Primary cilia dysfunction: A critical driver of metabolic diseases (Review)

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Received June 9, 2025; Accepted February 9, 2026

DOI: 10.3892/ijmm.2026.5860

Abstract. Cilia dysfunction has been identified as a crucial but frequently overlooked factor in the pathogenesis of metabolic diseases, including obesity and diabetes. This review examines the multifaceted roles of primary cilia in various metabolic tissues, framed by a central bidirectional model. This model posits a self-reinforcing cycle where disruptions in ciliary function contribute to dysregulated appetite control, impaired insulin secretion and increased fat storage. Conversely, the hallmarks of metabolic disease, including chronic inflammation, lipotoxicity and hyperglycemia, contribute to the impairment of ciliary structure and function, thereby accelerating disease progression. The review underscores this reciprocal causality and proposes that therapeutic strategies targeting ciliary function could break this vicious cycle. Emerging treatments aim to restore ciliary function and thereby mitigate the progression of metabolic diseases. By elucidating the mechanisms of this bidirectional relationship, this review aims to pave the way for innovative strategies that optimize clinical outcomes and improve patient quality of life.

Contents

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Key words: ciliary, metabolic disease, signal transduction, energetic homeostasis

1. Introduction

Metabolic diseases, such as obesity and diabetes, represent major public health challenges worldwide due to their increasing prevalence and associated complications (1). These diseases are complex and multifactorial, involving intricate interactions between genetic, environmental and lifestyle factors (2). One emerging area of interest in the study of metabolic diseases is the role of primary cilia, which are small, microtubule-based organelles that extend from the surface of most vertebrate cells (3). Historically viewed as vestigial, primary cilia are now recognized as critical sensory and signaling hubs that regulate a variety of cellular processes essential for maintaining homeostasis (4).

Primary cilia play a vital role in the function of several key metabolic tissues, including the hypothalamus, pancreatic islets, liver and adipose tissue (5-8). In the hypothalamus, cilia are involved in sensing and integrating hormonal signals that regulate appetite and energy balance. Disruption of ciliary function in hypothalamic neurons can lead to dysregulation of appetite control, resulting in conditions such as hyperphagia and obesity (9). In the pancreas, primary cilia are essential for the proper functioning of beta cells, which are responsible for insulin secretion (10). Ciliary dysfunction in these cells can impair insulin release and contribute to the development of diabetes. In addition to their roles in hypothalamic and pancreatic function, primary cilia are also crucial for the regulation of lipid metabolism (11). In adipose tissue, cilia-mediated signaling pathways influence the storage and mobilization of fat. Disruption of these pathways can lead to abnormal fat accumulation and inflammation, which are hallmarks of obesity (12). Similarly, in the liver, primary cilia are involved in regulating bile flow and cholesterol metabolism (13). Impaired ciliary function in hepatic cells can exacerbate metabolic imbalances, further complicating the clinical management of metabolic diseases.

Recent research has highlighted the significant impact of ciliary dysfunction on bone health, particularly in the context of diabetes (14). Diabetes is known to impair bone healing and increase the risk of fractures, with evidence suggesting that ciliary defects in osteoblasts contribute to these complications. Ciliary dysfunction in osteoblasts impairs bone formation and

mineralization, leading to weaker bones and delayed fracture healing (15). This underscores the broader implications of ciliary dysfunction beyond traditional metabolic tissues and highlights the interconnected nature of metabolic and skeletal health.

Understanding the mechanisms by which primary cilia influence metabolic processes is crucial for developing targeted therapies for metabolic diseases. Current therapeutic approaches often focus on managing symptoms rather than addressing underlying causes. However, emerging treatments that aim to restore ciliary function offer promising new avenues for intervention. These include gene therapy techniques to correct genetic defects affecting ciliogenesis, as well as small molecules that enhance ciliary signaling pathways.

This review explored the multifaceted roles of primary cilia in metabolic regulation and the impact of ciliary dysfunction on metabolic health. The evidence linking ciliary defects to obesity, diabetes and their complications were examined and potential therapeutic strategies aimed at restoring ciliary function were discussed. By shedding light on this underrecognized aspect of metabolic disease, the study esteems to pave the way for innovative treatments that improve clinical outcomes and enhance the quality of life for individuals affected by these conditions.

2. Cilia structure and function

Cilia are slender, microtubule-based projections ubiquitously distributed on the surfaces of nearly all mammalian cells (16). They are categorized into two primary structural types: Motile cilia and primary (or sensory) cilia (17). Motile cilia are found abundantly present on specialized, multiciliated cells, where they facilitate fluid movement or cell locomotion (18). Conversely, most cells feature a single, non-motile primary cilium that plays a crucial role in sensory signaling. Despite their lack of movement, primary cilia are central to orchestrating key regulatory pathways involved in growth, development and cellular homeostasis (19).

Architecture of primary and motile cilia. The basic ciliary architecture consists of an axoneme core of microtubule doublets surrounded by a membrane. The axoneme extends from a modified centriole termed the basal body, which migrates and docks at the cell surface to nucleate the cilium (20). All cilia feature a ring of nine peripheral microtubule doublets in the axoneme. In motile cilia, the axoneme also contains a central pair of microtubules, producing a 9+2 configuration. This central pair enables ATP-driven motor protein dynein to generate motility for fluid flow or cell movement (21). By contrast, primary cilia lack the central pair, resulting in a 9+0 axoneme that renders them immotile.

The transition zone, located at the ciliary base, acts as a selective gateway that regulates protein access to the ciliary compartment. Transition fibers anchor both the basal body and the transition zone to the cellular membrane. This zone features Y-shaped structures that connect the axoneme to the ciliary membrane, playing a crucial role in controlling protein trafficking (22). Notably, the composition of the ciliary membrane is distinct from that of the general cell surface. The importation of proteins into the cilium is mediated by intraflagellar transport (IFT), which utilizes the axoneme as a track. IFT is instrumental in the assembly and maintenance of cilia, actively transporting structural components, signaling molecules and receptors to and from the ciliary compartment (Fig. 1) (23,24).

IFT and ciliogenesis. IFT is essential for the bidirectional movement of cargo proteins along the axoneme, a process powered by the motor proteins kinesin and dynein, which are part of multiprotein IFT complexes (25,26). Anterograde transport, facilitated by kinesin-2 family motors, moves cargos from the base to the tip of the cilium, promoting ciliary assembly. Conversely, retrograde transport, executed by cytoplasmic dynein, brings proteins back to the cell body for recycling or degradation. The subunit, a crucial scaffolding component of the IFT particle complex B, is indispensable for ciliogenesis. The absence of IFT proteins halts cilia formation and leads to ciliopathies (27).

The ciliogenesis process begins with the transformation of the mother centriole into the basal body, which then migrates and docks at the membrane to nucleate the axoneme (28). Distal appendages on the mature basal body facilitate membrane attachment and serve as docking sites for transition fibers. The docking of the basal body relies on the distal appendage centrosomal protein 164 (CEP164), while appendage proteins CEP83 and are involved in recruiting receptors that regulate vesicular trafficking to the ciliary base (29-31). Following docking, transition fibers extend from the basal body, setting the stage for axoneme growth through IFT-driven processes.

Signaling pathways coordinated by primary cilia. Primary cilia act as cellular antennas, extending into the extracellular environment to detect mechanical and chemical signals, including growth factors, nutrients, lipids, odorants, light and fluid flow. These signals are then translated into cellular responses, regulating vital developmental and homeostatic pathways such as cell growth, proliferation, differentiation, migration, polarity and tissue morphogenesis (32). Notable signaling pathways modulated by primary cilia include Hedgehog (Hh), Wnt, Notch, Hippo, G protein-coupled receptors (GPCR), mTOR, transforming growth factor (TGF)β, receptor tyrosine kinase (RTK) and planar cell polarity pathways.

