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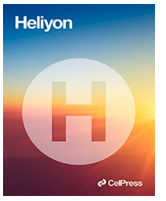

Review article

Decoding the connection between lncRNA and obesity: Perspective from humans and *Drosophila*

Dau Dayal Aggarwal [a,*], Prachi Mishra [a], Gaurav Yadav [a], Shrishti Mitra [a], Yashvant Patel [b], Manvender Singh [c], Ranjan Kumar Sahu [d], Vijendra Sharma [e]

[a] *Department of Biochemistry, University of Delhi South Campus, New Delhi, India*
[b] *Department of Zoology, Banaras Hindu University, Varanasi, India*
[c] *Department of Biotechnology, UIET, MD University, Rohtak, India*
[d] *Department of Neurology, Houston Methodist Research Insititute, Houston, Tx, USA*
[e] *Department of Biomedical Sciences, University of Windsor, Ontario, Canada*

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ABSTRACT

Background: Obesity is a burgeoning global health problem with an escalating prevalence and severe implications for public health. New evidence indicates that long non-coding RNAs (lncRNAs) may play a pivotal role in regulating adipose tissue function and energy homeostasis across various species. However, the molecular mechanisms underlying obesity remain elusive.
Scope of review: This review discusses obesity and fat metabolism in general, highlighting the emerging importance of lncRNAs in modulating adipogenesis. It describes the regulatory networks, latest tools, techniques, and approaches to enhance our understanding of obesity and its lncRNA-mediated epigenetic regulation in humans and *Drosophila*.
Major conclusions: This review analyses large datasets of human and *Drosophila* lncRNAs from published databases and literature with experimental evidence supporting lncRNAs role in fat metabolism. It concludes that lncRNAs play a crucial role in obesity-related metabolism. Cross-species comparisons highlight the relevance of *Drosophila* findings to human obesity, emphasizing their potential role in adipose tissue biology. Furthermore, it discusses how recent technological advancements and multi-omics data integration enhance our capacity to characterize lncRNAs and their function. Additionally, this review briefly touches upon innovative methodologies like experimental evolution and advanced sequencing technologies for identifying novel genes and lncRNA regulators in *Drosophila*, which can potentially contribute to obesity research.

1. Brief overview of obesity as a global issue

Over the past few decades, the rates of obesity have increased at an alarming pace, affecting individuals of all ages and socio-economic spectrums [1–3]. According to the World Health Organization (WHO), in 2016, >2 billion adults were overweight; of these, >650 million were obese [4]. This escalating prevalence is concerning due to the associated health risks and the burden it places on healthcare systems. Obesity not only elevates the susceptibility to chronic conditions like diabetes [5], cardiovascular conditions [6], and specific forms of cancer [7] but also diminishes life quality and heightens mortality rates [8,9].

* Corresponding author.
E-mail address: daudayal@south.du.ac.in (D. Dayal Aggarwal).

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New evidence infers that lncRNAs participate in various biological processes, such as gene regulation, epigenetic modification, energy metabolism, and adipose tissue biology [10,11]. Despite their role in diverse biological processes, many lncRNAs still need to be characterized. One of the challenges in the study of long non-coding RNAs (lncRNAs) is discerning their functional significance and conservation across diverse species. Compared to humans, *Drosophila*, a common proxy model for human obesity, has a simpler genome, with about 14,000 protein-coding genes and around 2500 lncRNAs. This simplicity facilitates the characterization and understanding of lncRNA functions in *Drosophila*. lncRNAs play roles in various aspects of fly biology, including embryo development, neural networking, gonadal function, and stress resistance [12]. Some of the mechanisms and functions of lncRNAs in *Drosophila* are conserved in humans.

This review discusses the genetic framework of obesity and explores the functions of lncRNAs related to obesity and related metabolism in humans and *Drosophila*, identifying adipogenesis-linked lncRNAs through a comprehensive search. We explored diet-induced obesity in *Drosophila* and highlighted the genetic tools that are potentially advantageous to work with *Drosophila* system. We have also discussed cutting-edge tools and techniques for characterizing lncRNAs and their functions in both *Drosophila* and

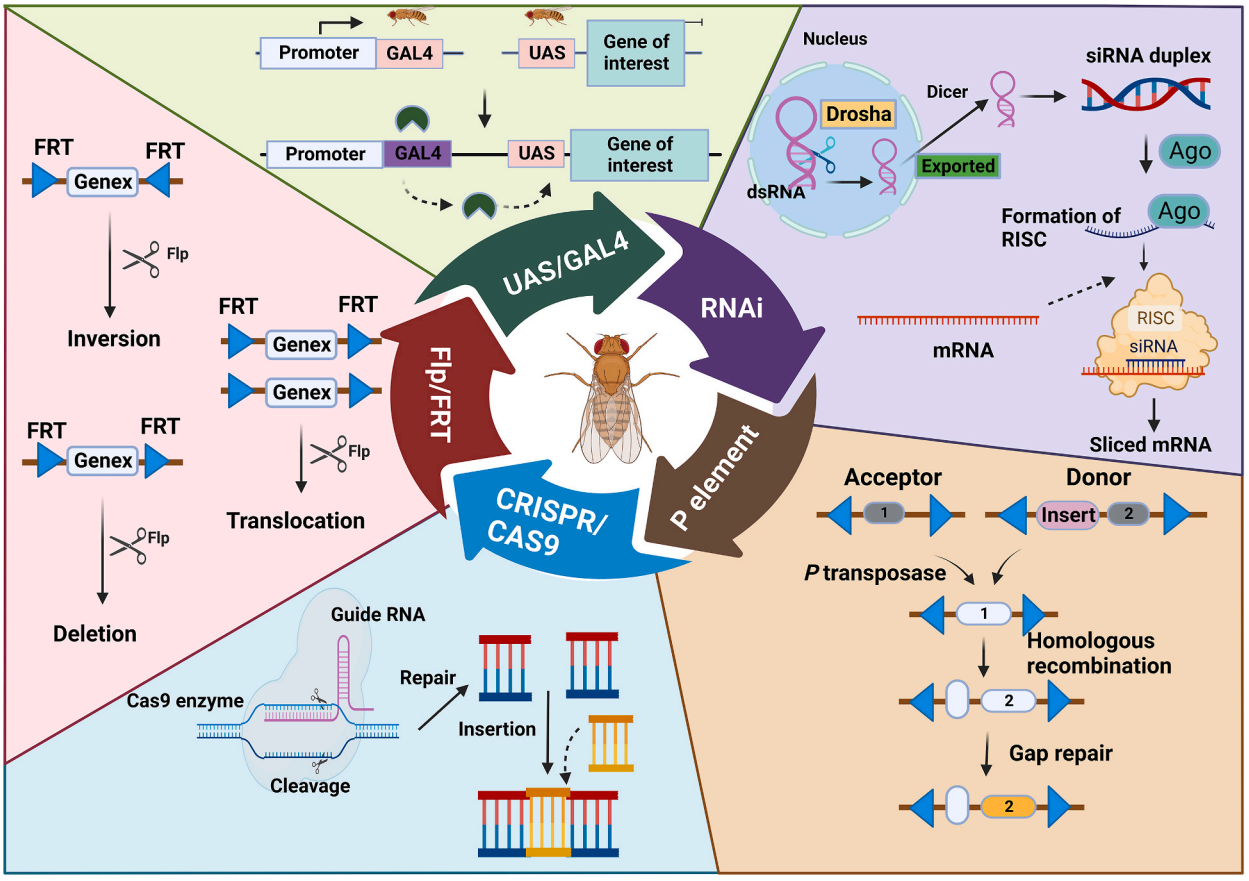

Fig. 1. *Drosophila* as a genetic tool box

ShRNA - The processing of siRNA and shRNA to facilitate gene knockdown is depicted in a simplified graphic.Transduced shRNA moves from the nucleus to the cytoplasm through Dicer to create a siRNA-like molecule that resembles transfected siRNA. Once associated with the RISC complex, this siRNA initiates the degradation of target mRNA.

RNAi - Initially, long dsRNA undergoes processing by Drosha in the nucleus. This results in the production of short dsRNA, which is then exported to the cytoplasm. Once there, it binds with Dicer and is cleaved into small fragments known as siRNA. These siRNA fragments associate with the RISC complex and Ago proteins, leading to mRNA degradation.

Flp/FRT - The Flp/FRT method enables DNA manipulation in living organisms through site-directed recombination. Induced FLP recombinase protein recognizes the FRT sites and excises the DNA region between these two FRT recognition sites.

CRISPR/Cas9 - The CRISPR-Cas9 genome editing technique utilizes the natural DNA-snipping enzyme Cas9, which is found in bacteria. This technique allows for targeting and modification of specific genes.

