPFR-cAMP-PKA-CREB signal pathway *in vivo*, and subsequently activates the downstream CREB transcription factor (Chen et al., 2013). Moreover, they found that JH signal pathway is critical for maintenance of sexually dimorphic sleep by regulating sex-relevant genes, in which the sexually dimorphic sleep induced by JH signals is a change of sleep drive and independent of the circadian clock (Wu et al., 2018).

8. Epigenetic regulation

8.1. Posttranscriptional regulation

The core of developmental biology is to understand how the developmental signals are controlled in a spatial and temporal manner to guide cell fate decisions, tissue patterning and adult homeostasis. Currently, most research focuses on the identification of transcriptional targets and consequences of developmental signal transduction. However, very little is known regarding the molecular and cellular mechanisms of how developmental signals are produced, received and interpreted. Jian Zhu's group utilizes the *Drosophila* wing morphogenesis as a model system to understand how developmental signals are initiated and transduced across the cell membrane. They uncovered an epigenetic control mechanism for Notch signal production (Du et al., 2016), revealed a crucial role of the RNA regulatory machinery and cell polarity determinants in cell reception of the Wingless signal (Liu et al., 2016a), and finally, developed a model by which cells utilize protein posttranslational modifications to convert differential concentration gradient of Hh morphogen into distinct developmental outcomes (Su et al., 2011; Zhang et al., 2014). These original findings not only increase our understanding of molecular networks on how cells produce, recognize and interpret developmental signals, but also establish a causal link between misregulation of developmental signaling and diseases.

A hallmark of aging in mammals is the occurrence of age-dependent ectopic fat accumulation (EFA), which contributes to age-related tissue deterioration and dysfunction. By using a fly model, Renjie Jiao's group assessed the molecular basis of age-dependent EFA formation (Yan et al., 2017). They characterized the occurrence of age-dependent EFA in *Drosophila* and identified HDAC6, a cytosolic histone deacetylase, as a suppressor of EFA. Their study suggests that, in an age-dependent manner, EFA mainly appears in the thoracic jump muscles of adult flies. Further, they identified the suppressors of age-dependent EFA, dHDAC6 and dHsc4 (*Drosophila* heat shock cognate gene 4) which are proteostatic regulators. The genetic and biochemical analyses indicated that dHDAC6 maintains the proteostasis of lipid droplet protein PLIN2 by regulating the acetylation level of dHsc4. The dHDAC6-dHsc4-PLIN2 axis links proteostasis to fat metabolism during aging. Together, their results point out that it is the protein quality rather than the protein quantity of PLIN2 that controls age-dependent EFA.

8.2. piRNA

Small noncoding RNAs (ncRNAs) including miRNAs, siRNAs and piRNAs play important roles in regulating gene expression through a variety of mechanisms. P-element induced wimpy testis (PIWI)-interacting RNAs (piRNAs), a subset of small ncRNAs (~24–30 nt in length), associate with PIWI proteins and play conserved roles in silencing transposons, and thus maintaining genome integrity and germline development. Previous studies suggested two models for piRNA production, including the primary processing and the feed-forward amplification pathways (Brennecke et al., 2007; Gunawardane et al., 2007). Dahua Chen' group investigated the role of argonaute 3 (AGO3) Slicer activity in regulating piRNA biogenesis. They showed that AGO3 inhibits the homotypic Aubergine:Aubergine (Aub:Aub) Ping-Pong process and the expression of an AGO3 Slicer mutant causes ectopic accumulation of Armitage. AGO3 also coexists and interacts with Armitage in the mitochondrial fraction. Moreover, they found that AGO3 acts in conjunction with Zucchini to control the dynamic subcellular localization of Armitage between mitochondria and nuage. Thus, these findings uncover a new mechanism that regulates secondary piRNA amplification (Huang et al., 2014). Rongwen Xi's group found that *Pelo* (*Dom34*)-*Hbs1* mRNA surveillance complex is required for transposon silencing, but not required for piRNA biogenesis in the *Drosophila* germline. Their results suggest that Pelo may silence transposable elements at the translational level (Yang et al., 2015).

8.3. Discovery of a novel DNA modification

N6-methyladenine (6mA) is one of the most abundant types of DNA methylation, and plays epigenetic roles in regulating a number of

of biological processes in bacteria (Wion and Casadesus, 2006). However, the role of 6mA in higher eukaryotes has long been a mystery. Using *Drosophila* as a model, Dahua Chen's group recently showed that 6mA is present in the *Drosophila* DNA at a relatively high level at the very earliest embryonic stages, but at low levels at the late embryonic stages. Moreover, they found that the dynamic modification of 6mA in early embryos is actively regulated by the *Drosophila* DMAD (DNA N6-methyladenine demethylase) protein, a homolog of Ten-eleven translocation (Tet) protein. Using the *DMAD* mutant flies, they found that DMAD is essential for *Drosophila* development and suppresses adenine methylation in genome. DMAD has no apparent *in vivo* role in regulating the conversion of 5mC to 5hmC, but can directly catalyze 6mA demethylation *in vivo* and *in vitro*. Using high-throughput sequencing analysis, they found that the expression levels of these 6mA peaks related transposons in *DMAD* mutant ovary sample were significantly higher than those in wild type. Taken together, their findings suggest that DMAD-mediated 6mA mode methylation is correlated with transposon expression (Zhang et al., 2015).

9. Future of the fruit fly research

Drosophila has made significant contributions to scientific research, and in the future, it undoubtedly holds a great promise to help biologists to investigate the mysterious fundamental questions in many aspects. For example, germ cells are the only type of cells that can pass the genetic materials from one generation to the next. One of the most fundamental questions in life science is how the primordial germ cells specify during early embryogenesis. *Drosophila* will provide an excellent model to elucidate the molecular basis underlying the specification of pole cells from biomolecular particles (germ plasm). In the future, it would be interesting to assemble functional germ plasm in the cell-free system, and fly should be a good candidate.