Hh signaling. The Hh signaling pathway is significantly modulated by primary cilia (33). Cilia provide a specialized compartment that aids in the processing of Glioma-associated oncogene homolog (Gli) the family of Zn-finger transcription factors, which are crucial for the transduction of Hh signals. In the absence of Hh ligands such as Sonic Hh (Shh), Gli2 and Gli3 are processed into their activator and repressor forms via proteolytic cleavage (34). This processing is facilitated by the ciliary kinase protein kinase A (PKA), the scaffolding protein kinesin family member 7 (Kif7) and a protease complex. The binding of Shh to its receptor, patched 1 (PTCH1) located on the cilia, alleviates the inhibition of Smoothened (SMO) by PTCH1, leading to the accumulation of SMO within the cilia (35). This accumulation prevents the proteolytic processing of Gli proteins, enriching the Gli2/3 activator form and triggering the expression of Hh target genes.

Wnt signaling. Primary cilia also influence Wnt signaling, a pathway that involves the regulated proteolysis of the

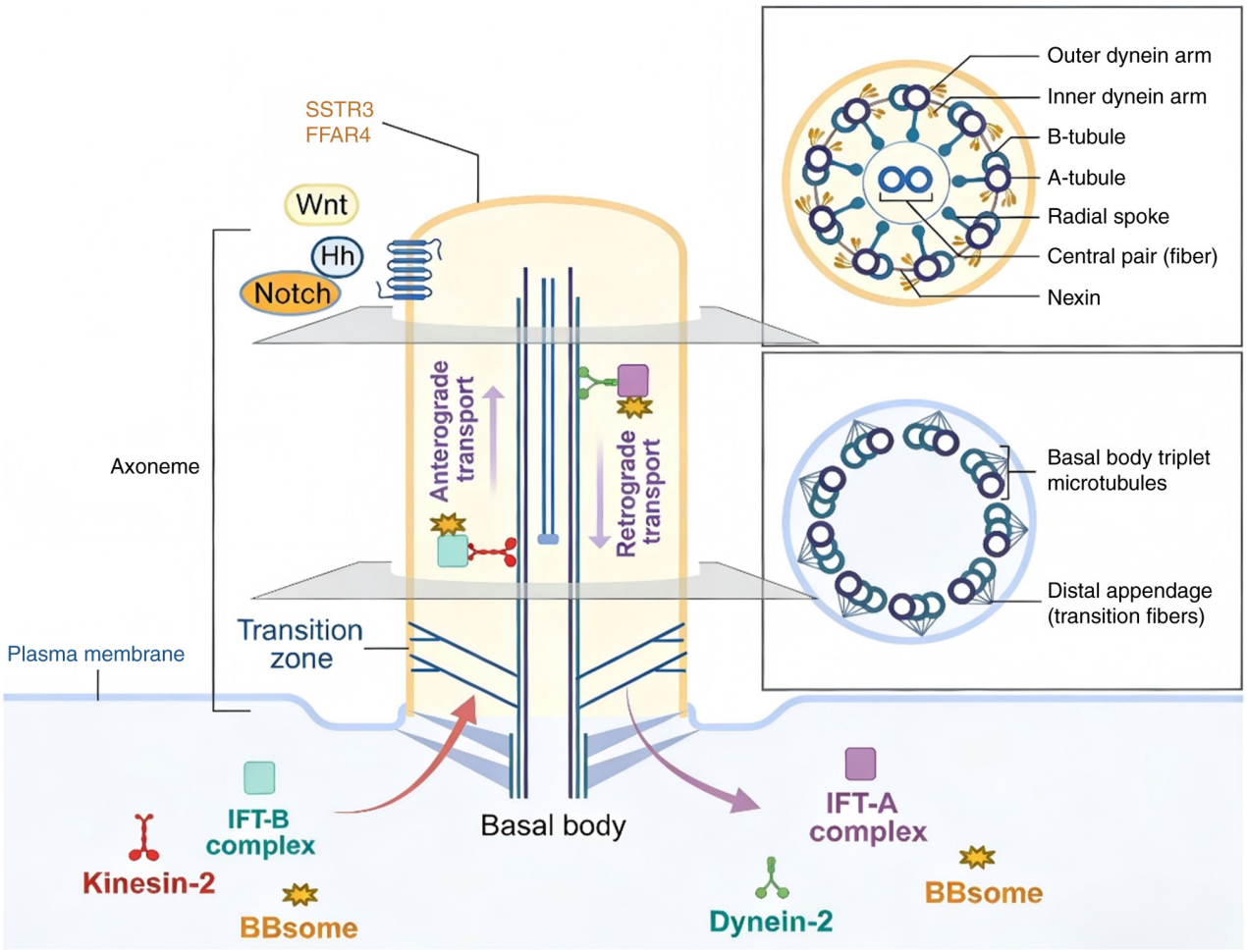

Figure 1. Basic structure of cilia. A typical cilium consists of an axoneme composed of nine pairs of microtubules. Each pair of microtubules originates from the inner two microtubules of the basal body microtubule triplets. The axoneme is surrounded by a specialized ciliary membrane, which is separated from the cell membrane by a transition fiber region. Cilia are broadly classified into two types (9+2 or 9+0 structures) based on the presence or absence of a central pair of microtubule singlets in the axoneme. Cilia are assembled and maintained by IFT, a process that relies on the microtubule motor proteins dynein 2 and cytoplasmic kinesin to transport the IFT protein complex and its associated cargo up and down the length of the cilium. SSTR3, somatostatin receptor 3; FFAR4, free fatty acid receptor 4; Wnt, wingless/integrated; Hh, Hedgehog; IFT-A complex, intraflagellar transport A complex; BBSome, Bardet-Biedl syndrome complex.

transcription co-activator β-catenin (36). The ciliary protein Kif3a plays a role in inhibiting β-catenin signaling by facilitating its degradation (37). Consequently, the loss of cilia results in enhanced Wnt signaling activity. The interplay between Hh and Wnt signaling is pivotal in determining cell fate during developmental processes. Furthermore, cilia contribute to the orientation of the mitotic spindle and the regulation of oriented cell divisions through planar cell polarity signaling (38).

mTOR and Yes-associated protein (YAP)/transcriptional coactivator with PDZ-binding motif (TAZ). The master regulator of metabolism, mTOR, is localized to primary cilia and plays a role in regulating ciliary length (39). mTOR supports ciliogenesis and the docking of ciliary vesicles. Of note, the length of cilia can influence mTOR activity by modulating the expression of its inhibitors, such as the DEP domain-containing mTOR-interacting protein, an endogenous suppressor of mTOR signaling. Additionally, the Hippo pathway effectors YAP/TAZ are recruited to primary cilia under conditions of serum starvation (40). This recruitment inhibits the activity of YAP/TAZ, thereby limiting cell proliferation. Ciliogenesis is promoted, whereas deciliation activates YAP/TAZ-dependent transcription, highlighting the complex interplay between cilia and cellular signaling pathways (41).

RTKs. Primary cilia serve as a niche for growth factor receptors such as platelet-derived growth factor (PDGF), insulin-like growth factor (IGF) and fibroblast growth factor, facilitating the initiation of intracellular signaling cascades that govern cell proliferation and differentiation. Notably, the PDGF receptor α is specifically localized to the primary cilia of fibroblasts, where ligand binding triggers MEK/ERK and mTOR signaling pathways (42). Disruptions in PDGF signaling are linked to ciliopathy phenotypes, highlighting the unique role of ciliary compartmentalization in modulating RTK signaling, potentially eliciting distinct cellular responses compared to activation at the cell surface (43).