GAL4/UAS system - This is utilized for the targeted expression of specific genes. In this system, flies are engineered to carry two distinct transgenes. The first transgene expresses Gal4, a transcriptional activator protein, under the control of a tissue-specific enhancer. The second transgene harbors the Gal4 DNA binding sequence, known as the Upstream Activating Sequence (UAS), positioned adjacent to the target gene (Gene X). Through this arrangement, flies exhibit the expression of the gene of interest, "Gene X," in a tissue-specific manner. The combination of these transgenes is typically achieved through the mating of parental flies, each carrying one transgene, and selecting F1 offspring that inherit both transgenes.

humans. Additionally, we address innovative experimental evolution and re-sequencing strategies for dissecting obesity-related genes and lncRNAs, particularly within the fly model system. In brief, this review offers a comprehensive understanding of lncRNA functions in obesity-related metabolism in humans and *Drosophila*, emphasizing the advantages and limitations of employing *Drosophila* in obesity research.

2. Multifactorial nature of common obesity

The subject of obesity genetics in humans is complex. Monogenic obesity results from single gene mutations following a Mendelian pattern, representing a rare yet severe form of obesity that often emerges early in life. The key genes linked to monogenic obesity and body mass index (BMI) changes include Leptin [13], Leptin receptor [14], melanocortin-4-receptor [15,16], pro-opiomelanocortin [17], Brain-derived neurotrophic factor [18], and Neurotrophic Receptor Tyrosine Kinase 2 [19]. On the other hand, polygenic obesity, also referred to as common obesity, arises from the combined influence of multiple genetic variants, each exerting a modest effect [20,21]. Noteworthy variants like those in genes *fto, mc4r, insig2* [22], and others contribute to shaping susceptibility to obesity, spanning genes linked to appetite regulation, fat storage, and energy expenditure. The recent investigations uncovered over 1100 independent loci linked to obesity in humans [23]. Nevertheless, a limitation emerges as only a few of these loci exhibit sustained replication within genome-wide association studies [24]. This constraint is linked to the significant diversity inherent in human populations, compounded by the effects of interaction with environmental factors. To overcome these challenges, it is imperative to use the proxy models for human obesity. These models should emulate the intricate nature of human obesity and its interconnected complexities, empowering researchers to reveal genomic drivers of obesity. Furthermore, studying genetics and epigenetics improves our understanding of the causes and course of obesity. Epigenetic control, through DNA methylation, histone modifications, and lncRNAs, significantly affects obesity susceptibility. This regulatory symphony shapes adipogenesis, appetite regulation, and metabolic homeostasis.

3. *Drosophila* genetic toolbox: advancing obesity research

Drosophila (fruit fly), has emerged as a highly advantageous model organism for investigating mechanisms of complex human traits, including obesity. Several vital factors support the use of *Drosophila* in obesity research.

1. *Drosophila* shares a substantial genetic similarity with humans, with approximately 70 % of its genes having homologs in humans. This genetic conservation provides a simplified and manageable system for exploring the molecular underpinnings of obesity.
2. *Drosophila* possesses a well-annotated genome that can be easily manipulated, allowing for precise genetic modifications and targeted investigations of specific genes and pathways implicated in obesity.
3. The rapid reproductive cycle and short lifespan of *Drosophila* offer favorable conditions for cost-effective experiments, enabling multi-generational studies and extensive genetic screens.

Drosophila has conserved metabolic and physiological pathways crucial for energy balance, lipid metabolism, and hunger regulation. Grasping these pathways is key to insights into obesity's development and progression. Studying flies also offers a range of versatile genetic manipulation tools, enabling the efficient exploration of gene function and the underlying genetic components of traits and diseases (see illustrations in Fig. 1). For example, GAL4/UAS (bipartite system) enables targeted gene expression, allowing researchers to precisely control when and where a gene of interest is expressed [25,26]. RNA interference (RNAi) permits gene suppression, which enables the investigation of gene function by reducing the expression of particular target genes [27,28]. Further, *P-element* transposon system allows for random transgenic insertions and facilitates the scanning of novel genes involved in specific processes [29]. The CRISPR/Cas9 system facilitates accurate editing of the genome, hence permitting targeted introduction of desired mutations or alterations in the *Drosophila* genome [30,31]. The Flp/FRT system enables site-specific recombination, facilitating the excision or integration of particular DNA sequences [32,33]. Short hairpin RNA (shRNA) can be used for silencing gene expression, providing long-term and stable knockdown of a target gene [34]. The UAS/GAL4 system allows for gene overexpression, enabling the study of gene function by increasing the expression of specific target genes. Homologous recombination provides for precise genetic modifications, facilitating the introduction of specific changes in the *Drosophila* genome [35]. Further, optogenetics enables the control of neuronal activity using light-sensitive proteins, allowing to uncover the role of specific neurons in behavior and physiology [36]. These genetic manipulation tools make *Drosophila* a powerful model organism for dissecting the genetic basis of traits and diseases.

4. Diet-induced obesity in *Drosophila*

Numerous studies on *Drosophila* have investigated molecular underpinnings of obesity and metabolic disorders induced by high-calorie diets. For examples, flies fed a high-sugar diet exhibited increased body weight [37], elevated lipid levels [38], and reduced insulin sensitivity compared to those on a standard diet [26]. This sugar diet-induced obesity was accompanied by dysregulation of lipid metabolism and insulin signaling pathways. Moreover, flies fed a high-fat diet demonstrated enhanced triglyceride accumulation and altered metabolic gene expression profiles. The high-fat diet also induced insulin resistance and impaired glucose tolerance in the flies [27]. Similarly, high-fructose diet fed flies exhibited increased body weight, lower levels of circulating glucose and increased concentrations of carbohydrates, lipids, and uric acid compared to control flies [39]. Additionally, flies exposed to intermediate temperatures between 15 °C and 27 °C displayed heightened lipid content, with glycogen stores following a similar trend [40]. In a

study, Zhang et al. [41] utilized the RNAi knockdown of *dSec16* in the fly's insulin-like peptide-producing cells (IPCs), resulting in obesity-like phenotypes. *dSec16* knockdown flies exhibited higher food intake, no changes in body weight, and elevated lipid levels, mirroring characteristics associated with obesity. These studies suggest that high-calorie diets, including high-sugar, high-fat, high-protein, and high-fructose components, along with environmental factors, can induce obesity-like phenotypes in *Drosophila*. *Drosophila* model of diet-induced obesity mirrors critical features of human obesity, such as elevated body weight, poor glucose tolerance, insulin resistance, and altered lipid metabolism.

5. Comparative organ involvement in fat metabolism: humans and *Drosophila*

Humans and *Drosophila* share a series of events occurring in various organs for fat metabolism (Table 1). For instance, adipose tissue is a storage site for triglycerides, which undergo lipolysis, breaking down into free fatty acids in humans. In the fly system, fat bodies are the analogs in the function of adipose tissue, i.e., storing triglycerides that are also subjected to lipolysis [42,43]. In lipolysis, particular enzymes, like hormone-sensitive lipase in humans [44] and Brummer lipase in *Drosophila* [45], are engaged to break down stored fats, leading to the liberation of unbound fatty acids**.** Subsequently, these liberated fatty acids are conveyed to other organs to be utilized for energy production. These free fatty acids are then transported to other organs for energy utilization. In humans, skeletal muscles play a crucial role in fatty acid oxidation. Fatty acids are transported into the muscle cells, where they undergo β-oxidation, a process involving the coordinated action of several enzymes, including carnitine palmitoyltransferase I (CPT-I) and acyl-CoA dehydrogenase [46].

Similarly, flight muscles participate in fatty acid oxidation, breaking down fatty acids into acetyl-CoA through a process analogous to β-oxidation in *Drosophila* [47]. This generates energy for muscle contraction and other metabolic activities. In humans, the liver plays a crucial role in the metabolism of fatty acids, participating in β-oxidation (further breakdown of fats) and the synthesis of ketone bodies [48]. Enzymes such as acetyl-CoA carboxylase, fatty acyl-CoA synthetase, and HMG-CoA synthase are involved in these processes. Similarly, in *Drosophila*, fat bodies [49] and the equivalent liver-like [50] functions metabolize fatty acids, generating energy and intermediates for various metabolic pathways. Both in humans and *Drosophila*, the brain significantly regulates fat metabolism, playing a pivotal role in governing feeding behavior and energy balance through hormonal and nutrient signals.