Neuroscience is another field that significantly benefits from fruit fly research. The recent produced 3D image of a fruit fly's brain enables the scientist to trace connections between neurons across the entire organ (Zheng et al., 2018), providing the possibility to conduct more comprehensive studies on the mechanism underlying the neurological disorders. Except for the well-established fly system in studying neurodevelopment, more and more fly experts started to focus on investigating the molecular and cellular basis of behaviors. Given the huge difference of brain structure between fruit fly and vertebrates, it might be not suitable to use fruit fly to study the function of some mammal specific brain tissues, such as cerebellum and hippocampus; however, for some behaviors that are common across the species, such as innate behaviors, fruit fly has a great potential to improve our understanding on the underlying mechanisms. For example, hundreds of the conserved genes associated with sleep and waking have been identified across species, and the fruit fly-based studies have given valuable insights into the molecular mechanisms of sleep regulation (Cirelli, 2009), providing more alternative ways to treat sleep disorders.

At last but not the least, fruit fly can also contribute to other fields of science. For example, it has been recently revealed that the fruit fly olfactory circuit can solve the identification of similar images with a variant of a computer science algorithm (Dasgupta et al., 2017). This interesting discovery provides a conceptually new algorithm for solving a fundamental computational problem, which opens a new door and inspires the scientist to improve the online search engines. Moreover, fruit fly has been used in space research to help addressing the effects of long-duration space missions on an astronaut's body and the way in which the body responds to new and stressful environments (Hateley et al., 2016; Hosamani et al., 2016).

References

Adams, M.D., Celniker, S.E., Holt, R.A., Evans, C.A., Gocayne, J.D., Amanatides, P.G., Scherer, S.E., Li, P.W., Hoskins, R.A., Galle, R.F., George, R.A., Lewis, S.E., Richards, S., Ashburner, M., Henderson, S.N., Sutton, G.G., Wortman, J.R., Yandell, M.D., Zhang, Q., Chen, L.X., Brandon, R.C., Rogers, Y.H., Blazej, R.G., Champe, M., Pfeiffer, B.D., Wan, K.H., Doyle, C., Baxter, E.G., Helt, G., Nelson, C.R., Gabor, G.L., Abril, J.F., Agbayani, A., An, H.J., Andrews-Pfannkoch, C., Baldwin, D., Ballew, R.M., Basu, A., Baxendale, J., Bayraktaroglu, L., Beasley, E.M., Beeson, K.Y., Benos, P.V., Berman, B.P., Bhandari, D., Bolshakov, S., Borkova, D., Botchan, M.R., Bouck, J., Brokstein, P., Brottier, P., Burtis, K.C., Busam, D.A., Butler, H., Cadieu, E., Center, A., Chandra, I., Cherry, J.M., Cawley, S., Dahlke, C., Davenport, L.B., Davies, P., de Pablos, B., Delcher, A., Deng, Z., Mays, A.D., Dew, I., Dietz, S.M., Dodson, K., Doup, L.E., Downes, M., Dugan-Rocha, S., Dunkov, B.C., Dunn, P., Durbin, K.J., Evangelista, C.C., Ferraz, C., Ferriera, S., Fleischmann, W., Fosler, C., Gabrielian, A.E., Garg, N.S., Gelbart, W.M., Glasser, K., Glodek, A., Gong, F., Gorrell, J.H., Gu, Z., Guan, P., Harris, M., Harris, N.L., Harvey, D., Heiman, T.J., Hernandez, J.R., Houck, J., Hostin, D., Houston, K.A., Howland, T.J., Wei, M.H., Ibegwam, C., Jalali, M., Kalush, F., Karpen, G.H., Ke, Z., Kennison, J.A., Ketchum, K.A., Kimmel, B.E., Kodira, C.D., Kraft, C., Kravitz, S., Kulp, D., Lai, Z., Lasko, P., Lei, Y., Levitsky, A.A., Li, J., Li, Z., Liang, Y., Lin, X., Liu, X., Mattei, B., McIntosh, T.C., McLeod, M.P., McPherson, D., Merkulov, G., Milshina, N.V., Mobarry, C., Morris, J., Moshrefi, A., Mount, S.M., Moy, M., Murphy, B., Murphy, L., Muzny, D.M., Nelson, D.L., Nelson, D.R., Nelson, K.A., Nixon, K., Nusskern, D.R., Pacleb, J.M., Palazzolo, M., Pittman, G.S., Pan, S., Pollard, J., Puri, V., Reese, M.G., Reinert, K., Remington, K., Saunders, R.D., Scheeler, F., Shen, H., Shue, B.C., Siden-Kiamos, I., Simpson, M., Skupski, M.P., Smith, T., Spier, E., Spradling, A.C., Stapleton, M., Strong, R., Sun, E., Svirskas, R., Tector, C., Turner, R., Venter, E., Wang, A.H., Wang, X., Wang, Z.Y., Wassarman, D.A., Weinstock, G.M., Weissenbach, J., Williams, S.M., WoodageT, Worley, K.C., Wu, D., Yang, S., Yao, Q.A., Ye, J., Yeh, R.F., Zaveri, J.S., Zhan, M., Zhang, G., Zhao, Q., Zheng, L., Zheng, X.H., Zhong, F.N., Zhong, W., Zhou, X., Zhu, S., Zhu, X., Smith, H.O., Gibbs, R.A., Myers, E.W., Rubin, G.M., Venter, J.C., 2000. The genome sequence of *Drosophila melanogaster*. Science 287, 2185–2195.
Bellen, H.J., Tong, C., Tsuda, H., 2010. 100 years of *Drosophila* research and its impact on vertebrate neuroscience: a history lesson for the future. Nat. Rev. Neurosci. 11, 514–522.
Bi, J., Xiang, Y., Chen, H., Liu, Z., Gronke, S., Kuhnlein, R.P., Huang, X., 2012. Opposite and redundant roles of the two *Drosophila* perilipins in lipid mobilization. J. Cell Sci. 125, 3568–3577.
Bi, J., Wang, W., Liu, Z., Huang, X., Jiang, Q., Liu, G., Wang, Y., Huang, X., 2014. Seipin promotes adipose tissue fat storage through the ER Ca^{2+}-ATPase SERCA. Cell Metabol. 19, 861–871.
Brennecke, J., Aravin, A.A., Stark, A., Dus, M., Kellis, M., Sachidanandam, R., Hannon, G.J., 2007. Discrete small RNA-generating loci as master regulators of transposon activity in *Drosophila*. Cell 128, 1089–1103.
Buchon, N., Silverman, N., Cherry, S., 2014. Immunity in *Drosophila melanogaster*—from microbial recognition to whole-organism physiology. Nat. Rev. Immunol. 14, 796–810.
Cao, L., Wang, P., Gao, Y., Lin, X., Wang, F., Wu, S., 2014. Ubiquitin E3 ligase dSmurf is essential for Wts protein turnover and Hippo signaling. Biochem. Biophys. Res. Commun. 454, 167–171.
Chen, D., Wu, C., Zhao, S., Geng, Q., Gao, Y., Li, X., Zhang, Y., Wang, Z., 2014. Three RNA binding proteins form a complex to promote differentiation of germline stem cell lineage in *Drosophila*. PLoS Genet. 10, e1004797.
Chen, D., Wang, S., Tao, X., Zhou, L., Wang, J., Sun, F., Sun, M., Gao, X., 2018a. *Hsp83* regulates the fate of germline stem cells in *Drosophila* ovary. J. Genet. Genomics 45, 219–222.
Chen, D.S., Wang, Q., Huang, H.D., Xia, L.X., Jiang, X.Y., Kan, L.J., Sun, Q.M., Chen, D.H., 2009. Effete-mediated degradation of Cyclin A is essential for the maintenance of germline stem cells in *Drosophila*. Development 136, 4133–4142.
Chen, H., Liu, Z., Huang, X., 2010. *Drosophila* models of peroxisomal biogenesis disorder: peroxins are required for spermatogenesis and very-long-chain fatty acid metabolism. Hum. Mol. Genet. 19, 494–505.
Chen, J., Xu, N., Huang, H., Cai, T., Xi, R., 2016. A feedback amplification loop between stem cells and their progeny promotes tissue regeneration and tumorigenesis. eLife 5, pii: e14330.
Chen, J., Xu, N., Wang, C., Huang, P., Huang, H., Jin, Z., Yu, Z., Cai, T., Jiao, R., Xi, R., 2018b. Transient Scute activation via a self-stimulatory loop directs enteroendocine cell pair specification from self-renewing intestinal stem cells. Nat. Cell Biol. 20, 152–161.
Chen, W., Shi, W., Li, L., Zheng, Z., Li, T., Bai, W., Zhao, Z., 2013. Regulation of sleep by the short neuropeptide F (sNPF) in *Drosophila melanogaster*. Insect Biochem. Mol. Biol. 43, 809–819.
Cirelli, C., 2009. The genetic and molecular regulation of sleep: from fruit flies to humans. Nat. Rev. Neurosci. 10, 549–560.