GPCRs. GPCRs, pivotal in detecting extracellular signals, are enriched within the membranes of cilia (44). An example includes the somatostatin receptor 3 (SSTR3), which is preferentially localized to neuronal cilia (45). Activation of ciliary GPCRs can induce localized Ca^{2+} signaling, underscoring the importance of ciliary compartmentalization in achieving signaling specificity through subtype-selective GPCR

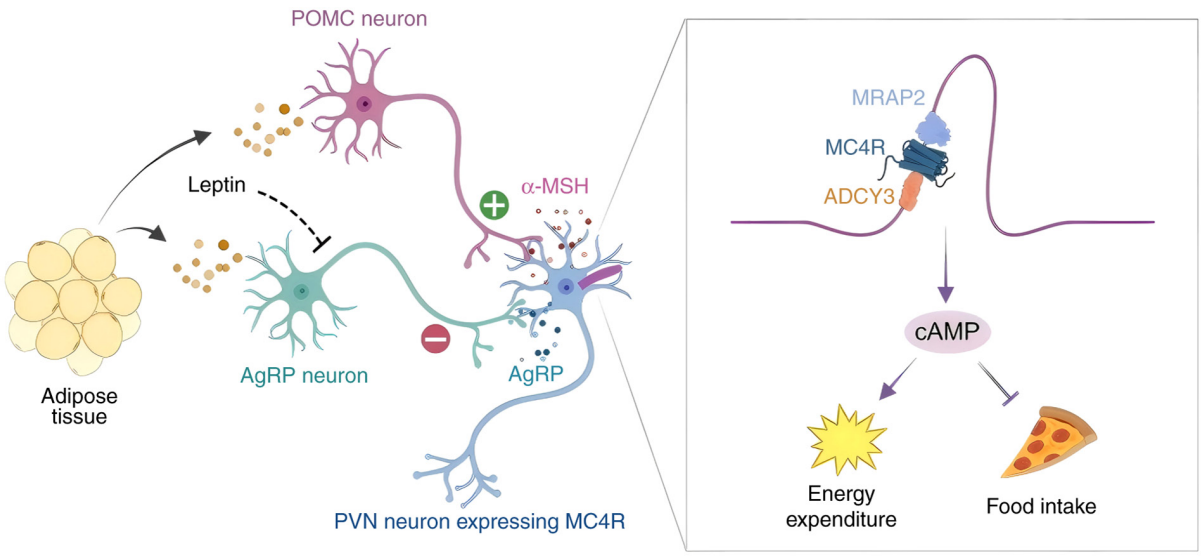

Figure 2. Role of cilia in regulation of food intake and energy expenditure. The arcuate nucleus is composed of different types of ciliary neurons, including anorexigenic neurons expressing POMC and orexigenic neurons expressing AgRP. Leptin, secreted by adipose tissue, activates leptin receptors in the arcuate nucleus, where it increases the transcription of POMC and decreases the transcription of AgRP. POMC-expressing neurons are activated to accelerate the secretion of α-MSH, which activates MC4R in the PVN, leading to decreased food intake and increased energy expenditure. PVN, paraventricular nucleus; POMC neuron, pro-opiomelanocortin neuron; AgRP neuron, agouti-related peptide neuron; α-MSH, α-melanocyte-stimulating hormone; PVN, paraventricular nucleus; MC4R, melanocortin 4 receptor; MRAP2, melanocortin 2 receptor accessory protein 2; ADCY3, adenylate cyclase 3; cAMP, cyclic adenosine monophosphate.

localization (46). Furthermore, cilia facilitate the integration of multiple signaling pathways, including Wnt, Hedgehog and RTK, by housing components of these pathways and enabling crosstalk with GPCRs (47).

TGFβ superfamily signaling. Cilia influence the TGFβ superfamily's signaling mechanisms via receptor complexes comprising type I and II serine/threonine kinases (48). Localization of TGFβ receptors to cilia enhances ligand-mediated activation, with ciliary loss leading to impaired signaling. This cilia-mediated control is crucial for regulating developmental and homeostatic processes. The ciliary protein Tectonic plays a significant role in mediating TGFβ signals, interacting with Shh and canonical Wnt pathways (49,50).

Notch signaling. Primary cilia enhance Notch signaling pathway activation through the regulated intramembrane proteolysis of Notch receptors, which releases an intracellular fragment that activates gene transcription (51). Both Notch receptors and their ligands, such as Delta, are localized to cilia, emphasizing the cilia's role in facilitating Notch pathway processing. The disruption of ciliogenesis adversely affects Notch-dependent developmental processes, illustrating the functional significance of ciliary regulation in signal transduction (52).

Primary cilia in immune cells. Recent research has definitively identified functional primary cilia within the immune system. A study utilized an Arl13b - mCherry transgenic mouse model, where the ciliary membrane protein Arl13b is fused to the red fluorescent protein mCherry for specific labeling, revealed that 13.4±0.9% of spleen cells and 20.3±0.9% of thymus cells possess primary cilia measuring 3-6 μm in length (53). This challenges the long-standing paradigm that lymphocytes are non-ciliated. While the specific immune cell subtypes that are ciliated require further characterization, this finding implies a conserved role for ciliary architecture and IFT in immune cells. The presence of these signaling organelles suggests they may serve as specialized sensory platforms in lymphoid tissues, potentially detecting local cytokines, pathogens or metabolic signals to modulate immune responses. This expands the physiological landscape of cilia-mediated signaling into immunoregulation, with possible implications for inflammatory aspects of metabolic diseases (53,54).

3. Role of cilia in lipid metabolism diseases

Cilia in obesity

Appetite regulation. Arcuate nucleus pro-opiomelanocortin (POMC) neurons possess primary cilia interacting with melanocortin 4 receptor (MC4R) to regulate satiety signaling (5,55). Ablating IFT88 in POMC neurons caused cilia loss, reduced POMC firing and decreased α-melanocyte stimulating hormone (α-MSH) release (5). Further analysis found altered trafficking and dysfunctional signaling of the MC4R satiety receptor in cilia-defective POMC neurons. This caused impaired POMC neuron response to α-MSH and defective propagation of satiety signals to downstream nuclei like the paraventricular nucleus. MC4R activation normally induces membrane depolarization, action potential firing and α-MSH secretion in POMC neurons (55). However, optogenetic and electrophysiology experiments revealed loss of these MC4R responses in POMC neurons lacking cilia. This MC4R/POMC signaling axis is critical for appetite regulation (56). Accordingly, disrupting the axis through cilia defects caused hyperphagia, reduced energy expenditure and obesity in mice (Fig. 2).

Obesity is commonly linked with the aging process. The MC4R is crucial in the hypothalamic leptin-melanocortin pathway for combating obesity (57). Research indicates that

primary cilia containing MC4R in hypothalamic neurons of rats progressively shorten with age, which correlates with metabolic decline and increased fat accumulation. This phenomenon, a condition termed 'age-associated ciliopathy' is a progressive functional decline in a specific tissue or organ system. This decline results from the deterioration of primary cilia structure, which occurs as a direct consequence of the biological aging process. It is driven by the upregulation of leptin-melanocortin signaling due to excessive nutrient intake. However, dietary restriction or inhibition of ciliogenesis-associated kinase 1 can alleviate or reverse this condition. Genetically induced shortening of MC4R-bearing cilia in hypothalamic neurons results in decreased responsiveness to melanocortin, leading to reduced thermogenesis in brown adipose tissue, lower energy expenditure, increased appetite and subsequent obesity and leptin resistance (58). Therefore, while leptin exerts anti-obesity effects in the short term, prolonged leptin-melanocortin signaling contributes to the age-related shortening of MC4R cilia, heightening the risk of obesity.