Hormones like leptin and insulin are vital in this regulation in humans. Similarly, although the specific hormones involved have not been extensively studied in *Drosophila*, evidence suggests neuropeptides like Neuropeptide F (NPF), Diuretic hormone 44 (DH44), and Adipokinetic hormone (AKH, released from corpora cardiaca (CC) a pair of neurosecretory cells in the brain) play roles in these processes. NPF is thought to regulate feeding behavior and energy balance based on nutrient availability [51], while DH44 is involved in water and ion balance regulation, potentially influencing nutrient sensing and energy balance. AKH acts similarly to vertebrate glucagon, releasing energy stores, especially lipids, from the fat body to provide energy during increased activity and stress periods [52]. In humans, pancreas secretes insulin and glucagon hormones to control energy metabolism, whereas the gut is involved in nutrient absorption and metabolism. Adipocytes store fats and make hormones like adiponectin and leptin that affect metabolic processes. However, the equivalent of *Drosophila*'s pancreas is fat bodies, that store fat and regulate metabolism, while the gut tissues absorb and metabolize nutrients. In *Drosophila*, the CC analog of the pancreas in humans controls energy metabolism, while the gut is responsible for nutrition absorption and metabolic processing [52]. Adipocytes in *Drosophila* store fat and create hormones like adiponectin that affect the organism's metabolic functions. Although there are variations in complexity and scale, the underlying principles governing fat metabolism and energy management remain the same throughout different species.

6. Fat digestion and mobilization in humans and *Drosophila*

In humans, the digestion of dietary fats, also known as triacylglycerols (TAGs), occurs within the gut lumen, facilitated by lipases and bile salts. These enzymes break down TAGs, leading to the absorption of monoglycerides (MAG) and free fatty acids (FAs) across the epithelium [53,54]. Following absorption, the MAGs and FAs are reconverted into TAGs. The resulting TAG molecules are subsequently enveloped within lipoprotein particles and released into the bloodstream for circulation. If these TAGs are not immediately utilized for energy generation, they are transported to designated lipid storage sites, such as adipocytes. Lysophosphatidic acid (LPA) and phosphatidic acid (PA) can be biosynthesized within mitochondria; however, they require transportation to the endoplasmic reticulum (ER). This relocation is essential as the ER houses the terminal enzymes to catalyze the triacylglycerol synthesis. The process of lipid mobilization begins with the activation of protein kinase A (PKA), which is activated by several hormones, including epinephrine, norepinephrine, and glucagon [55]. Once PKA is activated, it phosphorylates perilipin 1 (PLIN1), a protein that inhibits the activity of adipose triglyceride lipase (ATGL) [56]. This phosphorylation effectively negates the inhibitory impact of PLIN1 on ATGL, allowing ATGL to become activated. Furthermore, PKA-mediated phosphorylation of hormone-sensitive lipase (HSL) results in

Table 1
A summary table on the organs/tissues and enzymes/hormones involved in fat metabolism and carbohydrate homeostasis in Human and *Drosophila*.

Function	Human (enzymes/hormones)	*Drosophila* (enzymes/hormones)
Lipid storage	Adipose tissue (Leptin, Adiponectin, Ghrelin, Insulin)	Fat body (Unpaired, NPF, ILPs, Ecdysteroids)
Lipid mobilization	Adipose tissue (Glucagon, Epinephrine), liver (Catecholamines)	Fat body (AKH, ILPs), oenocytes (Lipase)
Glycogen storage	Liver (Insulin, Glucagon)	Fat body and oenocytes (ILPs), oenocytes.
Carbohydrate homeostasis	Pancreatic α and β cells (Insulin, Glucagon)	Neurosecretory neurons (ILPs), corpora cardiaca (AKH)

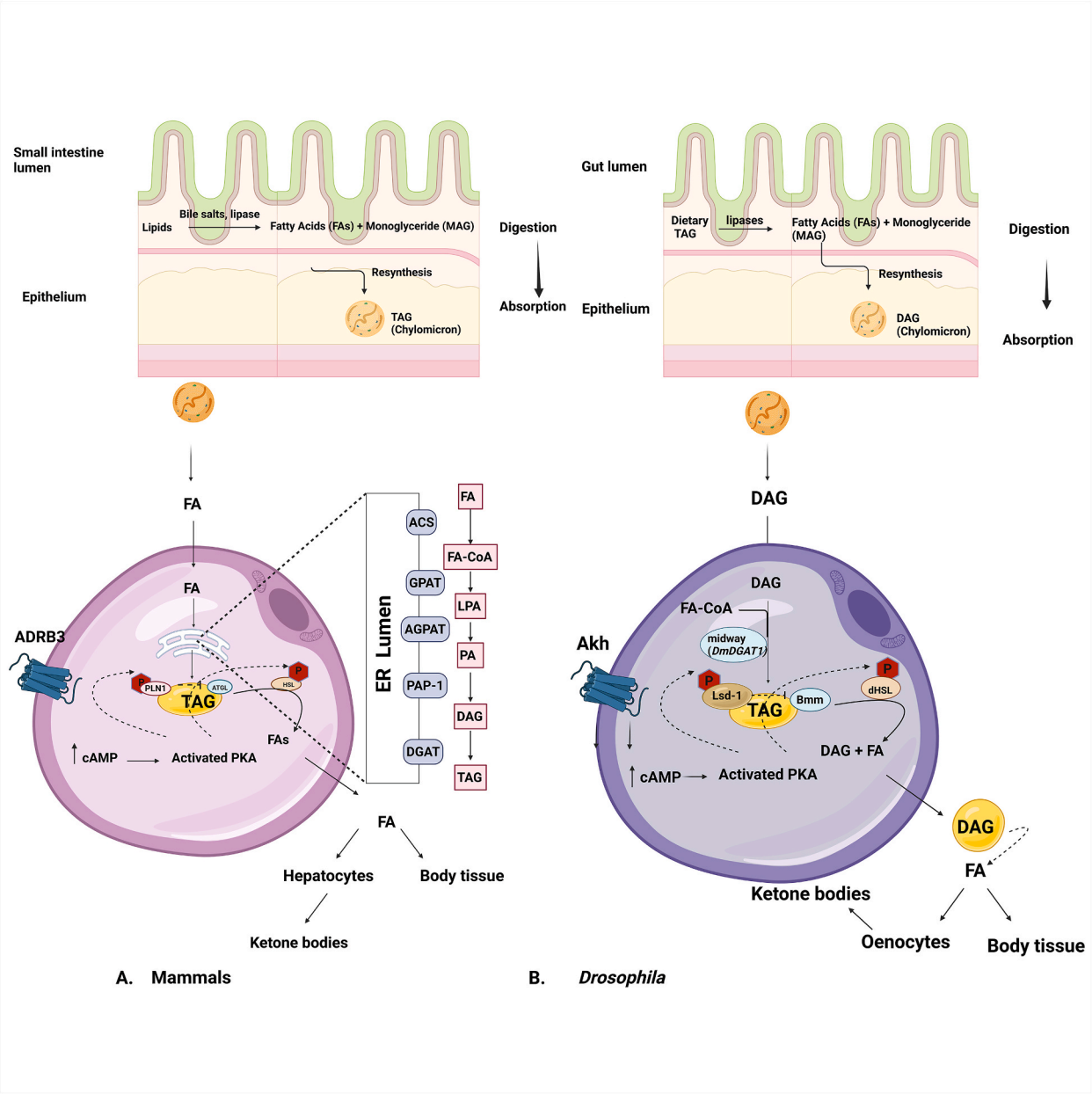

Fig. 2. Homology of lipid metabolism pathway between Drosophila and mammals
Mammals: **Digestion and storage.**
Triglycerides (TAG) undergo breakdown facilitated by lipase and bile salts, aiding absorption in the epithelium and leading to the reformation of TAG from MAG and FAs. LPA and PA must be transported to the endoplasmic reticulum ER, where terminal enzymes are present for the synthesis of triglycerides. Subsequently, TAG is broken down by lipoprotein lipase into glycerol and FAs, which can be taken up by adipocytes. **Mobilization.** PKA phosphorylates PLIN1, alleviating its inhibition of adipose triglyceride lipase (ATGL). PKA also phosphorylates hormone-sensitive lipase (HSL). Together, ATGL and HSL catalyze the breakdown of TAG into FA from lipid droplets. These released FAs are then utilized by various body tissues for energy production. Additionally, hepatocytes use FAs to generate ketone bodies, serving as an energy source for the brain and muscles.
Digestion and storage: Dietary fats, DAG, are broken down in the gut by lipases into MAG and FAs. Further, MAG and FAs assembled into lipoprotein particles, with DAG serving as the circulating lipids in flies. Fat body cells endocytose lipoprotein particles through a lipoprotein receptor-mediated mechanism. DAG is then utilized to synthesize triglycerides (TAG) by the enzyme DGAT1, expressed by a midway gene. The resulting TAG is deposited into lipid droplets through an unknown mechanism. Mobilization: β3 agonists activate GPCR, triggering PKA phosphorylation of PLIN1 homolog lsd-1. The significance of this step is unclear. Akh receptor signaling prompts Brummer, an ATGL homolog, to catalyze lipid droplet TAG breakdown into DAG and FAs. Released DAG is taken up by lipoprotein particles, absorbed by body tissues, and broken down into FAs by lipoprotein lipase.
See references.

the activation of both ATGL and HSL [57]. This dual activation initiates the enzymatic cleavage of triglycerides (TAGs) into constituent fatty acids (FAs), a reaction occurring within lipid droplets. The released FAs are abrorbed by adipocytes and various body tissues, serving as an essential energy source.