Dai, P., Akimaru, H., Ishii, S., 2003. A hedgehog-responsive region in the *Drosophila* wing disc is defined by debra-mediated ubiquitination and lysosomal degradation of Ci. Dev. Cell 4, 917–928.

Dasgupta, S., Stevens, C.F., Navlakha, S., 2017. A neural algorithm for a fundamental computing problem. Science 358, 793–796.

Ding, L., Lei, Y., Han, Y., Li, Y., Ji, X., Liu, L., 2016. Vimar is a novel regulator of mitochondrial fission through Miro. PLoS Genet. 12, e1006359.

Ding, L., Yang, X., Tian, H., Liang, J., Zhang, F., Wang, G., Wang, Y., Ding, M., Shui, G., Huang, X., 2018. Seipin regulates lipid homeostasis by ensuring calcium-dependent mitochondrial metabolism. EMBO J. 37, e97572.

Du, J., Zhang, J., He, T., Li, Y., Su, Y., Tie, F., Liu, M., Harte, P.J., Zhu, A.J., 2016. Stuxnet facilitates the degradation of polycomb protein during development. Dev. Cell 37, 507–519.

Fan, W., Lam, S.M., Xin, J., Yang, X., Liu, Z., Liu, Y., Wang, Y., Shui, G., Huang, X., 2017. *Drosophila* TRF2 and TAF9 regulate lipid droplet size and phospholipid fatty acid composition. PLoS Genet. 13, e1006664.

Gonzalez, C., 2013. *Drosophila melanogaster*: a model and a tool to investigate malignancy and identify new therapeutics. Nat. Rev. Cancer 13, 172–183.

Gunawardane, L.S., Saito, K., Nishida, K.M., Miyoshi, K., Kawamura, Y., Nagami, T., Siomi, H., Siomi, M.C., 2007. A slicer-mediated mechanism for repeat-associated siRNA 5' end formation in *Drosophila*. Science 315, 1587–1590.

Guo, J., Guo, A., 2005. Crossmodal interactions between olfactory and visual learning in *Drosophila*. Science 309, 307–310.

Guo, T., Lu, Y., Li, P., Yin, M.X., Lv, D., Zhang, W., Wang, H., Zhou, Z., Ji, H., Zhao, Y., Zhang, L., 2013. A novel partner of Scalloped regulates Hippo signaling via antagonizing Scalloped-Yorkie activity. Cell Res. 23, 1201–1214.

Guo, Z., Wang, Z., 2009. The glypican Dally is required in the niche for the maintenance of germline stem cells and short-range BMP signaling in the *Drosophila* ovary. Development 136, 3627–3635.

Han, H., Pan, C., Liu, C., Lv, X., Yang, X., Xiong, Y., Lu, Y., Wu, W., Han, J., Zhou, Z., Jiang, H., Zhang, L., Zhao, Y., 2015. Gut-neuron interaction via Hh signaling regulates intestinal progenitor cell differentiation in *Drosophila*. Cell Discov. 1, 15006.