Ventral medial hypothalamus SF1 neurons also require primary cilia for regulating food intake (59). SF1 neuronal cilia modulate activity and calcium dynamics through ATP/P2Y purinergic receptor and γ-aminobutyric acid type B receptor signaling (60). Selectively ablating IFT88 in SF1 neurons abolished cilia and altered calcium oscillations. This caused overactivity of SF1 neurons, hyperphagia, reduced energy utilization and pronounced diet-induced obesity (61). Further characterization found changes in genes regulating feeding and metabolism, such as agouti related peptide (AGRP), melanin concentrating hormone and cocaine and amphetamine regulated transcript (62). Thus, ciliary signaling regulates hunger/satiety neuronal function to suppress overeating and weight gain.

Olfactory cilia detect food odors, with their ablation causing hyperphagia (63). Deleting IFT88 eliminates olfactory cilia and receptors like cyclic nucleotide-gated channel α2, a core ion channel essential for olfactory signal transduction, disrupting odor detection and discrimination (64). Electro-olfactogram recordings confirmed loss of odor-evoked responses. Further RNA sequencing revealed reduced expression of adenylate cyclase 3 and other olfactory signaling molecules. Behaviorally, mice lacking olfactory cilia exhibited hyperphagia, glucose intolerance, increased adiposity, liver steatosis and weight gain on a high-fat diet. This demonstrates the key role of olfactory cilia in controlling food seeking behaviors that impact energy balance and obesity susceptibility (65).

Tetratricopeptide repeat domain 21B (THM1) (also known as TTC21B or IFT139) encodes a component of the intraciliary transport-A complex and mutations in this gene are present in 5% of patients with ciliary diseases (66). Research has demonstrated that adult mice lacking Thm1 develop obesity, diabetes, hypertension and fatty liver, with notable sex differences in susceptibility to weight gain and metabolic dysfunction (67). When Thm1 conditional knockout mice were pair-fed with control mice, obesity and related disorders were prevented, indicating that excessive food intake contributes to the obesity phenotype. Thm1 knockdown leads to increased localization of adenylyl cyclase III in primary cilia, resulting in cilia with shortened, bulbous distal tips on neurons in the hypothalamic arcuate nucleus, a key center for regulating feeding and activity. In pre-obese Thm1 conditional knockout mice, expression of the anorexigenic hormone POMC in the arcuate nucleus was reduced by 50%, contributing to hyperphagia (68). Fasting in these mice did not alter the expression of POMC or the Agrp, suggesting an impaired ability to perceive peripheral signaling changes (69). Therefore, ciliary defects due to THM1 gene mutations reduce sensitivity to ingestive signals, disrupting appetite regulation and leading to hyperphagia, obesity and metabolic disorders.

The PI3K-3 phosphoinositide dependent protein kinase 1 (PDK1)-forkhead box (Fox)O1 signaling pathway plays a role in regulating energy homeostasis. When unphosphorylated by PDK1, FoxO1 is active and located in the nucleus, where it represses POMC expression and stimulates Agrp expression (70). Activation of leptin and insulin results in the phosphorylation of FoxO1 and its export from the nucleus, allowing STAT3 to bind to the POMC and Agrp promoters, which activates POMC neurons and inhibits AgRP neurons (71). In conditions of excess energy, leptin signaling activates mTOR, promoting phosphorylation and inhibiting adenosine monophosphate-activated protein kinase (AMPK), thereby suppressing food intake (72).

Adipogenesis. Primary cilia play a pivotal role in suppressing adipocyte differentiation by modulating Hh pathway signaling. Specifically, the transcriptional repressor is a form of Gli3 (Gli3R) inhibits the expression of peroxisome proliferator-activated receptor γ (PPARγ), a key regulator of adipogenesis (73). Disruption of ciliogenesis through the knockdown of intraflagellar transport protein IFT88 or other ciliary genes results in the absence of primary cilia, preventing the formation of Gli3R (74). Consequently, this leads to the derepression of the PPARγ promoter. RNA interference targeting IFT88 in 3T3-L1 preadipocytes has shown a significant upregulation of PPARγ expression in the absence of cilia, facilitating enhanced differentiation into mature adipocytes (75). This is evidenced by increased lipid droplet formation, as indicated by Oil Red O staining, and elevated expression of adipogenic markers such as fatty acid binding protein 4, lipoprotein lipase, adiponectin and C/EBPα, as confirmed by quantitative PCR and immunoblot analyses (8). Furthermore, the activation of Hh signaling using the agonist purmorphamine or by expressing Gli3R can mitigate the accelerated adipogenesis resulting from ciliary loss.

Adult mesenchymal stem cells, including preadipocytes, have a cellular sensory structure called primary cilia. Preadipocytes with these cilia are prevalent around blood vessels in adipose tissue and become active in response to high-fat diets (76). Disruption of cilia in mouse preadipocytes significantly affects the expansion of white adipose tissue. Researchers have identified that the localization of the omega-3 fatty acid receptor free fatty acid receptor 4/G protein-coupled receptor 120 (FFAR4/GPR120) within cilia, which promotes adipogenesis, depends on tubby-like protein 3, an essential adaptor of the IFT-A complex that mediates the ciliary entry of specific membrane proteins. FFAR4 agonists and omega-3 fatty acids, but not saturated fatty acids, stimulate mitogenesis and adipogenesis by rapidly increasing cyclic (c)AMP production within cilia, resulting in the phosphorylation and nuclear

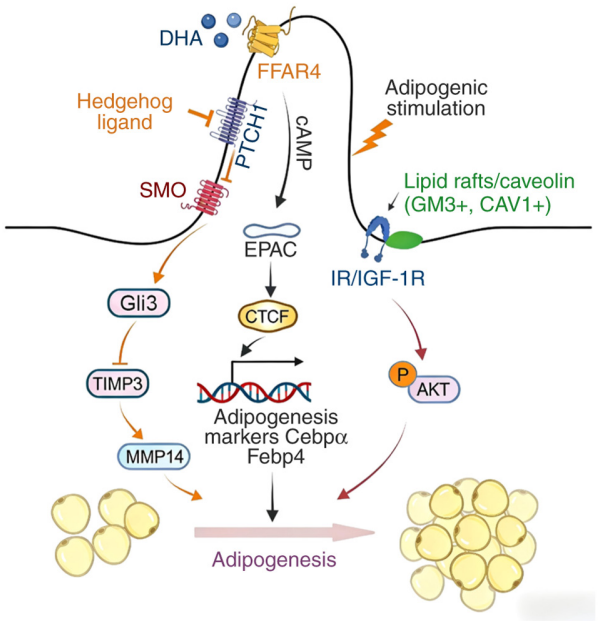

Figure 3. Role of cilia in adipogenesis. DHA fatty acids activate FFAR4 on cilia, leading to an increase in cAMP levels and the activation of EPAC signaling. EPAC signaling, in turn, leads to CTCF-dependent recruitment of p300 to the PPARγ and CEBPα loci, thereby facilitating chromatin remodeling. This process results in the adipose transcriptional activation of PPARγ and C/EBPα, which upregulate the expression of adipose synthesis genes and promote the differentiation of preadipocytes into adipocytes. In regions where IR (and possibly IGF1R) is present around the base of the cilium, adipogenic stimuli induce the aggregation of lipid rafts containing CAV1 and GM3. This aggregation activates the IR/IGF1R-Akt cascade, thereby promoting adipogenesis. In addition, the Hh signaling pathway regulates the expression of TIMP3 through the transcription factor Ci/Gli. Gli3R is a transcriptional repressor from the Gli family of proteins that can inhibit TIMP3, allowing MMP14 to be active. MMP14 promotes adipogenesis through mechanisms involving the activation of the master regulators PPARγ and C/EBPα. DHA, docosahexaenoic acid; FFAR4, free fatty acid receptor 4; PTCH1, patched 1; SMO, smoothened; GLI3, GLI family zinc finger protein 3; TIMP3, tissue inhibitor of metalloproteinases 3; MMP14, matrix metalloproteinase 14; cAMP, cyclic adenosine monophosphate; EPAC, exchange protein directly activated by cAMP; C/EBPα, CCAAT/enhancer-binding protein α; FABP4, fatty acid-binding protein 4; IR/IGF-1R, insulin receptor/insulin-like growth factor 1 receptor; GM3, monosialodihexosylganglioside; CAV1, caveolin-1.

translocation of CCCTC-binding factor (CTCF). Within the nucleus, phosphorylated CTCF acts as a scaffold, recruiting the histone acetyltransferase p300 to form an activation complex at the regulatory regions of key adipogenic genes, such as PPARγ and CCAAT/enhancer-binding protein α (CEBPα). P300 catalyzes local histone hyperacetylation, opening the chromatin. This facilitates the binding of the transcriptional machinery and adipogenic factors, including PPARγ and CEBPα, creating a positive feedback loop, which initiates adipogenesis (8). Dietary omega-3 fatty acids specifically boost the number of adipocytes, facilitating the creation of new adipocytes and promoting the storage of saturated fatty acids to maintain a healthy balance of adipose tissue (8) (Fig. 3).