In *Drosophila*, lipids from the diet undergo enzymatic breakdown by lipases within the gut, forming monoglycerides (MAG), diacylglycerols (DAGs) and fatty acids (FAs). These products are subsequently encapsulated within lipoprotein particles [43]. The prevalent circulating lipid particle in *Drosophila* is diacylglycerols. Fat body cells in *Drosophila* internalize lipoprotein particles. DAG is utilized to synthesize TAG through the action of the enzyme DGAT1. During mobilization in *Drosophila*, the β-3 Agonist triggers PKA activation by binding to their specific G protein-coupled receptors. This results in the phosphorylation of perilipin 1 (PLIN 1) homolog lipid storage droplet - 1 (lsd-1). Additionally, Akh receptor signaling stimulates Brummer, initiating TAG breakdown into DAG and FAs, which are subsequently free into circulation. The released DAG is taken up by lipoprotein particles, which are then endocytosed by tissues and broken down into FAs using lipoprotein lipase [58,59]. A schematic of fat metabolism and mobilization in humans and *Drosophila* is presented in Fig. 2.

7. Exploring lncRNAs

Long non-coding RNAs (lncRNAs) constitute a subset of RNA molecules that are transcribed from DNA but lacking protein-coding feature [60]. Unlike protein-coding genes, lncRNAs are defined by their length, which generally surpasses 200 nucleotides. They are transcribed by RNA polymerase II, undergo post-transcriptional modifications, and can be processed similarly to messenger RNAs (mRNAs) [60]. lncRNAs are diverse in structure and function [61], and their regulatory roles [62] in numerous biological processes have gained significant attention in recent years.

7.1. Discovery

The discovery of lncRNAs has significantly expanded our understanding of gene regulation and functional elements in both human and *Drosophila* systems. In humans, the first reported lncRNA is H19, identified in 1990 [63]. H19 is imprinted and expressed exclusively from the maternal allele. It plays a crucial role in embryonic development and has been implicated in various diseases, including cancer [64]. Another notable human lncRNA is XIST, discovered in 1991 [65]. XIST is typically involved in X chromosome inactivation in females and ensures proper dosage compensation. Its discovery revolutionized our understanding of epigenetic regulation [66]. In *Drosophila*, the first reported lncRNA is roX1 (RNA-on-X 1), discovered in 1996 [67]. roX1 is essential for dosage compensation in males, where it contributes to the upregulation of the single male X chromosome [67].

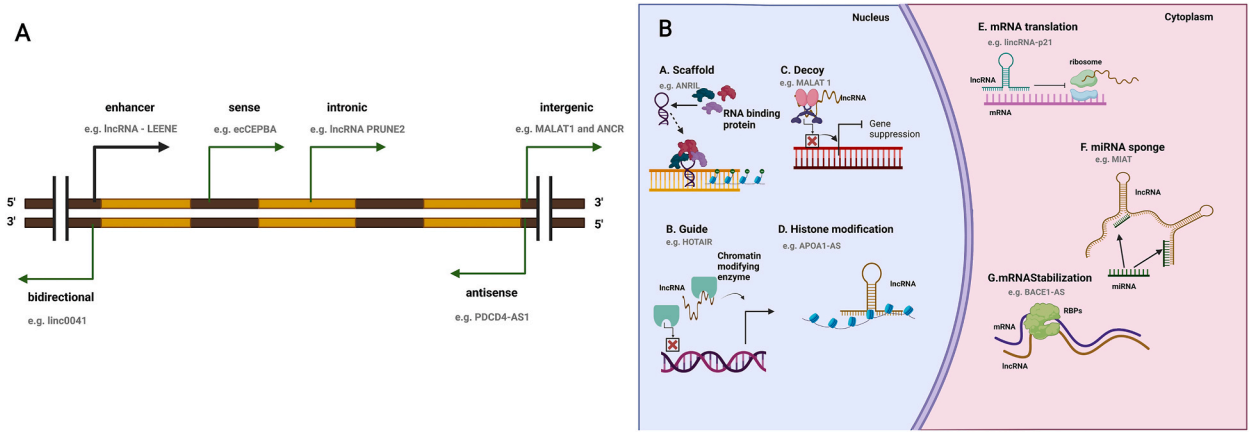

Fig. 3. A: Characterization of lncRNAs based on genomic location
(1) Enhancer lncRNAs (e.g., lncRNA-LEENE), stems from the promoter enhancer region. (2) Sense lncRNAs, (e.g., ecCEPBA), share the transcription orientation with adjacent protein-encoding genes. (3) Intron lncRNAs, such as lncRNA PRUNE2, are transcribed from within gene introns. (4) Intergenic lncRNAs, like MALAT1, are autonomously transcribed non-coding RNAs found between two protein-coding genes. (5) Antisense lncRNAs, e.g., PDCD4-AS1, have a transcription orientation opposite to adjacent protein-encoding genes. (6) Bidirectional lncRNAs, including large intergenic noncoding RNA (linc), allow simultaneous transcription from the same and opposite directions of neighboring protein-encoding genes.
B: Mechanisms of lncRNA action
Nuclear lncRNAs can function as (a) dynamic molecular scaffolds (e.g., ANRIL), providing a platform for assembling multiple enzymatic complexes, (b) guides for factors at specific genomic loci to regulate the genome, e.g., HOTAIR (c) decoys (molecular sinks) that limit the availability of certain regulatory factors (e.g., MALAT 1), and (d) regulators of epigenetic modulation through histone modification (e.g., APDA1-AS). Cytoplasmic lncRNAs can function as (e) regulators of transcription by either increasing or repressing it (LincRNA-p21), (f) molecular sponges such as lncRNA MIAT for miRNAs in the cytosol, and (g) stabilizers of mRNA in the cytosol for example BACE-AS.

7.2. Characterizing lncRNAs role in adipogenesis

lncRNAs originate from diverse genomic regions, including introns, intergenic spaces, antisense strands, enhancers, pseudogenes, repeat elements, and imprinting control regions (Fig. 3A [68]). Despite lacking protein-coding capacity, lncRNAs exhibit unique characteristics. Firstly, they are often expressed cell- or tissue-specific [69], allowing them to play context-specific roles in gene regulation. Secondly, lncRNAs display dynamic expression patterns during development and in reaction to environmental stimuli or pathological conditions [70]. Thirdly, they exert their functions through diverse mechanisms, including chromatin remodeling, transcriptional regulation, post-transcriptional modulation, and interaction with other RNA molecules or proteins [62]. Additionally, lncRNAs can act as scaffolds, facilitating platforms for the assembly of molecular complexes; decoys, influencing the availability of RNA molecules; guides, directing other interactions; or enhancers to modulate gene expression. They contribute to various biological processes, including development, cellular differentiation, and disease progression (Fig. 3B [68]).

We retrieved lncRNA-specific transcripts from various databases and screened over 200,000 lncRNA-specific transcripts for humans and >2000 lncRNAs for *Drosophila*. With a thorough literature search using Google Scholar to characterize their known functions in lipid metabolism based on reliable empirical evidence, we briefly summarize a few well-recognized lncRNAs and their roles in adipogenesis in Table 2, along with a catalogue of all such lncRNAs in Supplementary Table 1. Adipose tissue (AT) can be classified into two types: (i) brown adipose tissue (BAT) and (ii) white adipose tissue (WAT). BAT generates heat through the UCP1 protein in mitochondria-rich brown adipocytes. In humans, BAT deposits are scattered and reduced with advancing age. Contrarily, WAT is composed of white adipocytes containing a solo lipid droplet, located as subcutaneous adipose tissue (sWAT) beneath the skin and visceral adipose tissue (vWAT) near abdominal organs [71]. Abdominal obesity, which is linked to a higher likelihood of obesity-related conditions, is correlated with the expansion of visceral white adipose tissue (vWAT) [72].

Brite or beige adipocytes, which emerge in white adipose tissue (WAT) upon thermogenic stimuli, exhibit a brown cell-like morphology with abundant tiny lipid droplets and high mitochondrial content [90]. Recent studies have revealed the significance of lncRNAs in regulating adipogenesis and adipocyte biology by interacting with transcription factors like PGC-1 alpha, EBF2, ZBTB7B, ZFP516, and PRDM16 [71].

One such lncRNA, Blnc1, located in the nucleus, acts as a scaffold and an enhancer to modulate gene expression, explicitly

Table 2
lncRNA and its role in adipogenesis, along with known mechanisms from empirical evidence in human and *Drosophila*.