Haramis, A.P., Begthel, H., van den Born, M., van Es, J., Jonkheer, S., Offerhaus, G.J., Clevers, H., 2004. *De novo* crypt formation and juvenile polyposis on BMP inhibition in mouse intestine. Science 303, 1684–1686.

Hateley, S., Hosamani, R., Bhardwaj, S.R., Pachter, L., Bhattacharya, S., 2016. Transcriptomic response of *Drosophila melanogaster* pupae developed in hypergravity. Genomics 108, 158–167.

Hosamani, R., Leib, R., Bhardwaj, S.R., Adams, C.M., Bhattacharya, S., 2016. Elucidating the "Gravome": quantitative proteomic profiling of the response to chronic hypergravity in *Drosophila*. J. Proteome Res. 15, 4165–4175.

Hu, L., Xu, J., Yin, M.X., Zhang, L., Lu, Y., Wu, W., Xue, Z., Ho, M.S., Gao, G., Zhao, Y., Zhang, L., 2016. Ack promotes tissue growth via phosphorylation and suppression of the Hippo pathway component Expanded. Cell Discov. 2, 15047.

Huang, H., Li, Y., Szulwach, K.E., Zhang, G., Jin, P., Chen, D., 2014. AGO3 Slicer activity regulates mitochondria-nuage localization of Armitage and piRNA amplification. J. Cell Biol. 206, 217–230.

Huang, H.L., Wang, S., Yin, M.X., Dong, L., Wang, C., Wu, W., Lu, Y., Feng, M., Dai, C., Guo, X., Li, L., Zhao, B., Zhou, Z., Ji, H., Jiang, J., Zhao, Y., Liu, X.Y., Zhang, L., 2013a. Par-1 regulates tissue growth by influencing hippo phosphorylation status and hippo-salvador association. PLoS Biol. 11, e1001620.

Huang, S., Zhang, Z., Zhang, C., Lv, X., Zheng, X., Chen, Z., Sun, L., Wang, H., Zhu, Y., Zhang, J., Yang, S., Lu, Y., Sun, Q., Tao, Y., Liu, F., Zhao, Y., Chen, D., 2013b. Activation of Smurf E3 ligase promoted by smoothened regulates hedgehog signaling through targeting patched turnover. PLoS Biol. 11, e1001721.

Huang, Y., Huang, S., Lam, S.M., Liu, Z., Shui, G., Zhang, Y.Q., 2016. Acsl, the *Drosophila* ortholog of intellectual-disability-related ACSL4, inhibits synaptic growth by altered lipids. J. Cell Sci. 129, 4034–4045.

Ji, S.M., Li, C.Y., Hu, L., Liu, K.H., Mei, J., Luo, Y.W., Tao, Y., Xia, Z.P., Sun, Q.M., Chen, D.H., 2017. Bam-dependent deubiquitinase complex can disrupt germline stem cell maintenance by targeting cyclin A. Proc. Natl. Acad. Sci. U. S. A. 114, 6316–6321.

Jiang, F., Lu, F., Li, P., Liu, W., Zhao, L., Wang, Q., Cao, X., Zhang, L., Zhang, Y.Q., 2016. *Drosophila* homolog of FMRP maintains genome integrity by interacting with Piwi. J. Genet. Genomics 43, 11–24.

Jiang, X.Y., Xia, L.X., Chen, D.S., Yang, Y.Y., Huang, H.D., Yang, L.L., Zhao, Q.D., Shen, L.J., Wang, J., Chen, D.H., 2008. Otefin, a nuclear membrane protein, determines the fate of germline stem cells in *Drosophila* via interaction with smad complexes. Dev. Cell 14, 494–506.

Jin, Y., Xu, J., Yin, M.X., Lu, Y., Hu, L., Li, P., Zhang, P., Yuan, Z., Ho, M.S., Ji, H., Zhao, Y., Zhang, L., 2013. Brahma is essential for *Drosophila* intestinal stem cell proliferation and regulated by Hippo signaling. eLife 2, e00999.

Koontz, L.M., Liu-Chittenden, Y., Yin, F., Zheng, Y., Yu, J., Huang, B., Chen, Q., Wu, S., Pan, D., 2013. The Hippo effector Yorkie controls normal tissue growth by antagonizing scalloped-mediated default repression. Dev. Cell 25, 388–401.

Li, B., Wong, C., Gao, S.M., Zhang, R., Sun, R., Li, Y., Song, Y., 2018. The retromer complex safeguards against neural progenitor-derived tumorigenesis by regulating notch receptor trafficking. eLife 7, e38181.

Li, C.Y., Kan, L.J., Chen, Y., Zheng, X.D., Li, W.N., Zhang, W.X., Cao, L., Lin, X.H., Ji, S.M., Huang, S.J., Zhang, G.Q., Liu, X.H., Tao, Y., Wu, S.A., Chen, D.H., 2015a. Ci antagonizes Hippo signaling in the somatic cells of the ovary to drive germline stem cell differentiation. Cell Res. 25, 1152–1170.

Li, J.C., 1927. Development in *DROSOPHILA MELANOGASTER*. Genetics 12, 1–58.

Li, M., Wen, S., Guo, X., Bai, B., Gong, Z., Liu, X., Wang, Y., Zhou, Y., Chen, X., Liu, L.,

Chen, R., 2012. The novel long non-coding RNA *CRG* regulates *Drosophila* locomotor behavior. Nucleic Acids Res. 40, 11714–11727.

Li, Q., Li, Y., Wang, X., Qi, J., Jin, X., Tong, H., Zhou, Z., Zhang, Z.C., Han, J., 2017a. Fbxl4 serves as a clock output molecule that regulates sleep through promotion of rhythmic degradation of the GABAA receptor. Curr. Biol. 27, 3616–3625 e3615.

Li, T., Tian, Y., Li, Q., Chen, H., Lv, H., Xie, W., Han, J., 2015b. The Neurexin/N-Ethylmaleimide-sensitive factor (NSF) interaction regulates short term synaptic depression. J. Biol. Chem. 290, 17656–17667.