Fas-binding factor 1 (FBF1) is a core component of ciliary transition fibers that mediates stress-induced cilium-to-promyelocytic leukemia protein-nuclear body signaling to initiate cellular senescence (77). Of note, the absence of FBF1 results in a notable paradox: Fbf1tm1a/tm1a mice, which are a genetically modified model carrying a 'knockout-first' tm1a allele in the FbF1 locus, despite progressively becoming obese, do not develop adverse metabolic complications throughout their lifespan. The lack of FBF1 leads to the upregulation of the ciliary program in white adipose tissue through an A-kinase anchoring protein 9 (AKAP9)-dependent, cilia-regulated PKA signaling pathway. AKAP9, a scaffold protein enriched at the ciliary base, anchors PKA and facilitates its compartmentalized activation (78). Additionally, it significantly enhances adipogenesis through Hh signaling regulated by Bardet-Biedl syndrome proteins. The combined effect of increased ciliogenesis and expansion of adipose tissue highlights a potential explanation for the phenomenon of 'healthy obesity' observed in Fbf1tm1a/tm1a mice (78). This study suggests that targeting preadipocyte cilia could represent a promising strategy for combating metabolic disorders.

Injured skeletal muscle has the ability to regenerate; however, with aging or in the case of muscular dystrophies, muscle tissue tends to be replaced by fat. Following injury, fibro/adipogenic progenitors (FAPs) within the muscle begin to proliferate and differentiate into adipocytes (79). These FAPs actively form primary cilia, which mediate intercellular communication, including Hh signaling. Studies have shown that genetic ablation of cilia in FAPs inhibits intramuscular fat formation both after injury and in a mouse model of Duchenne muscular dystrophy. Furthermore, preventing FAP ciliation not only improved myofiber regeneration post-injury but also mitigated the reduction in myofiber size observed in muscular dystrophy models (80). Hh signaling via FAP cilia controls the expression of tissue inhibitor of metalloproteinases 3 (TIMP3), a secreted inhibitor of metalloproteinases (MMPs), which in turn suppresses MMP14 activity to prevent adipogenesis. Additionally, a pharmacological agent that mimics TIMP3 effectively blocked the differentiation of FAPs into adipocytes, suggesting a potential therapeutic approach to counteract the fatty degeneration of skeletal muscle (80). Thus, it may be concluded that Hh signaling through FAP cilia is crucial in regulating the regenerative processes of skeletal muscle in response to injury.

Research has shown that C3H10T1/2 mesenchymal progenitor cells, crucial for cilia formation, exhibit significantly longer cilia compared to control cells and are unable to differentiate into adipocytes (81). The elongated cilia hinder the accumulation of caveolin-1 and/or monosialodihexosylganglioside (GM3)-positive lipid rafts surrounding the ciliary base. Caveolin-1 is a scaffold protein essential for caveolae formation and insulin receptor stabilization, and GM3 is a ganglioside enriched in lipid rafts that promotes insulin receptor retention, which are all critical components involved in the compartmentalization of insulin signaling. Impaired accumulation of these components at the ciliary base disrupts local lipid raft microdomains, leading to the accumulation of insulin receptor proteins at the ciliary base and subsequent inhibition of insulin-Akt signaling (82). In trichostatin knockout mice, adipogenic progenitor cells have elongated cilia, which disrupts lipid raft dynamics. Knockout mice fed a chronically high-fat diet displayed reduced body fat and smaller adipocytes compared to wild-type mice (82). Therefore, primary cilia may play a role in regulating adipogenic signaling by controlling lipid raft dynamics around the cilia (Fig. 3).

Glucose homeostasis. Primary cilia on pancreatic islet cells are pivotal for the maintenance of normal glucose homeostasis, with defects in cilia contributing to impaired insulin secretion and the exacerbation of metabolic dysfunction associated with obesity (83,84). These non-motile cilia are present on all types of islet endocrine cells, including insulin-producing β-cells, glucagon-secreting α-cells, somatostatin-releasing δ-cells, and pancreatic polypeptide-containing PP cells. PP cells are a distinct islet endocrine subtype that regulates exocrine and endocrine pancreatic activity via autocrine and paracrine signaling. These cilia project into the central lumen of the pancreatic ducts (85).

Positioned strategically, cilia play a critical role in sensing fluid flow and modulating Ca^{2+} signaling dynamics, crucial for stimulus-secretion coupling in β-cells (86). The influx of Ca^{2+} in response to glucose metabolism acts as a fundamental trigger for the biphasic secretion of insulin. Experimental deletion of the intraflagellar transport protein IFT88, or disruption of other genes involved in ciliogenesis specifically within β-cells, has been shown to impair glucose-induced Ca^{2+} influx. Such perturbation in Ca^{2+} signaling leads to the loss of both first and second-phase insulin releases in response to glucose, as demonstrated in static islet incubations (87). This diminished insulin secretion capacity was corroborated *in vivo* through observed impaired glucose tolerance tests in conditional IFT88 knockout mice.

Furthermore, islet cilia enhance insulin secretion by facilitating the proper localization of insulin secretory granules at the plasma membrane (83). The absence of cilia disrupts the normal clustering of insulin granules near the ciliary base, a region where they are primed for glucose-responsive exocytosis. Super-resolution imaging techniques have highlighted the preferential localization of granules in proximity to ciliary bases (88). The absence of cilia interrupts the trafficking of these granules along microtubules, leading to aberrant docking and compromised insulin release. Additionally, primary cilia are implicated in supporting exosome secretion, a process that aids in the trafficking of secretory granules, thereby optimizing insulin secretion (80,89). Cilia have been shown to support exosome secretion from β-cells by acting as the trigger for a specific paracrine signaling cascade. They ensure that the specific signaling receptors, particularly Ephrin type-A receptor 2 (EphA2), are selectively packaged into exosomes to regulate the function of neighboring cells. Cilia defects prevent EphA2 from ever reaching the endosomal sorting complexes required for transport pathway, a conserved membrane trafficking system that mediates the sorting, degradation, or recycling of ubiquitinated membrane proteins (87). This impairment in an auxiliary secretion route likely further aggravates deficits in granule docking and release.

In summary, primary cilia orchestrate multiple aspects of stimulus-secretion coupling, including Ca^{2+} signaling dynamics, the trafficking and docking of insulin granules and exosome functionality. The disruption of these processes by diabetes and obesity-induced cilia defects significantly compromises insulin release and glucose regulation, propagating a detrimental cycle where hyperglycemia induces further cilia loss, exacerbating insulin secretion impairment and amplifying metabolic disease challenges. Unraveling these intricate mechanisms sheds light on new avenues for understanding β-cell dysfunction and its relevance to metabolic diseases.