Sr. no.	lncRNA	Adipogenesis regulation	Sample	Mechanism	Reference
Human					
1	**Blnc1**	Upregulated	HEK293 cells	Scaffold; Promotes brown and beige adipocyte differentiation and function by forming Blnc1/hnRNP/UEBF2 ribonucleoprotein complex	[73]
2	**LINC00473**	Downregulated	Human primary adipocytes	Scaffolds, guides, and enhancers to modulate gene expression and mitochondrial functions in human thermogenic adipocytes	[74] [75]
3	**ADINR**	Upregulated	Human mesenchymal stem cells (hMSCs); Adipocytes (human adipose tissue)	Enhancer, histone modification; Facilitating the recruitment of MLL3/4 complex (involved in the maintenance of H3K4me3 and the removal of H3K27me3) by binding PA1	[76]
4	**SRA**	Downregulated	Vascular smooth muscle cells (VSMCs)	Promotes adipogenic differentiation in part by stimulation of *PPARγ* transcriptional activity, mitotic clonal expansion and IGF-1 signaling	[77] [78]
5	**HOTAIR**	–	Primary preadipocytes from human	Antisense/intergenic; Promotes preadipocyte differentiation with unknown mechanisms	[79]
6	**H19**	Upregulated	3T3-L1 adipocytes, cell lines	modifying chromatin histone by binding to MDB1; inhibit adipogenetic differentiation	[80]
7	**NEAT1**	Upregulated	Adipocyte-derived stem cells (ADSCs)	Interacts with miR-140, impacting adipogenesis. miR-140 targets and inhibits C/EBPα, a crucial adipogenic transcription factor	[81]
8	**TINCR**	Downregulated	Primary human ADSCs (hADSCs)	Acted as a ceRNA for miR-31, targeting C/EBP-a	[82]
9	**Meg3**	Downregulated	Human hepatocellular carcinoma cell line HepG2	Inversely regulate the expression of lipogenesis-related genes, the over-expression of this gene may alleviate lipid over-deposition	[83]
10	**Dio3os**	–	BAT	Insulin resistance and brown adipocyte differentiation by impairing the activity of the PRDM16/PGC-1a complex	[84]
11	**lncRNA-p19461**	Downregulated	Blood components and adipose tissue	Strong correlation with obesity and regulates insulin resistance	[85]
Drosophila					
1	**lncRNA-IBIN**	–	Larvae, adult flies and cell culture	Overexpression of lincRNA-IBIN affected the expression of Toll pathway -mediated genes	[86]
2	**IRAR**	–	Larvae	Direct regulation of insulin receptor transcripts by IRAR through FOXO binding under nutritional stress	[87]
3	**CR44138**	Downregulated	Adult flies	Showed downregulation in E(z) mutants; e(z) mutation leads to lipid metabolism, drug metabolism, nucleotide metabolism	[88]
4	**CR18854**	–	Adult flies	Suppress enlarged lysosome phenotype induced by fat body specific kd of dFIG4	[89]

stimulating thermogenic gene expression. Blnc1 interacts with the ribonucleoprotein complex, Blnc1/hnRNP-U/EBF2, and plays a pivotal role in brown and beige adipogenesis [91]. By enhancing EBF2's transcriptional activity on the Ucp1 promoter, which is crucial for brown adipocyte differentiation, Blnc1 contributes to the regulation of thermogenesis. Moreover, Blnc1 exerts control over PPAR-gamma binding on gene promoters, influencing brown and white adipocytes differentiation [91]. This regulatory loop involving EBF2 and Blnc1 is vital for thermogenesis-related gene expression during brown adipogenesis.

LncRNA LINC00473 acts as scaffolds, guides, and enhancers to modulate gene expression and mitochondrial functions in human thermogenic adipocytes. It strongly correlates with UCP1 expression and is reduced in obesity and type-2 diabetes. LINC00473 increases during differentiation and in response to cAMP in progenitor cells [92]. Noticeably, LINC00473 translocates from the nucleus and engages in interactions with proteins located in the mitochondria and lipid droplets, demonstrating its role as a scaffold. LINC00473 affects lipolysis, process of respiration, and the regulation of genes associated with mitochondrial oxidative metabolism, serving as a guide. Depletion of PLIN1, a protein associated with lipid droplets, impairs cAMP-responsive LINC00473 expression and lipolysis, illustrating bidirectional interactions between PLIN1, LINC00473, and mitochondrial functions. Moreover, LINC00473's role as a histone modulator by affecting chromatin structure and gene regulation positions it as a critical regulator of thermogenic adipocyte function [93]. It plays a crucial role of facilitating communication between organelles and in the metabolism of energy in humans.

ADINR (adipogenic differentiation induced noncoding RNA) serves as an enhancer, as it plays a key role in C/EBPα gene transcription and adipogenic differentiation. It interacts with the MLL3/4 histone methyltransferase complex member PA1 to regulate histone modifications in the C/EBPα locus during adipogenesis, influencing gene expression patterns in white adipose tissue differentiation [94].

SRA, the first characterized lncRNA during adipogenesis, also acts as an enhancer, impacting lipid metabolism in adipocytes. It enhances glucose uptake and metabolism in adipose tissue by stimulating Akt and FOXO1 phosphorylation in response to insulin [77]. Additionally, SRA affects signaling pathways during early adipocyte differentiation by inhibiting p38 MAPK and JNK phosphorylation, influencing adipocyte differentiation and lipid storage [77,78].

HOTAIR (HOX antisense intergenic RNA) is expressed in the human gluteal fat. Previous studies have demonstrated that its expression doubles during the development of gluteal preadipocytes. Its ectopic expression in abdominal preadipocytes induces the expression of key adipogenic markers, including LPL (lipoprotein lipase), FABP4, AdipoQ, and PPARγ, without affecting the rate of cell proliferation [79]. This shows a transcriptional mechanism at the root of preadipocyte formation. HOTAIR regulates adipogenesis at the molecular level, yet the precise mechanism is still not understood.

LncRNA H19 acts as a scaffold, guide, and enhancer to modulate gene expression in lipid metabolism. It promotes adipogenesis and enhances brown adipocyte differentiation by functioning as a scaffold, facilitating PPARγ's transcriptional activity, driving adipocyte differentiation, and lipid storage. Additionally, it acts as a guide to affect SREBP activation, regulating lipid biosynthesis. Moreover, H19 serves as an enhancer by modifying chromatin histone by binding to MDB1 [80], thereby maintaining brown fat's energy metabolism and resisting obesity development as a histone modulator in 3T3-L1 cell lines.

In *Drosophila*, one prominent example is the lncRNA called lncRNA-IBIN, which has been identified in adipose tissue. It has been found to regulate lipid storage and breakdown by interacting with critical genes involved in fat metabolism. LincRNA-IBIN overexpression in the adipose tissue influenced gene expression of Toll pathway. The upregulation of lincRNA-IBIN in healthy flies led to a notable elevation in hemolymph sugar levels. This was achieved by facilitating the activation of genes that are essential for glucose uptake. LincRNA genes are mainly involved in *Drosophila* immune system, and the lincRNA-IBIN links innate immune responses to metabolic activities [86]. LincRNA-IBIN overexpression in the adipose tissue influenced gene expression of Toll pathway. The upregulation of lincRNA-IBIN in healthy flies led to a notable elevation in hemolymph sugar levels. This was achieved by facilitating the activation of genes that are essential for glucose uptake. LincRNA genes are mainly involved in *Drosophila* immune system, and the lincRNA-IBIN links innate immune responses to metabolic activities. Another study posited that lncRNA IRAR overexpression in fly phenotypes was highly sensitive to environmental changes in nutrition regimes, while CRISPR-generated null mutants were not [87]. The insulin receptor transcript expression level has been established as the underlying mechanism. These studies collectively demonstrate that lncRNAs play an essential role in regulating metabolic processes and adipogenesis in *Drosophila* models of obesity. However, empirical evidence is limited on the characterization of lncRNA and their function to clearly link them with metabolism in *Drosophila*.