Li, W., Yao, A., Zhi, H., Kaur, K., Zhu, Y.C., Jia, M., Zhao, H., Wang, Q., Jin, S., Zhao, G., Xiong, Z.Q., Zhang, Y.Q., 2016. Angelman syndrome protein Ube3a regulates synaptic growth and endocytosis by inhibiting BMP signaling in *Drosophila*. PLoS Genet. 12, e1006062.

Li, W.Q., Li, W.N., Zou, L.H., Ji, S.M., Li, C.Y., Liu, K.H., Zhang, G.Q., Sun, Q.M., Xiao, F., Chen, D.H., 2017b. Membrane targeting of inhibitory Smads through palmitoylation controls TGF-beta/BMP signaling. Proc. Natl. Acad. Sci. U. S. A. 114, 13206–13211.

Li, Y., Zhou, Z., Zhang, X., Tong, H., Li, P., Zhang, Z.C., Jia, Z., Xie, W., Han, J., 2013a. *Drosophila* neuroligin 4 regulates sleep through modulating GABA transmission. J. Neurosci. 33, 15545–15554.

Li, Z., Liu, S., Cai, Y., 2014a. Differential notch activity is required for homeostasis of malpighian tubules in adult *Drosophila*. J. Genet. Genomics 41, 649–652.

Li, Z., Liu, S., Cai, Y., 2015c. EGFR/MAPK signaling regulates the proliferation of *Drosophila* renal and nephric stem cells. J. Genet. Genomics 42, 9–20.

Li, Z., Zhang, Y., Han, L., Shi, L., Lin, X., 2013b. Trachea-derived Dpp controls adult midgut homeostasis in *Drosophila*. Dev. Cell 24, 133–143.

Li, Z., Guo, Y., Han, L., Zhang, Y., Shi, L., Huang, X., Lin, X., 2014b. Debra-mediated Ci degradation controls tissue homeostasis in *Drosophila* adult midgut. Stem Cell Rep. 2, 135–144.

Lin, G., Xu, N., Xi, R., 2008. Paracrine Wingless signalling controls self-renewal of *Drosophila* intestinal stem cells. Nature 455, 1119–1123.

Lin, G., Xu, N., Xi, R., 2010. Paracrine unpaired signaling through the JAK/STAT pathway controls self-renewal and lineage differentiation of *Drosophila* intestinal stem cells. J. Mol. Cell Biol. 2, 37–49.

Liu, C., Bai, X., Sun, J., Zhang, X., Li, Y., 2015. Behavioral switch of food preference upon sugar deficiency is regulated by GPCRs in *Drosophila*. J. Genet. Genomics 42, 409–412.

Liu, K., Shen, D., Shen, J., Gao, S.M., Li, B., Wong, C., Feng, W., Song, Y., 2017a. The super elongation complex drives neural stem cell fate commitment. Dev. Cell 40, 537–551 e536.

Liu, L., Tian, Y., Zhang, X.Y., Zhang, X., Li, T., Xie, W., Han, J., 2017b. Neurexin restricts axonal branching in columns by promoting ephrin clustering. Dev. Cell 41, 94–106 e104.

Liu, M., Li, Y., Liu, A., Li, R., Su, Y., Du, J., Li, C., Zhu, A.J., 2016a. The exon junction complex regulates the splicing of cell polarity gene dlg1 to control Wingless signaling in development. eLife 5, e17200.

Liu, Q., Yang, X., Tian, J., Gao, Z., Wang, M., Li, Y., Guo, A., 2016b. Gap junction networks in mushroom bodies participate in visual learning and memory in *Drosophila*. eLife 5, e13238.

Liu, S., Li, K., Gao, Y., Liu, X., Chen, W., Ge, W., Feng, Q., Palli, S.R., Li, S., 2018. Antagonistic actions of juvenile hormone and 20-hydroxyecdysone within the ring gland determine developmental transitions in *Drosophila*. Proc. Natl. Acad. Sci. U. S. A. 115, 139–144.

Liu, T.Q., Wang, Q., Li, W.Q., Mao, F.Y., Yue, S.S., Liu, S., Liu, X.N., Xiao, S., Xia, L.X., 2017c. Gcn5 determines the fate of *Drosophila* germline stem cells through degradation of Cyclin A. FASEB J. 31, 2185–2194.

Liu, W., Jiang, F., Bi, X., Zhang, Y.Q., 2012. *Drosophila* FMRP participates in the DNA damage response by regulating G2/M cell cycle checkpoint and apoptosis. Hum. Mol. Genet. 21, 4655–4668.

Liu, Y., Wang, W., Shui, G., Huang, X., 2014a. CDP-diacylglycerol synthetase coordinates cell growth and fat storage through phosphatidylinositol metabolism and the insulin pathway. PLoS Genet. 10, e1004172.

Liu, Z., Huang, Y., Hu, W., Huang, S., Wang, Q., Han, J., Zhang, Y.Q., 2014b. dAcsl, the *Drosophila* ortholog of acyl-CoA synthetase long-chain family member 3 and 4, inhibits synapse growth by attenuating bone morphogenetic protein signaling via endocytic recycling. J. Neurosci. 34, 2785–2796.

Lv, X., Pan, C., Zhang, Z., Xia, Y., Chen, H., Zhang, S., Guo, T., Han, H., Song, H., Zhang, L., Zhao, Y., 2016. SUMO regulates somatic cyst stem cell maintenance and directly targets the Hedgehog pathway in adult *Drosophila* testis. Development 143, 1655–1662.

Ma, B., Chen, Y., Chen, L., Cheng, H., Mu, C., Li, J., Gao, R., Zhou, C., Cao, L., Liu, J., Zhu, Y., Chen, Q., Wu, S., 2015a. Hypoxia regulates Hippo signalling through the SIAH2 ubiquitin E3 ligase. Nat. Cell Biol. 17, 95–103.

Ma, M., Zhao, H., Zhao, H., Binari, R., Perrimon, N., Li, Z., 2016. Wildtype adult stem cells, unlike tumor cells, are resistant to cellular damages in *Drosophila*. Dev. Biol. 411, 207–216.