Inflammation and metabolic homeostasis. Primary cilia play a crucial role in suppressing inflammatory pathways, the dysregulation of which can disrupt metabolic homeostasis and contribute to the development of obesity (90). Notably, specific hypothalamic neurons, equipped with primary cilia, modulate inflammation through signaling mediated by somatostatin and leptin receptors (91). The SSTR3, selectively localized to neuronal cilia, is a Gai-coupled receptor, inhibits adenylyl cyclase, and reduces cAMP levels and PKA activity. The suppression of the cAMP/PKA pathway which alters the availability and function of the transcriptional co - activator CBP/p300. CBP/p300 is a pair of highly homologous histone acetyltransferases that facilitate gene activation by acetylating histones and recruiting transcription machinery. This suppression inhibits NF-κB - mediated cytokine production (92,93). The absence of SSTR3 in hypothalamic arcuate nucleus POMC neurons amplifies the inflammatory response to lipopolysaccharides, leading to increased release of cytokines such as IL-6, IL-1β and TNFα. Furthermore, SSTR3 activation within POMC neuron cilia curtails inflammation-induced ceramide production and endoplasmic reticulum stress, underscoring the anti-inflammatory effects vital for preserving the normal function and satiety signaling of POMC neurons. Disruption of this ciliary SSTR3 pathway perturbs satiety signaling and feeding behaviors, impacting energy balance (94).

In the context of obesity, hyperleptinemia triggers the relocalization of the leptin receptor (LepR) away from neuronal cilia within the mediobasal hypothalamus (MBH), impairing leptin sensing (58). This alteration in LepR trafficking, evidenced through immunofluorescence staining and live cell imaging, leads to diminished leptin pathway activation, as indicated by reduced STAT3 phosphorylation (95). Mice exhibiting disrupted ciliary trafficking of LepR develop leptin resistance, characterized by overeating, decreased energy expenditure and exacerbated dietary-induced obesity. However, restoring the proper ciliary localization of LepR in MBH neurons can reestablish leptin sensitivity and ameliorate obesity-related phenotypes, highlighting the significance of LepR signaling integrity in hypothalamic neuronal cilia for maintaining normal appetite regulation (58).

Adipocyte cilia also mitigate inflammation by modulating responses to cytokines such as TNF (78). In obese mice on a high-fat diet, adipocyte cilia become shortened, losing SSTR3 localization. Compared to their lean counterparts, obese visceral fat exhibits reduced cilia prevalence and length, with cilia loss intensifying TNFα-induced inflammation (75). This is characterized by increased NF-κB pathway activity, elevated production of pro-inflammatory cytokines and higher levels of macrophage markers like F4/80, establishing the role of adipocyte cilia in curbing inflammation during obesity (96).

Beyond these tissue-specific mechanisms, the chronic low-grade inflammation that drives increased fat storage and fatty liver disease involves critical inter-organ communication. The progression of metabolic dysfunction-associated steatotic liver disease (MASLD) is supported by a spleen-liver axis that modulates systemic inflammation. This process is characterized by an enrichment of splenic myeloid-derived suppressor cells (MDSCs) and natural killer T (NKT) cells, along with

a loss of hepatic T and B cells. Correlation analysis confirms a selective, strong positive correlation between the distribution of spleen and liver MDSC and NKT cells, indicating that the spleen-liver axis modulates obesity-induced immune dysregulation in a cell-specific manner, as demonstrated by recent research (97). Furthermore, spleen-derived signals can directly amplify hepatic inflammation. Leukotriene B4 (LTB4) released by the spleen enhances liver TNF production both *in vivo* and *in vitro*, identifying LTB4 as a spleen-derived endocrine signal that promotes hepatic TNF production during systemic inflammation (98). All these findings focusing on pro-inflammatory processes lend credence to the significance of the liver-spleen axis in non-alcoholic fatty liver disease/MASLD pathogenesis (99). This axis represents a critical systemic circuit through which inflammatory signals are amplified and disseminated, contributing to the metabolic dysfunction driven by ciliary defects in metabolic tissues.

Overall, by regulating key inflammatory, metabolic and endocrine pathways in the hypothalamus and adipose tissue, primary cilia suppress local and systemic abnormalities that can disturb energy homeostasis and promote obesity. Further studies are needed to elucidate the complex molecular intersections between ciliary dysfunction and inflammation in metabolic disease.

Nutrient digestion/absorption. When cells face nutrient deprivation, they encounter an energetic crisis that is managed through metabolic reorganization and adjustments in organelle functions. Primary cilia, which are microtubule-based organelles on the cell surface, have the capability to integrate various metabolic and signaling cues. Primary cilia have been shown to sense glutamine availability and respond by elongating via an asparagine synthetase (ASNS), dependent mechanism that promotes ciliary tubulin acetylation and stabilization, thereby enhancing ciliary length under nutrient replete conditions (100). During nutrient deprivation, cilia elongate, which occurs independently of mTOR complex 1 (mTORC1), even when mitochondrial function, ATP supply and AMPK activation are compromised. Of note, the removal or supplementation of glutamine, under both *in vivo* and *in vitro* nutritional stress, is necessary and sufficient to regulate mitochondrial mitophagy. This process depends on the production of glutamate from ASNS, leading to either the elongation or retraction of cilia. Cells with IFT88 gene mutations that lack cilia show glutamate-dependent mitochondrial anaphase during metabolic stress, due to reduced ASNS expression and activity at the ciliary base (100). These findings suggest that primary cilia are responsive to cellular glutamine levels through ASNS during periods of metabolic stress.

Given that certain commensal microbes metabolize nutrients in manners protective against obesity, the regulation of their populations through cilia-mediated antimicrobial secretion directly impacts nutritional absorption. Additionally, cilia within the biliary tract facilitate the circulation of bile necessary for the digestion and absorption of lipids and fat-soluble vitamins. Disruptions to motile cilia in the biliary system can alter bile flow and contribute to gallstone disease (101).

In summary, through the coordinated regulation of epithelial barrier function, antimicrobial release, microbiome composition, bile flow and nutrient absorption, intestinal cilia exert a profound influence on metabolism related to obesity. Elucidating these intricate roles underscores the importance of intestinal cilia in maintaining metabolic health and offers potential avenues for targeting obesity and its associated metabolic disorders.

Type 2 diabetes (T2D). Insufficient adaptive β-cell compensation is a hallmark of T2D (102). Primary cilia, which are versatile sensory appendages, play a crucial role in regulating diverse cellular functions. Studies have identified a notably higher number of downregulated genes associated with cilia in the pancreatic islets of diabetes-susceptible New Zealand Obese mice compared to diabetes-resistant B6-ob/ob mice (103). Among the 327 mouse cilia genes with altered expression, 81 had human homologs that were also impacted in islets from diabetic individuals. In non-diabetic mouse and human islets, there was a significant overlap in the upregulation of ciliary genes linked to cell-cycle progression. Suppression of KIF3A, a critical gene for ciliogenesis, through short hairpin RNA, disrupted cell division in MIN6 β-cells and primary pancreatic islet cells in both mice and humans, as shown by decreased bromodeoxyuridine incorporation (103). Collectively, these results highlight the vital role of ciliary gene regulation in islet functionality and the risk of developing T2D.