8. Crosstalk between lncRNAs, microRNAs, and protein-coding genes

Crosstalk between lncRNAs, microRNAs, and protein-coding genes represents a fascinating and intricate area of research, providing valuable insights into the regulatory networks governing gene expression. Numerous studies have demonstrated the roles of lncRNAs in influencing adipogenesis, the process of fat cell formation. For example, *H19*, interacts with *miR-30a*, which targets C8orf4, a crucial transcription factor involved in adipogenesis. By acting as a sponge for *miR-30a*, *H19* prevents its inhibitory effect on *C8orf4*, promoting adipogenesis. In human adipose-derived stem cells (hADSCs), *H19* knockdown reduced *C8orf4* levels and inhibited adipogenic differentiation. Conversely, inhibiting *miR-30a* increased *C8orf4* levels and enhanced adipogenesis, with partial reversal upon *H19* knockdown [95]. Similarly, NEAT1 lncRNA interacts with *miR-140*, impacting adipogenesis. *miR-140* targets and inhibits C/EBPα, a crucial adipogenic transcription factor. NEAT1 sponges *miR-140*, enabling C/EBPα translation and promoting adipogenesis. In mouse preadipocytes, NEAT1 knockdown reduced α levels and inhibited adipogenic differentiation, while *miR-140* inhibition increased C/EBPα levels and promoted adipogenesis, with partial reversal of NEAT1 knockdown effects [96]. Additionally, other lncRNAs have been implicated in adipogenesis. In obese mice, lncRNA Gomafu decreased hepatic glucose production, increased insulin sensitivity,

and behaved as a miR-139 sponge, de-repressing Foxo1 [97]. The upregulation of LncRNA Gm10768 during periods of fasting has been found to impact glucose tolerance and hyperglycemia in diabetic mice by regulating miR-214 and activating transcription factor 4 [98]. Terminal differentiation-induced ncRNA (TINCR) and lncRNA Meg3 were shown to modulate adipogenic differentiation. TINCR acted as a ceRNA for miR-31, targeting C/EBP-α [99], while Meg3 stimulated 3T3-L1 preadipocytes differentiation by functioning as an miR-217 sponge [100]. These investigations highlight the complex interplay of lncRNAs and miRNAs in adipogenesis and offer potential avenues for understanding adipose tissue development and metabolic regulation.

LncRNA plays a significant role in regulating adipogenesis, as well as controlling glucose uptake and insulin signaling in adipose tissue metabolism. They also play a role in lipid metabolism regulation by modulating lipid droplet production, lipolysis, and lipid storage in adipocytes. Along with this, they influence oxidative metabolism and mitochondrial function, which are crucial for energy production and thermogenesis in adipose tissue. Furthermore, lncRNAs impact the endocrine operations of adipose tissue by controlling the secretion of adipokines, which contribute to systemic metabolic homeostasis. Moreover, they play a crucial role in maintaining adipocyte identity and regulating adipocyte differentiation by interacting with key transcription factors. Understanding the broader roles of lncRNA in metabolism provides insights into the complex regulatory networks governing energy balance and metabolic disorders.

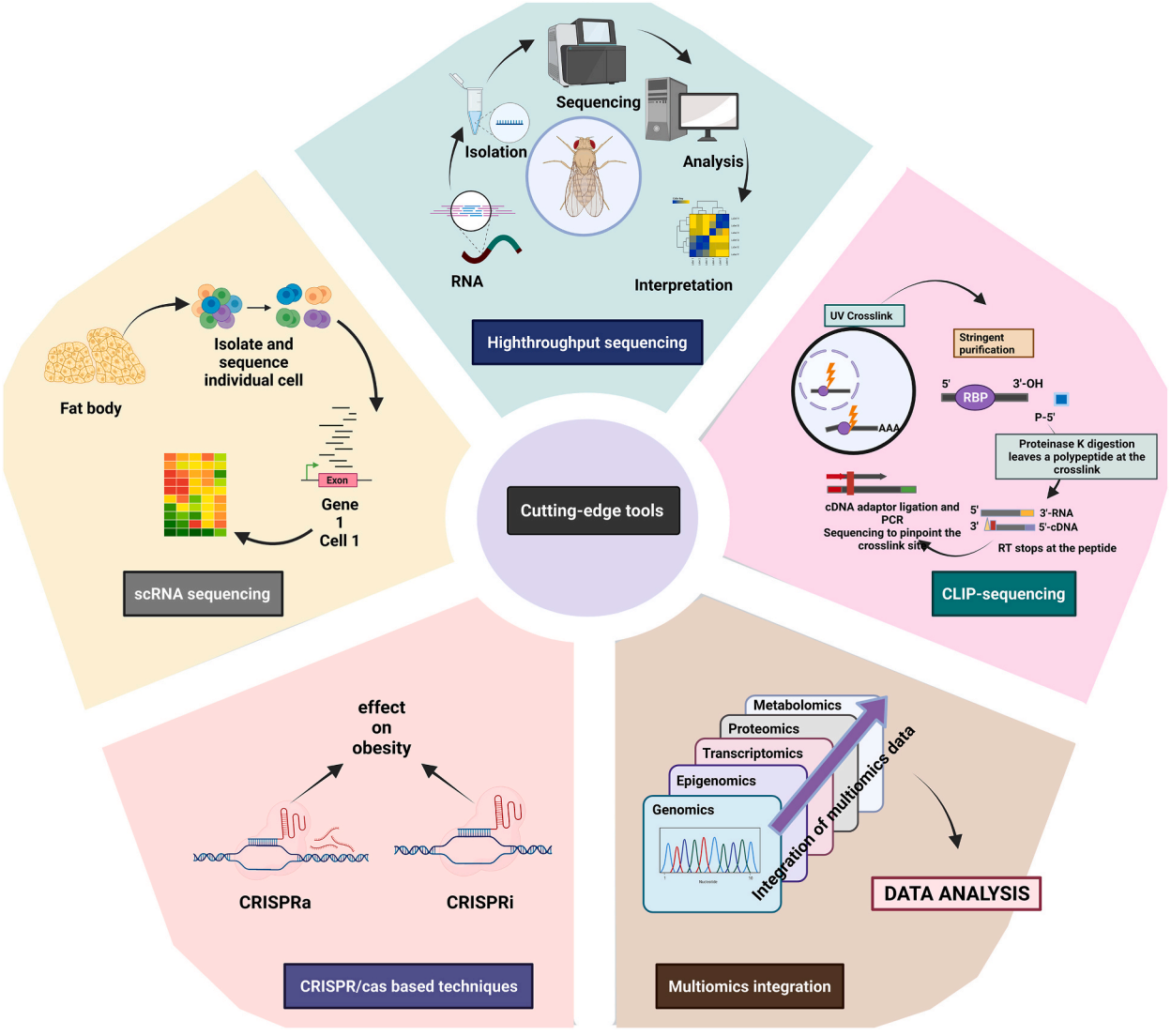

Fig. 4. Cutting-edge tools in unraveling the role of lncRNAs in obesity (clockwise from the top) a. Highthroughput sequencing b. CLIP-sequencing c. Multiomics integration d. CRISPR/Cas based techniques e. scRNA sequencing.

9. Challenges and considerations in studying lncRNAs in *Drosophila* obesity models

Studying lncRNAs in obesity models of *Drosophila* present several challenges and limitations that need to be considered. One challenge lies in accurately annotating and characterizing lncRNAs in the *Drosophila* genome. Due to the relatively small number of known lncRNAs and the complexity of their functional roles, accurately identifying and classifying *Drosophila* lncRNAs remains a challenge. Additionally, the lack of comprehensive functional annotations for many lncRNAs hinders their study in the context of obesity [101]. Another limitation is the difficulty in establishing direct causality between specific lncRNAs and obesity-related phenotypes. While numerous lncRNAs have been noticed as differentially expressed in obesity models [102,103], establishing their functional significance requires further experimental validation, such as gain-of-function or loss-of-function studies, to establish a direct link between specific lncRNAs and obesity-related phenotypes. Moreover, the conservation of lncRNAs between *Drosophila* and humans is not always straightforward [104]. Although *Drosophila* serves as an excellent model organism for studying basic biological processes, including genetics of obesity, the functional conservation of lncRNAs and their regulatory roles may not be fully preserved across species. This limitation necessitates cautious extrapolation of findings from *Drosophila* to humans and highlights the importance of validating observations in mammalian models or human. Furthermore, technical challenges in quantifying and detecting lncRNAs accurately pose limitations. Traditional RNA sequencing methods exhibited limitations in detecting low-abundance lncRNAs [105], leading to potential biases in expression profiling. Therefore, advancements in sequencing technologies and the development of specialized computational tools are required to improve the sensitivity and accuracy of lncRNA detection and quantification in obesity models. Finally, the dynamic nature of lncRNA expression and their cell or tissue-specific regulation poses additional challenges. lncRNAs can exhibit highly dynamic expression patterns in response to various stimuli or in different developmental stages [106], making their study in obesity models complex. Comprehensive temporal and spatial profiling of lncRNA expression is essential to capture their dynamic nature and understand their functional relevance in specific cellular contexts. Despite these challenges and limitations, studying lncRNAs in *Drosophila* obesity models provides valuable insights into their potential roles in obesity-related pathways. By acknowledging these challenges and implementing appropriate experimental designs and validation strategies, researchers can overcome limitations and advance our understanding of the functional significance of lncRNAs in *Drosophila* and potentially translate these findings to human obesity research.