Ma, X., Huang, J., Tian, Y., Chen, Y., Yang, Y., Zhang, X., Zhang, F., Xue, L., 2017. Myc suppresses tumor invasion and cell migration by inhibiting JNK signaling. Oncogene 36, 3159–3167.

Ma, X., Guo, X., Richardson, H.E., Xu, T., Xue, L., 2018. POSH regulates Hippo signaling through ubiquitin-mediated expanded degradation. Proc. Natl. Acad. Sci. U. S. A. 115, 2150–2155.

Ma, X., Chen, Y., Xu, W., Wu, N., Li, M., Cao, Y., Wu, S., Li, Q., Xue, L., 2015b. Impaired Hippo signaling promotes Rho1-JNK-dependent growth. Proc. Natl. Acad. Sci. U. S. A. 112, 1065–1070.

Ma, Z., Liu, Z., Huang, X., 2010. OSBP- and FAN-mediated sterol requirement for

spermatogenesis in *Drosophila*. Development 137, 3775—3784.

Park, M., Wu, X., Golden, K., Axelrod, J.D., Bodmer, R., 1996. The wingless signaling pathway is directly involved in *Drosophila* heart development. Dev. Biol. 177, 104—116.

Qian, Y., Cao, Y., Deng, B., Yang, G., Li, J., Xu, R., Zhang, D., Huang, J., Rao, Y., 2017. Sleep homeostasis regulated by 5HT2b receptor in a small subset of neurons in the dorsal fan-shaped body of *Drosophila*. eLife 6, e26519.

Reiter, L.T., Potocki, L., Chien, S., Gribskov, M., Bier, E., 2001. A systematic analysis of human disease-associated gene sequences in *Drosophila melanogaster*. Genome Res. 11, 1114—1125.

Ren, Q., Li, H., Wu, Y., Ren, J., Guo, A., 2012. A GABAergic inhibitory neural circuit regulates visual reversal learning in *Drosophila*. J. Neurosci. 32, 11524—11538.

Ren, W., Zhang, Y., Li, M., Wu, L., Wang, G., Baeg, G.-H., You, J., Li, Z., Lin, X., 2015. Windpipe controls *Drosophila* intestinal homeostasis by regulating JAK/STAT pathway via promoting receptor endocytosis and lysosomal degradation. PLoS Genet. 11, e1005180.

Rui, M., Qian, J., Liu, L., Cai, Y., Lv, H., Han, J., Jia, Z., Xie, W., 2017. The neuronal protein Neurexin directly interacts with the Scribble-Pix complex to stimulate F-actin assembly for synaptic vesicle clustering. J. Biol. Chem. 292, 14334—14348.

Shan, L., Wu, C., Chen, D., Hou, L., Li, X., Wang, L., Chu, X., Hou, Y., Wang, Z., 2017. Regulators of alternative polyadenylation operate at the transition from mitosis to meiosis. J. Genet. Genomics 44, 95—106.

Shen, J., Lu, J., Sui, L., Wang, D., Yin, M., Hoffmann, I., Legler, A., Pflugfelder, G.O., 2014. The orthologous Tbx transcription factors Omb and TBX2 induce epithelial cell migration and extrusion *in vivo* without involvement of matrix metalloproteinases. Oncotarget 5, 11998—12015.

Su, Y., Ospina, J.K., Zhang, J., Michelson, A.P., Schoen, A.M., Zhu, A.J., 2011. Sequential phosphorylation of smoothened transduces graded hedgehog signaling. Sci. Signal. 4 ra43.

Sun, J., Liu, C., Bai, X., Li, X., Li, J., Zhang, Z., Zhang, Y., Guo, A., Li, Y., 2017. *Drosophila* FIT is a protein-specific satiety hormone essential for feeding control. Nat. Commun. 8, 14161.

Sun, J., Wei, H.M., Xu, J., Chang, J.F., Yang, Z., Ren, X., Lv, W.W., Liu, L.P., Pan, L.X., Wang, X., Qiao, H.H., Zhu, B., Ji, J.Y., Yan, D., Xie, T., Sun, F.L., Ni, J.Q., 2015. Histone H1-mediated epigenetic regulation controls germline stem cell self-renewal by modulating H4K16 acetylation. Nat. Commun. 6, 8856.

Sun, M., Xing, G., Yuan, L., Gan, G., Knight, D., With, S.I., He, C., Han, J., Zeng, X., Fang, M., 2011. Neuroligin 2 is required for synapse development and function at the *Drosophila* neuromuscular junction. J. Neurosci. 31, 687—699.

Sun, P., Quan, Z.H., Zhang, B.D., Wu, T.Q., Xi, R.W., 2010. TSC1/2 tumour suppressor complex maintains *Drosophila* germline stem cells by preventing differentiation. Development 137, 2461—2469.

Tan, C., 1942. The nature of the race-differential chromosomes in *Drosophila montium* De Meijere. Sci. Rec. 178—187.

Tan, C.C., 1946. Mosaic dominance in the inheritance of color patterns in the lady-bird beetle, *Harmonia axyridis*. Genetics 31, 195—210.

Tang, M., Yuan, W., Fan, X., Liu, M., Bodmer, R., Ocorr, K., Wu, X., 2013. Pygopus maintains heart function in aging *Drosophila* independently of canonical Wnt signaling. Circ. Cardiovasc. Genet. 6, 472—480.

Tang, S., Guo, A., 2001. Choice behavior of *Drosophila* facing contradictory visual cues. Science 294, 1543—1547.

Tang, W., Wang, D., Shen, J., 2016. Asymmetric distribution of Spalt in *Drosophila* wing squamous and columnar epithelia ensures correct cell morphogenesis. Sci. Rep. 6, 30236.

Tian, Y., Bi, J., Shui, G., Liu, Z., Xiang, Y., Liu, Y., Wenk, M.R., Yang, H., Huang, X., 2011. Tissue-autonomous function of *Drosophila* seipin in preventing ectopic lipid droplet formation. PLoS Genet. 7, e1001364.