Kidney epithelial cell metabolic adaptation. Organs and cells need to adapt to the shear stress induced by biofluids. Studies have demonstrated that shear stress promotes mitochondrial biogenesis and metabolic reprogramming in renal epithelial cells to ensure energy production and cellular adaptation (104). This stress also stimulates lipophagy, which facilitates the production of fatty acids that mitochondria use to produce ATP through β-oxidation (105). This flow-induced process relies on primary cilia located at the tips of epithelial cells (104). Evidence from a unilateral ureteral obstruction mouse model revealed that the absence of urinary flow disrupts cilia-dependent lipophagy and mitochondrial biogenesis, culminating in lipid droplet accumulation, thereby demonstrating that fluid flow is a critical driver of lipid metabolism and metabolic adaptation in renal epithelial cells *in vivo* (104). Shear stress activates two signaling pathways originating from primary cilia. The first pathway increases mitochondrial mass by upregulating two key regulators of mitochondrial protein expression: PPARγ coactivator 1α, a master transcriptional coactivator of mitochondrial biogenesis, and mitochondrial transcription factor A, a nuclear-encoded protein essential for mitochondrial DNA transcription and replication. The second pathway involves the activation of lipophagy, a form of selective autophagy, to degrade lipid droplets (104). Fatty acids generated from lipophagy and cytoplasmic lipolysis are then used to enhance ATP production in mitochondria (106). Primary cilia-dependent lipophagy and mitochondrial biogenesis are essential for supporting energy-demanding cellular processes such as glucose reabsorption, gluconeogenesis and cytoskeletal remodeling (104). These findings underscore the crucial role of primary cilia and autophagy in converting mechanical forces into biological and physiological responses.

4. Impact of lipid metabolism abnormalities on cilia

Metabolic abnormalities set in motion a self-perpetuating cycle wherein ciliary defects, induced by a high-fat diet and

subsequent metabolic disturbances, further aggravate weight gain and associated health issues (107). The disruption of anorexigenic signaling from hypothalamic neuronal cilia leads to unchecked hyperphagia. Dysfunctional pancreatic islet cilia hinder insulin secretion, aggravating glucose intolerance. Furthermore, shortened adipocyte cilia amplify inflammatory responses, driving excessive adipose tissue growth and ectopic fat storage. Impaired biliary cilia affect bile circulation and cholesterol metabolism, highlighting the tissue-specific consequences of obesity on cilia and their contribution to systemic metabolic imbalances.

Neuronal cilia. Emerging research indicates that obesity itself compromises ciliary structure and function through various mechanisms, setting off a deleterious cycle that exacerbates metabolic dysfunction. In neurons critical for appetite and glucose regulation, consumption of a high-fat diet has been shown to adversely affect cilia prevalence and morphology in the hypothalamus, cortex and hippocampus (96,108). Specifically, palmitic acid exposure led to a reduction in axoneme length and a decrease in the incidence of cilia within hypothalamic POMC and AgRP neurons (109). A similar deterioration was observed in hippocampal neurons subjected to saturated fatty acids *in vitro*. The hyperactivation of inflammatory pathways is a likely culprit behind neuronal cilia disruption. In POMC neurons, saturated fatty acids were found to prompt ceramide production and activate NF-κB, processes mediated by the ciliary somatostatin receptor SSTR3 (110). Counteracting this inflammation was shown to mitigate the loss of POMC cilia. Furthermore, a prolonged high-fat diet contributed to the mislocalization of the leptin receptor and disrupted leptin signaling specifically within MBH neuronal cilia that are instrumental in appetite regulation (91,111).

Pancreatic islet cilia. Pancreatic islet cilia are also vulnerable to the deleterious effects of chronic hyperglycemia and elevated free fatty acids characteristic of obesity (10). Hyperglycemia induced the accumulation of oxidative stress markers like 4-hydroxynonenal, a major bioactive aldehyde end-product of lipid peroxidation in β-cell cilia. Elevated glucose levels impaired ciliary Hh signaling, while palmitate hindered intraflagellar transport, compounding disruptions from glucotoxicity and lipotoxicity that impair insulin secretion by affecting ciliary signaling involved in Ca^{2+} dynamics and exocytosis.

Adipocyte cilia. Adipocyte cilia exhibited notable structural and functional impairments in the context of obesity. Cilia in obese visceral fat were shortened, with compromised motility and mechanosensation (108). Proteomic analyses identified a reduction in structural and signaling proteins, such as IFT88, smoothened and riboflavin kinase, in cilia from obese adipocytes, suggesting that alterations in ciliary signaling contribute to pathological adipose tissue expansion and inflammation. Cilia in cholangiocytes also displayed shortened, sparse axonemes in models of biliary cirrhosis (112). The collective disruption of cilia functions across diverse tissues due to obesity-induced damage plays a critical role in amplifying metabolic abnormalities.

Osteoblast cilia. Fracture risk and impaired healing in diabetes pose significant health concerns. Type 1 diabetes mellitus (T1DM) is known to affect osteoblasts and their progenitor cells, making it a critical risk factor for compromised fracture repair (14). Primary cilia, essential organelles, play a key role in cell differentiation, proliferation and function during tissue development and homeostasis (113). Proper cilia formation and function depend on an efficient IFT system, with IFT80 being a core transport protein vital for cilia assembly and bone development (27,114,115). Studies have demonstrated that diabetes lowers IFT80 expression and disrupts cilia formation in osteoblasts, leading to defective fracture healing (14). Researchers examined the impact of T1DM on primary cilia in a streptozotocin (STZ)-induced diabetes mouse model and assessed the role of cilia in osteoblastic fracture healing by deleting IFT80 in an osteoblastic cell line using osterix (OSX)-cre (OSXcre/tTAIFT80f/f). Findings indicated that diabetes inhibited cilia gene expression and primary cilia formation to a similar extent as IFT80 deletion in normoglycemic mice. Both diabetic mice and normoglycemic mice with cilia-deficient osteoblasts (OSXcre/tTAIFT80f/f) exhibited delayed fracture healing, significantly reduced bone density and mechanical strength, lower expression of osteoblast markers, diminished angiogenesis and decreased proliferation of bone-lining cells at the fracture site. *In vitro* studies revealed that advanced glycation end products (AGEs) decrease IFT80 expression in osteoblast progenitor cells. The absence of AGEs and IFT80 significantly reduced the number and length of cilia, thus inhibiting the differentiation of primary osteoblast precursors (14). Increased Foxo1 expression was linked to defective fracture healing under diabetic conditions. Researchers discovered that STZ-induced T1D markedly increased Foxo1 expression in the femoral fracture callus, resulting in a significant decrease in IFT80 expression and primary cilia number (14,116). Ablation of Foxo1 in osteoblasts of OSXcre/tTAFoxo1f/f mice restored IFT80 expression and ciliogenesis, improving bone formation and mechanical strength in diabetic fracture callus. *In vitro*, AGEs impaired cilia formation in osteoblasts and reduced mineralized matrix production, which was rescued by Foxo1 gene deletion. Mechanistically, AGEs increased Foxo1 expression and transcriptional activity, inhibiting IFT80 expression and cilia formation (102). Thus, diabetes impairs fracture healing through Foxo1-mediated inhibition of ciliary IFT80 expression and primary cilia formation, resulting in compromised osteogenesis. Inhibition of Foxo1 and/or restoration of cilia formation could enhance fracture healing in diabetes.

Chronic hyperglycemia and metabolic intermediates, including inflammatory factors, reactive oxygen species (ROS) and AGEs, are recognized as major contributors to bone complications (117). Through the use of a diabetic Sprague Dawley rat model and an *in vitro* cellular model of diabetic bone loss, researchers have shown that diabetes impairs primary cilia, leading to bone deterioration. However, the addition of Icariin (ICA) has been found to mitigate this negative impact. ICA acts by scavenging ROS and preserving mitochondrial and primary cilia homeostasis in osteoblasts. Functional primary cilia provide anchoring and modification sites for Gli2, which in turn activates the primary cilia/Gli2/osteocalcin signaling pathway, enhancing osteoblast

differentiation (118). Thus, ICA shows promise as a therapeutic agent for preventing diabetes-induced bone loss.