10. Unlocking the potential of cutting-edge tools in unraveling the role of lncRNAs in obesity

Recent technological advancements transform lncRNA research (Fig. 4). For example, high-throughput sequencing technologies have played a key role in facilitating profiling of lncRNA expression patterns [107], leading to the detected explicitly differentially expressed lncRNAs associated with conditions such as obesity and diabetes [108–110]. In one study, Liu employed high-throughput RNA sequencing to identify 1268 differentially expressed lncRNAs in obese subjects [109]. Similarly, RNA-seq was used in mice and 1500 lncRNAs were identified [111]. Notably, 127 lncRNAs were shown to be peculiarly expressed in brown adipose tissue (BAT), targeting essential adipogenesis factors such as PPAR-gamma, C/EBP-, and C/EBP-beta.

Further, Shu et al. (2020) utilized high-throughput sequencing to discover lncRNAs implicated in insulin resistance in the liver [112], yielding information on their role in glucose homeostasis and diabetes pathogenesis. In another study, RNA sequencing compiled a compendium of 3149 adipose tissue-active lncRNAs, with 909 reported explicitly in BAT [112]. This feature was accomplished through deep RNA-seq analysis of adult subcutaneous adipose tissue (SAT), omental white adipose tissue, and fetal BATs. Significantly, single-cell RNA sequencing (scRNA-seq) has developed as a pivotal advancement, enabling high-resolution gene expression profiling at the single-cell level [113]. This technique has transformed the field, allowing researchers to dissect cellular heterogeneity and uncover cell-specific expression patterns of lncRNAs. Norreen-Thorsen utilized 527 visceral adipose tissue (VAT) and 646 SAT samples to pinpoint tissue-specific lncRNA expressions [114]. Furthermore, Gupta et al. (2022) employed scRNA-seq to reveal distinct lncRNA expression profiles in different adipose tissue cell types, shedding light on their potential regulatory roles in adipogenesis and metabolic homeostasis [115]. Another revolutionary tool is the CRISPR/Cas9 system, enabling precise genome editing and functional perturbation (activation/repression) of lncRNAs in a targeted manner [116]. For instance, an *in-vitro* study demonstrated that Dio3os knowckdown by CRISPR–Cas9 system in mouse embryonic fibroblasts activated DIO3 expression, reducing T3 levels and PRDM16 expression and inhibiting brown adipogenesis [117].

Moreover, CLIP-seq (crosslinking immunoprecipitation followed by sequencing) has emerged as a powerful technique for studying interactions between RNA molecules, for instance lncRNAs, and their binding partners or targets, such as RNA-binding proteins (RBPs), followed by RNA sequencing [118]. Further, high-resolution microscopy techniques enable researchers to directly observe the localization and movement of labeled lncRNAs within living cells and tissues, providing valuable insights into their spatial distribution and functional dynamics.

Amidst these progressive methodologies, the integration of multi-omics data has exemplified its utility in uncovering the intricate roles of lncRNAs in metabolism and obesity. For instance, Brunmeir et al. [119] integrated transcriptomic and epigenomic data to pinpoint lncRNAs central to adipogenesis and insulin resistance, unveiling novel regulators of key genes in murine adipocyte differentiation and insulin signaling pathways. Similarly, Wang et al. [120] merged transcriptomic and proteomic data, unveiling lncRNAs interacting with pivotal enzymes and transcription factors in lipid biosynthesis and storage. This multi-dimensional integration provides a comprehensive and systematic approach to deciphering the complex regulatory mechanisms of lncRNAs in obesity. Briefly, these new-genetaion tools enable the identification of key players, elucidation of functional pathways, and discovery of potential therapeutic targets, ultimately advancing our understanding of obesity and facilitating the development of novel strategies for its prevention and treatment.

11. From fly to human: translational insights from *Drosophila* lncRNA research in obesity

Preceding studies have suggested that many important pathways in *Drosophila* and humans are affected by lncRNAs in similar ways. One example is the identification of an lncRNA called CR32658 in *Drosophila*, which was found to regulate lipid metabolism and adiposity [121]. In human, lncRNA Dio3os was found to be associated with obesity and metabolic dysfunction [122]. Another study focused on an lncRNA called CR32385, which was found to modulate insulin signaling and adipogenesis in *Drosophila* [123] while lncRNA LncASIR in humans were identified with related functions, indicating conserved regulatory mechanisms across species [124]. Another very well studied lncRNA in flies, IRAR, was found to regulate insulin receptor transcript under nutritional stress and is directly involved in insulin signaling in *Drosophila* [87] and studies on lncRNA-p19461 in human show that it exhibits similar regulatory functions [85]. These examples may infer the translational potential of *Drosophila* lncRNA research for understanding human obesity. The conservation of lncRNA functions, the identification of homologous lncRNAs, and the elucidation of regulatory mechanisms contribute to our knowledge of human adiposity regulation.

12. Harnessing innovative genetic approaches to enhance obesity studies in *Drosophila*

Experimental evolution involving the imposition of high diet regimes has emerged as a powerful and indispensable strategy for the deliberate manipulation and subsequent study of *Drosophila*

Populations in the context of genetic analysis. By subjecting *Drosophila* to prolonged and controlled exposure to high-calorie diets across successive generations, we can selectively shape the evolutionary trajectory of these populations, facilitating the exploration of adaptive responses and the elucidation of underlying genetic mechanisms. This approach enables the intentional selection of desirable phenotypic traits, such as increased body weight or altered lipid metabolism, in response to the imposed dietary conditions. High diet regimes in experimental evolution studies involve the provision of nutrient-rich diets that exceed the standard nutritional

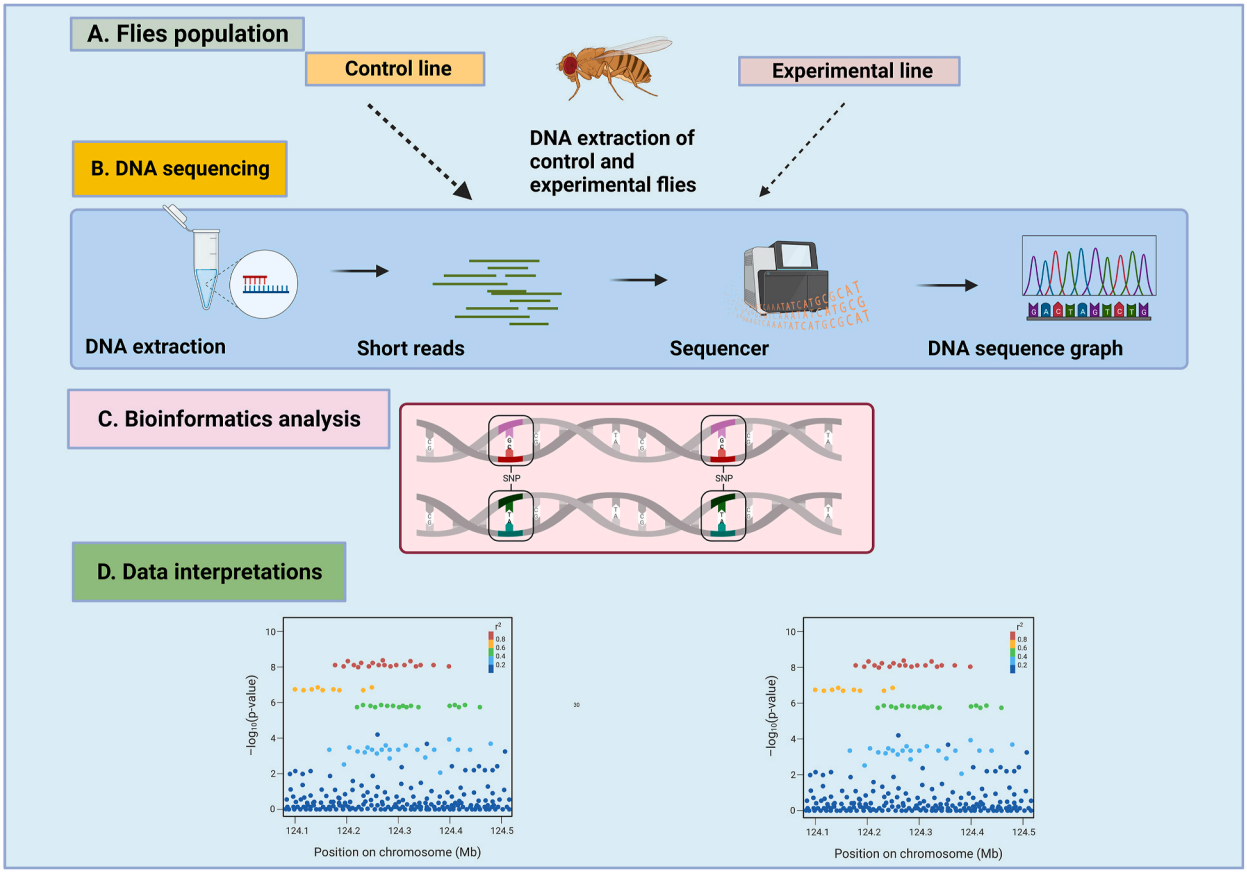

Fig. 5. Genome Wide Association Studies to trace genetic variants linked to a trait of interest
Genome Wide Association Studies (GWAS) aim to establish connections between allele or genotype frequency and trait status. The initial phase involves selecting a research population, such as cases and controls for a disease, and defining the specific condition (trait) under examination. Genotyping can be performed using Single-nucleotide Polymorphism (SNP) arrays with imputation or whole-genome sequencing (WGS). It is crucial to note that the frequencies and impact magnitudes of different alleles vary significantly among genetic variations. The majority of risk variants identified through GWAS are typically concentrated between the two axes.

requirements of *Drosophila*. These diets are typically formulated to contain higher levels of energy-rich macronutrients, including sugars, fats, and proteins, thereby promoting the manifestation of obesity-related traits and metabolic disorders. The sustained exposure to these high-calorie diets exerts selective pressure on the *Drosophila* populations, favoring the survival and reproduction of individuals that exhibit advantageous phenotypes in the context of the imposed dietary conditions (Fig. 5). Although there are many examples of evolving flies under abiotic stress conditions, there is no study where the flies have evolved in nutrient-rich conditions, which is among the focus of our research group.