Tian, Y., Li, T., Sun, M., Wan, D., Li, Q., Li, P., Zhang, Z.C., Han, J., Xie, W., 2013. Neurexin regulates visual function via mediating retinoid transport to promote rhodopsin maturation. Neuron 77, 311—322.

Wang, C., Guo, X., Dou, K., Chen, H., Xi, R., 2015a. Ttk69 acts as a master repressor of enteroendocrine cell specification in *Drosophila* intestinal stem cell lineages. Development 142, 3321—3331.

Wang, C., Zhao, R., Huang, P., Yang, F., Quan, Z., Xu, N., Xi, R., 2013. APC loss-induced intestinal tumorigenesis in *Drosophila*: roles of Ras in Wnt signaling activation and tumor progression. Dev. Biol. 378, 122—140.

Wang, C., Zhang, W., Yin, M.X., Hu, L., Li, P., Xu, J., Huang, H., Wang, S., Lu, Y., Wu, W., Ho, M.S., Li, L., Zhao, Y., Zhang, L., 2015b. Suppressor of Deltex mediates Pez degradation and modulates *Drosophila* midgut homeostasis. Nat. Commun. 6, 6607.

Wang, D., Li, J., Liu, S., Zhou, H., Zhang, L., Shi, W., Shen, J., 2017. Spalt is functionally conserved in *Locusta* and *Drosophila* to promote wing growth. Sci. Rep. 7, 44393.

Wen, D., Rivera-Perez, C., Abdou, M., Jia, Q., He, Q., Liu, X., Zyaan, O., Xu, J., Bendena, W.G., Tobe, S.S., Noriega, F.G., Palli, S.R., Wang, J., Li, S., 2015. Methyl farnesoate plays a dual role in regulating *Drosophila metamorphosis*. PLoS Genet. 11, e1005038.

Wen, K., Yang, L., Xiong, T., Di, C., Ma, D., Wu, M., Xue, Z., Zhang, X., Long, L., Zhang, W., Zhang, J., Bi, X., Dai, J., Zhang, Q., Lu, Z.J., Gao, G., 2016. Critical roles of long noncoding RNAs in *Drosophila* spermatogenesis. Genome Res. 26, 1233—1244.

Wion, D., Casadesus, J., 2006. N6-methyl-adenine: an epigenetic signal for DNA-protein interactions. Nat. Rev. Microbiol. 4, 183—192.

Wu, B., Ma, L., Zhang, E., Du, J., Liu, S., Price, J., Li, S., Zhao, Z., 2018. Sexual dimorphism of sleep regulated by juvenile hormone signaling in *Drosophila*. PLoS

Genet. 14, e1007318.

Wu, C., Chen, Y., Wang, F., Chen, C., Zhang, S., Li, C., Li, W., Wu, S., Xue, L., 2015. Pelle modulates dFoxO-mediated cell death in *Drosophila*. PLoS Genet. 11, e1005589.

Wu, H., Sun, L., Wen, Y., Liu, Y., Yu, J., Mao, F., Wang, Y., Tong, C., Guo, X., Hu, Z., Sha, J., Liu, M., Xia, L., 2016. Major spliceosome defects cause male infertility and are associated with nonobstructive azoospermia in humans. Proc. Natl. Acad. Sci. U. S. A. 113, 4134—4139.

Wu, X., 2010. Wg signaling in *Drosophila* heart development as a pioneering model. J. Genet. Genomics 37, 593—603.

Wu, X., Golden, K., Bodmer, R., 1995. Heart development in *Drosophila* requires the segment polarity gene *wingless*. Dev. Biol. 169, 619—628.

Wu, Y., Ren, Q., Li, H., Guo, A., 2012. The GABAergic anterior paired lateral neurons facilitate olfactory reversal learning in *Drosophila*. Learn. MEM 19, 478—486.

Xia, L., Zheng, X., Zheng, W., Zhang, G., Wang, H., Tao, Y., Chen, D., 2012. The niche-dependent feedback loop generates a BMP activity gradient to determine the germline stem cell fate. Curr. Biol. 22, 515—521.

Xia, L., Jia, S., Huang, S., Wang, H., Zhu, Y., Mu, Y., Kan, L., Zheng, W., Wu, D., Li, X., Sun, Q., Meng, A., Chen, D., 2010. The Fused/Smurf complex controls the fate of *Drosophila* germline stem cells by generating a gradient BMP response. Cell 143, 978—990.

Xiao, G., Wan, Z., Fan, Q., Tang, X., Zhou, B., 2014. The metal transporter ZIP13 supplies iron into the secretory pathway in *Drosophila melanogaster*. eLife 3, e03191.

Xiong, Y., Liu, C., Zhao, Y., 2015. Decoding Ci: from partial degradation to inhibition. Dev. Growth Differ. 57, 98—108.

Xu, K., Liu, X., Wang, Y., Wong, C., Song, Y., 2018. Temporospatial induction of homeodomain gene cut dictates natural lineage reprogramming. eLife 7, e33934.

Xu, N., Wang, S.Q., Tan, D., Gao, Y., Lin, G., Xi, R., 2011. EGFR, Wingless and JAK/STAT signaling cooperatively maintain *Drosophila* intestinal stem cells. Dev. Biol. 354, 31—43.

Yan, Y., Wang, H., Hu, M., Jiang, L., Wang, Y., Liu, P., Liang, X., Liu, J., Li, C., Lindstrom-Battle, A., Lam, S.M., Shui, G., Deng, W.M., Jiao, R., 2017. HDAC6 suppresses age-dependent ectopic fat accumulation by maintaining the proteostasis of PLIN2 in *Drosophila*. Dev. Cell 43, 99—111 e115.

Yang, F., Zhao, R., Fang, X., Huang, H., Xuan, Y., Ma, Y., Chen, H., Cai, T., Qi, Y., Xi, R., 2015. The RNA surveillance complex Pelo-Hbs1 is required for transposon silencing in the *Drosophila* germline. EMBO Rep. 16, 965—974.