Metabolic abnormalities lead to ciliary dysfunction, which in turn exacerbates metabolic abnormalities, and an understanding of this interrelationship is critical to the development of therapeutic interventions. This creates a vicious cycle: Ciliary dysfunction in osteoblasts impairs bone formation and reduces the synthesis and bioactivity of bone-derived hormones like osteocalcin. Given that osteocalcin is known to enhance pancreatic β-cell proliferation and insulin secretion, its deficiency contributes directly to worsening systemic glucose homeostasis, thereby exacerbating the underlying metabolic dysfunction (119). Exploring strategies to restore ciliary function and break this cycle opens promising avenues for novel antimetabolic disease therapies. In the future, investigating the subtle effects of metabolic abnormalities on cilia in a variety of metabolic diseases will be critical to identify timely opportunities for tissue-specific interventions.

5. Cilia as therapeutic targets for treating obesity

The development of small molecules that stabilize the cytoskeleton presents a promising strategy to combat obesity-induced ciliary loss in neurons crucial for appetite regulation. Despite the clinical limitations of epothilones due to their side effects, the search for microtubule-stabilizing agents with favorable safety profiles remains a high priority. Ciliobrevins, known for their specific inhibition of cytoplasmic dynein motors, offer another avenue for modulating cilia length and Hh signaling (120). Ciliobrevin D, at low doses, has been shown to prevent the excessive elongation of adipocyte cilia triggered by mTORC1 activation, thereby normalizing lipid accumulation (120,121). The exploration of this compound, along with related dynein inhibitors, could provide insights into normalizing cilia length and adipose tissue homeostasis in the context of obesity.

Gene therapy strategies aiming to overexpress depleted ciliary proteins offer a method to restore structural integrity. The disruption of ciliogenesis through knockdown of the IFT protein IFT88 can be counteracted by adeno-associated virus (AAV)-mediated overexpression of IFT88, which rescues cilia formation and corrects aberrant Hh signaling in deficient cells (122). Employing similar approaches for AAV delivery of axonemal proteins, which are downregulated in obesity, such as SSTR3, might reinstate normal ciliary assembly and sensory function in metabolic tissues (123). Furthermore, therapeutic modulation of autophagic pathways appears promising for correcting the truncation of neuronal cilia associated with obesity. The mTOR inhibitor rapamycin has been shown to normalize shortened neuronal cilia, likely by promoting autophagic flux via transcription factor EB (TFEB) activation (124). Small molecule agonists of TFEB could potentially replicate this effect, offering a novel therapeutic strategy (125).

Lastly, targeting receptors concentrated in ciliary membranes offers another therapeutic avenue. The serotonin 2c receptor (HT2cR), localized in neuronal cilia, plays a vital role in regulating appetite circuits (126). Agonists that enhance HT2cR activity specifically within cilia may potentiate satiety signaling. Furthermore, biased agonists that directly activate MC4R in POMC cilia (127), irrespective of α-MSH levels, could address defective satiety signaling resulting from ciliary dysfunction (55,56). Pharmacologically amplifying the activity of appetite-suppressing receptors in the remaining neuronal cilia may provide a means to mitigate hyperphagia and combat obesity despite structural ciliary deficits.

Significant work remains to translate basic findings on ciliary dysfunction in obesity into clinical therapies. Cilia are widespread, so cell type-specific manipulation will be imperative. For example, selectively stabilizing POMC neuronal cilia vs. pancreatic islet cilia may produce different therapeutic benefits. Additionally, distinct approaches may be needed to correct defects in motile cilia vs. non-motile primary cilia. Improved imaging methods and biomarkers would help stratify obese patients by the contribution of ciliary defects vs. other mechanisms, to select appropriate subgroups for cilia-targeted therapies.

Studies should optimize treatment regimens based on disease stage, since cilia dysfunction may exert more pronounced effects in initiating vs. perpetuating obesity. For example, enhancing ciliogenesis may have a greater impact early on, while stabilizing remaining cilia or augmenting ciliary signaling could give greater benefit in established obesity. Despite current challenges, rapid progress elucidating cilia biology in metabolic control continues, offering hope for novel therapeutic inroads against obesity by targeting this intricate signaling nexus.

6. Conclusions and outlook

This review synthesizes emerging evidence supporting a bidirectional relationship between primary cilia defects and obesity pathogenesis. Cilia are microscopic sensory organelles projecting from nearly all mammalian cell types. They serve vital signaling roles during development and homeostasis by detecting mechanical, chemical and biological cues and transducing these into intracellular signaling cascades (22). Cilia accomplish this through compartmentalization of receptors, ion channels and components of pathways like Hh, Wnt, receptor tyrosine kinase, mTOR and GPCR (16,19). Accordingly, specialized cilia in neuronal, endocrine and metabolic tissues help coordinate systemic energy balance. For example, hypothalamic neuronal cilia regulate appetite circuits through satiety hormone receptors like MC4R (58). Pancreatic islet cilia control insulin secretion dynamics (10). Gastrointestinal cilia modulate nutrient digestion and absorption. Adipocyte cilia restrain lipid accumulation and inflammation (128). Dysfunction of these metabolically relevant cilia promotes weight gain and complications. Conversely, obesity damages cilia integrity through inflammation, lipotoxicity, glucotoxicity and other stresses. High-fat diet and obesity disrupt cilia in appetite-regulating neurons, reducing satiety signaling (108). Islet cilia are impaired by hyperglycemia and lipotoxicity, compromising insulin secretion (83). Shortened adipocyte cilia exacerbate inflammation and ectopic fat deposition. These compounding hits on diverse tissue cilia precipitate a vicious cycle where cilia defects beget worsened metabolic dysfunction. Clarifying this bidirectional relationship reveals exciting new perspectives on obesity pathogenesis and highlights novel targets for intervention. Approaches targeting neuronal cilia may boost satiety signaling to reduce hyperphagia. Stabilizing

islet cilia could enhance glucose-responsive insulin secretion (84). Normalizing adipocyte cilia length and signaling may ameliorate inflammation from obesity (129). Elucidating such intersections between ciliopathies and metabolic disease creates new frontiers for obesity research and therapy development.

Progressing from these foundational insights will require developing new tools to assess cilia dysfunction in human obesity. The current understanding is derived largely from animal models, so improved imaging modalities and biomarkers to analyze cilia non-invasively in obese patients could enable translation to the clinic. Defining the specific contributions of distinct tissue cilia populations is crucial, as neuronal, endocrine and metabolic cilia likely fulfill unique roles (90), and differences between motile and primary cilia must be delineated. With obesity's heterogeneous nature, identifying patient subgroups with predominant cilia defects is imperative to select candidates for targeted treatment. Considerable heterogeneity likely exists in obese individuals regarding causal mechanisms. Biomarkers stratifying those with major cilia deficits could enable personalized therapy (1,2). Exploring pharmacological, gene or cell therapy approaches to prevent obesity-induced cilia deterioration or rebuild ciliary integrity represents an important direction (130). Small molecules stabilizing microtubules may protect neuronal cilia, while IFT protein overexpression could enable ciliogenesis (114,115). However, considering cilia's ubiquitous roles, potential unintended consequences of globally manipulating cilia require investigation. Understanding cell type-specific differences will be critical to avoid developmental or neurological impacts. Furthermore, defining optimal timing and duration of cilia-focused therapies based on disease stage requires further elucidation, as early intervention for prevention may differ from the treatment of established obesity. In summary, rapid discovery continues in this domain, bringing hope that leveraging intricate cilia biology could yield innovative solutions against the intractable obesity epidemic.

Acknowledgements

Not applicable.

Funding

This work was supported by the Shandong Provincial Natural Science Foundation (grant no. ZR2023QC058).

Availability of data and materials

Not applicable.

Authors' contributions

XW and YT conceived and designed the study. YJ, LS and PY collected and organized references. XW wrote the original draft. KX and LH processed the images. YT and YJ critically reviewed the manuscript. All authors read and approved the final manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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