Further, following the evolutionary manipulation through high diet regimes, comprehensive genetic analysis techniques can be employed to unravel the underlying genetic architecture and the molecular basis of the observed adaptive changes rather than limiting the resolution to phenotypic changes. Whole-genome sequencing (WGS), a high-throughput sequencing approach, can further facilitate the identification of genetic variants, including single nucleotide polymorphisms (SNPs), insertions, deletions, and structural variations, which may contribute to the evolved phenotypic traits [125]. Additionally, transcriptomics, the study of all RNA transcripts produced by the genome, provides insights into the differential gene expression patterns associated with the evolutionary response to high diet regimes. To further dissect the genetic basis of the evolved traits, genetic mapping techniques can be employed. Techniques such as quantitative trait loci (QTL) mapping and genome-wide association studies (GWAS) enable the identification of specific genomic regions that can be linked to the observed phenotypic changes [126], providing insights into candidate genes and pathways that are potentially involved in the adaptive response to high-calorie diets (Fig. 5).

Integrating experimental evolution with advanced genetic analysis techniques in *Drosophila* offers a comprehensive framework for investigating the genetic determinants underlying complex traits and the associated metabolic disorders. Through the precise manipulation of dietary conditions and the subsequent analysis of the evolved populations, it is possible to uncover the interplay of

Table 3
lncRNA databases in human and *Drosophila*.

Name	Website	Description	Reference
Human			
ChIPBase v2.0	http://rna.sysu.edu.cn/chipbase/	Uses ChIP-seq data to decode transcriptional regulatory networks of non-coding RNAs and protein-coding genes	[127]
deepBase	http://rna.sysu.edu.cn/deepBase/	Identification, expression, evolution and function of long non-coding RNAs	[128]
LncBook	http://bigd.big.ac.cn/lncbook	Enables users to decipher functional signatures of lncRNAs in human diseases and different biological contexts	[129]
LncExpDB	https://bigd.big.ac.cn/lncexpdb	an expression database of human lncRNAs that is devoted to providing comprehensive expression profiles of lncRNA genes	[130]
LNCipedia	http://www.lncipedia.org/	A public databse of human long non-coding RNAs	[131]
lncRNAdb	http://lncrnadb.com/	Manually curated database that provides annotations for long non-coding RNAs (lncRNAs) in eukaryotes	[132]
lncRNAKB	http://www.lncrnakb.org/	Integrated resource for exploring lncRNA biology in the context of tissue-specificity and disease association.	[133]
LncRNAWiki	http://lncrna.big.ac.cn/	Wiki-based, publicly editable database for human lncRNAs	[134]
lncRNome	http://genome.igib.res.in/lncRNome/	Searchable database that contains information on over 17,000 human lncRNAs	
LncTarD 2.0	https://lnctard.bio-database.com/	Database includes experimentally supported information on lncRNA-target regulations, their functions, and lncRNA-mediated regulatory mechanisms	[135]
Drosophila			
ChIPBase v2.0	http://rna.sysu.edu.cn/chipbase/	Uses ChIP-seq data to decode transcriptional regulatory networks of non-coding RNAs and protein-coding genes	[127]
CLIPdb	http://lulab.life.tsinghua.edu.cn/clipdb/	Database for protein-RNA interactions; characterizes the regulatory networks between RNA binding proteins (RBPs) and various RNA.	[136]
CRISPRlnc	http://www.crisprlnc.org	Database of validated CRISPR/Cas9 sgRNAs for lncRNAs	[137]
FlyAtlas 2	http://www.flyatlas2.org	Based on RNA-Seq data and used for studying the expression of genes in *Drosophila melanogaster*	[138]
FlyBase	http://flybase.org	Primary repository for *Drosophila* genes and genomes and is essential for researchers using it as a model organism	[139]
DroID	http://droidb.org/	Database of gene and protein interactions for the model organism *Drosophila*; includes protein-protein, TF-gene, miRNA-gene, and genetic interactions.	[140]
DVEX	http://www.dvex.org	Interactive database that produces Single-cell expression atlas of lncRNAs of the stage 6 *Drosophila*	[141]
LNCediting	http://bioinfo.life.hust.edu.cn/LNCediting/	Database that provides tools to predict the functional effects of RNA editing in lncRNAs	[142]
lncRNAdb	http://www.lncrnadb.org/	Manually curated database provides annotations for long non-coding RNAs (lncRNAs) in eukaryotes.	[132]
lncRNAtor	http://lncrnator.ewha.ac.kr/	Database for investigating the function of long non-coding RNAs (lncRNAs); contains data from TCGA, GEO, ENCODE, and modENCODE	[143]
LncVar	http://bioinfo.ibp.ac.cn/LncVar/	Database includes information on transcription factor binding sites and m6A modification sites of lncRNAs	[144]
NONCODE	http://www.noncode.org/	Details of annotation of lncRNAs; expression and functional data from re-annotated microarray studies	[145]
NPInter v3.0	http://www.bioinfo.org/NPInter/	Database that contains experimentally verified interactions between noncoding RNAs (ncRNAs) and biomolecules	[146]

genes, regulatory elements, and molecular pathways that coordinate the adaptive response to high-calorie diets. This highly technical and integrative approach allows for identifying specific genes and genetic variants that drive the observed phenotypic changes, as well as elucidating the regulatory networks and functional interactions involved in the adaptation to high dietary conditions. Moreover, the insights gained from *Drosophila* experimental evolution studies can have broader implications beyond the scope of this model organism.

13. lncRNA database humans and *Drosophila*

Database with web links of human and *Drosophila* long non-coding RNAs (lncRNAs) enables users to search for lncRNA, access detailed descriptions, and explore their functions, are described presented in Table 3.

14. Conclusions and future perspectives

The current crisis of obesity is a major public health concern, and it is essential to find effective ways to mitigate the rising prevalence of this condition. By exploring the molecular roots of obesity, we can better understand the mechanisms involved and develop innovative therapeutic strategies. New investigations have shown that lncRNAs may play a pivotal role in regulating adipose tissue function and energy homeostasis. Studying them offers a promising avenue for advancing our understanding of obesity. The study of lncRNAs in obesity benefits from the *Drosophila* model, which shares genetic similarities with humans and offers a simplified system for exploring the molecular underpinnings of obesity. While monogenic mutant models have been essential, we should also explore induced-obesity models encompassing a broader range of factors (genetics and epigenetics, including the environment) contributing to this complex condition. Furthermore, recent years have witnessed rapid advancements in omics technologies, interdisciplinary collaborations, and innovative genetic manipulation tools, providing a promising platform for future research. Many lncRNAs, whose functions have not been well characterized but are plausible candidates, should be subjected to comprehensive functional studies to uncover their roles in various biological processes, including obesity-related mechanisms. By translating discoveries from *Drosophila* and other proxy model studies into precision medicine, expanding omics investigations, understanding the interplay of genetics with environmental factors, and promoting data sharing and collaboration, we can take significant strides toward mitigating the global obesity crisis and addressing related health challenges.

Data availability statement

No data was used for the research described in the article.

CRediT authorship contribution statement

Dau Dayal Aggarwal: Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Software, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Prachi Mishra:** Writing – review & editing. **Gaurav Yadav:** Writing – review & editing. **Shrishti Mitra:** Writing – review & editing, Conceptualization. **Yashvant Patel:** Data curation. **Manvender Singh:** Validation, Data curation. **Ranjan Kumar Sahu:** Writing – review & editing, Software, Data curation. **Vijendra Sharma:** Writing – review & editing, Validation, Investigation.

Declaration of competing interest

There are no financial, professional, or personal affiliations that could be perceived as influencing the research presented in this review manuscript.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2024.e35327.

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