Yang, L.L., Chen, D.S., Duan, R.H., Xia, L.X., Wang, J., Qurashi, A., Jin, P., Chen, D.H., 2007. Argonaute 1 regulates the fate of germline stem cells in *Drosophila*. Development 134, 4265—4272.

Yang, Y.Y., Xu, S.L., Xia, L.X., Wang, J., Wen, S.M., Jin, P., Chen, D.H., 2009. The Bantam microRNA is associated with *Drosophila* fragile X mental retardation protein and regulates the fate of germline stem cells. PLoS Genet. 5, e1000444.

Yao, A., Jin, S., Li, X., Liu, Z., Ma, X., Tang, J., Zhang, Y.Q., 2011. *Drosophila* FMRP regulates microtubule network formation and axonal transport of mitochondria. Hum. Mol. Genet. 20, 51—63.

Yi, W., Zhang, Y., Tian, Y., Guo, J., Li, Y., Guo, A., 2013. A subset of cholinergic mushroom body neurons requires Go signaling to regulate sleep in *Drosophila*. Sleep 36, 1809—1821.

Yu, J., Lan, X., Chen, X., Yu, C., Xu, Y., Liu, Y., Xu, L., Fan, H.Y., Tong, C., 2016. Protein synthesis and degradation are essential to regulate germline stem cell homeostasis in *Drosophila* testes. Development 143, 2930—2945.

Zeng, X., Sun, M., Liu, L., Chen, F., Wei, L., Xie, W., 2007. Neurexin-1 is required for synapse formation and larvae associative learning in *Drosophila*. FEBS Lett. 581, 2509—2516.

Zhang, G., Huang, H., Liu, D., Cheng, Y., Liu, X., Zhang, W., Yin, R., Zhang, D., Zhang, P., Liu, J., Li, C., Liu, B., Luo, Y., Zhu, Y., Zhang, N., He, S., He, C., Wang, H., Chen, D., 2015. N6-methyladenine DNA modification in *Drosophila*. Cell 161, 893—906.

Zhang, J., Du, J., Lei, C., Liu, M., Zhu, A.J., 2014. Ubpy controls the stability of the ESCRT-0 subunit Hrs in development. Development 141, 1473—1479.

Zhang, K., Guo, J.Z., Peng, Y., Xi, W., Guo, A., 2007. Dopamine-mushroom body circuit regulates saliency-based decision-making in *Drosophila*. Science 316, 1901—1904.

Zhang, X., Ren, Q., Guo, A., 2013a. Parallel pathways for cross-modal memory retrieval in *Drosophila*. J. Neurosci. 33, 8784—8793.

Zhang, X., Luo, D., Pflugfelder, G.O., Shen, J., 2013b. Dpp signaling inhibits proliferation in the *Drosophila* wing by Omb-dependent regional control of bantam. Development 140, 2917—2922.

Zhang, Y., Chen, D., Wang, Z., 2009. Analyses of mental dysfunction-related ACSl4 in *Drosophila* reveal its requirement for Dpp/BMP production and visual wiring in the brain. Hum. Mol. Genet. 18, 3894—3905.

Zhang, Y., Guo, J., Guo, A., Li, Y., 2016. Nicotine-induced acute hyperactivity is mediated by dopaminergic system in a sexually dimorphic manner. Neuroscience 332, 149—159.

Zhang, Z., Li, X., Guo, J., Li, Y., Guo, A., 2013c. Two clusters of GABAergic ellipsoid body neurons modulate olfactory labile memory in *Drosophila*. J. Neurosci. 33, 5175—5181.

Zhang, Z., Feng, J., Pan, C., Lv, X., Wu, W., Zhou, Z., Liu, F., Zhang, L., Zhao, Y., 2013d. Atrophin-Rpd3 complex represses Hedgehog signaling by acting as a corepressor of CiR. J. Cell Biol. 203, 575—583.

Zhang, Z., Lv, X., Yin, W.C., Zhang, X., Feng, J., Wu, W., Hui, C.C., Zhang, L., Zhao, Y., 2013e. Ter94 ATPase complex targets k11-linked ubiquitinated ci to proteasomes for partial degradation. Dev. Cell 25, 636—644.

Zhao, R., Xuan, Y., Li, X.H., Xi, R.W., 2008. Age-related changes of germline stem cell

activity, niche signaling activity and egg production in *Drosophila*. Aging Cell 7, 344—354.

Zhao, S., Chen, D., Geng, Q., Wang, Z., 2013. The highly conserved LAMMER/CLK2 protein kinases prevent germ cell overproliferation in *Drosophila*. Dev. Biol. 376, 163—170.

Zheng, Z., Lauritzen, J.S., Perlman, E., Robinson, C.G., Nichols, M., Milkie, D., Torrens, O., Price, J., Fisher, C.B., Sharifi, N., Calle-Schuler, S.A., Kmecova, L., Ali, I.J., Karsh, B., Trautman, E.T., Bogovic, J.A., Hanslovsky, P., Jefferis, G., Kazhdan, M., Khairy, K., Saalfeld, S., Fetter, R.D., Bock, D.D., 2018. A complete electron microscopy volume of the brain of adult *Drosophila melanogaster*. Cell 174, 730—743.

Zhou, C., Rao, Y., Rao, Y., 2008. A subset of octopaminergic neurons are important for *Drosophila* aggression. Nat. Neurosci. 11, 1059—1067.

Zhou, C., Huang, H., Kim, S.M., Lin, H., Meng, X., Han, K.A., Chiang, A.S., Wang, J.W., Jiao, R., Rao, Y., 2012. Molecular genetic analysis of sexual rejection: roles of octopamine and its receptor OAMB in *Drosophila* courtship conditioning. J. Neurosci. 32, 14281—14287.

Zhou, Z., Yao, X., Li, S., Xiong, Y., Dong, X., Zhao, Y., Jiang, J., Zhang, Q., 2015. Deubiquitination of Ci/Gli by Usp7/HAUSP regulates Hedgehog signaling. Dev. Cell 34, 58—72.