

## Invited Mini Review

## Primary cilia in energy balance signaling and metabolic disorder

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Energy homeostasis in our body system is maintained by balancing the intake and expenditure of energy. Excessive accumulation of fat by disrupting the balance system causes overweight and obesity, which are increasingly becoming global health concerns. Understanding the pathogenesis of obesity focused on studying the genes related to familial types of obesity. Recently, a rare human genetic disorder, ciliopathy, links the role for genes regulating structure and function of a cellular organelle, the primary cilium, to metabolic disorder, obesity and type II diabetes. Primary cilia are microtubule based hair-like membranous structures, lacking motility and functions such as sensing the environmental cues, and transducing extracellular signals within the cells. Interestingly, the subclass of ciliopathies, such as Bardet-Biedle and Alström syndrome, manifest obesity and type II diabetes in human and mouse model systems. Moreover, studies on genetic mouse model system indicate that more ciliary genes affect energy homeostasis through multiple regulatory steps such as central and peripheral actions of leptin and insulin. In this review, we discuss the latest findings in primary cilia and metabolic disorders, and propose the possible interaction between primary cilia and the leptin and insulin signal pathways which might enhance our understanding of the unambiguous link of a cell's antenna to obesity and type II diabetes. [BMB Reports 2015; 48(12): 647-654]

## INTRODUCTION

Although metabolic disorders such as obesity and type II diabetes are increasingly global pandemic, their pathophysiology and molecular basis is not completely understood (1). Obesity is defined by excessive fat deposition in our body, predisposing to many diseases. The major culprit for obesity is quite

complex, due to many confounding genetics and environmental factors equivocally affecting the progress of the disease. Moreover, metabolic disorders are interrelated diseases exemplified by the association of obesity with insulin resistance, leading to development of type II diabetes (2). Genetic factors for obesity are poorly understood, and recent progress by genome-wide association studies support the notion of polygenic features of obesity which suggests that multiple genes, tissues and pathways contribute to the disease (3, 4). Intriguing subset of genes associated with obesity cause a dysfunction of primary cilia, which results in a rare pleiotropic human disorder called ciliopathy (5, 6). Primary cilia are microtubule based cellular organelles protruding 1 to 50 micrometer from the apical surface of cell membrane; they are considered as cellular antenna due to their function, as perceiving the sensory cues or processing the extracellular signaling which are important for cell functions (7). Genetic mutations causing disruption of ciliary structure or function are responsible for multiple congenital disorders in humans (6). Most of the primary cilia in mammals follow the rule of one cilium per cell; they are dynamic organelles because multiple regulatory steps are involved in ciliogenesis in a cell cycle dependent manner. Considering the size of ciliary genes in genome (which are predicted to about more than 1000 ciliary genes), more than 127 disorders currently share common clinical features of ciliopathies, and the list of confirmed ciliopathies will rapidly increase in the near future (8). Nonetheless, the direct association of obesity with ciliopathies are interestingly very limited to a couple of subtypes of ciliopathies, namely Bardet-Biedle and Alström syndrome (9). Although recent studies from mouse model system and human genetic studies are corroborating the link between cilia and obesity, we still need to be cautious on how extensively the primary cilia are involved in the pathogenesis of obesity.

Here, we overview the current updated literatures regarding the dysfunction of primary cilia affecting energy homeostasis in mouse model system or human. We also provide the possible link of primary cilia into key energy balance signaling pathways, leptin and insulin. We would like to highlight that better understanding of the role of primary cilia in regulating energy balance signaling might open a new avenue to treat globally prevalent obesity originating from an unexpected and vestigial ancient organelle, the primary cilia.

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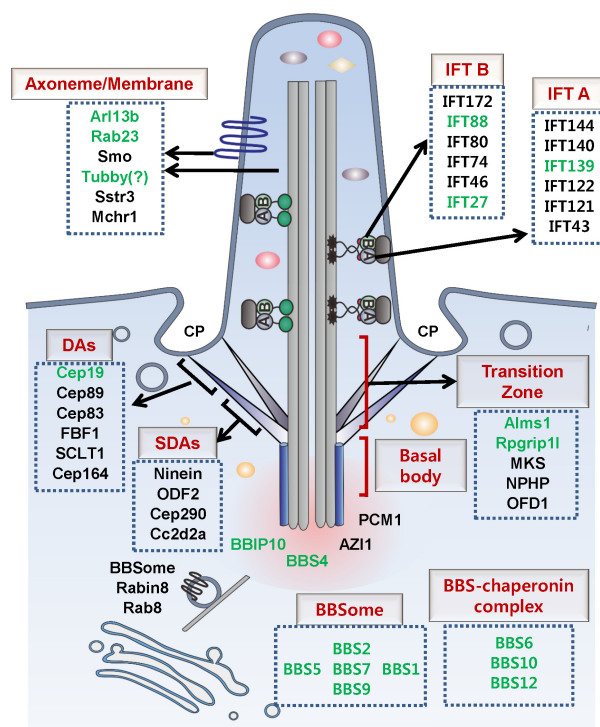
**Keywords:** Ciliogenesis, Ciliopathy, Insulin, Leptin, Obesity, Primary cilia

## PRIMARY CILIA AND CILIOPATHIES

Primary cilia are made of nine pairs of microtubule doublets, growing from the centrosome-derived basal body toward the outside of cell membrane, forming an elongated rod shape structure called axoneme which is encapsulated by a specialized cellular membrane (7). Ciliary membrane is continuous with cytoplasmic membrane, but its composition is unique by containing particular forms of phosphoinositides  $PI_{(4,5)}P_2$ , which are important for ciliary functions (10). Due to the dual recycling function of centrosome, as a basal body for cilia formation, and in cell division for spindle pole body, cilia show dynamic changes in form by assembling or disassembling the axoneme and ciliary membrane during quiescent ( $G_0/G_1$ ) or mitotic (M) phase (7). Assembling of cilia (ciliogenesis), requires highly ordered processes which start with the migration and docking of centrioles to the apical surface of membrane of the cells, triggering polymerization of tubulins from the base with the coordinated growth of ciliary membrane (11). To supply substances required for cilia extension in the growing tips, specialized cilia transport system, intraflagellar transports (IFTs) and motor proteins, are needed. Briefly, motor-driven bi-directional movement of the IFT protein complex transports the cargo proteins from the base to the growing tip, or vice versa. Directional movements of the two groups of transport protein complex, IFT A and B, are differently driven by two motor proteins, kinesin-II for anterograde IFT B, and cytoplasmic dynein for retrograde IFT A, respectively. Balanced transport systems are important for ciliogenesis and dysfunction of these causes abnormal cilia formation (12).

An interesting feature of cilia is compartmentalization of cilia from the base to the tip, implying functional specialization of ciliary subdomains (11). The ciliary axoneme nucleates from the base of mother centriole which consists of triplet microtubules, and distinguishable extra structures: the distal and subdistal appendage (DA and SDA) (13). Fibrous DA and SDA become mature form of the structure, with transition fibers forming a barrier from the cytosol compartment after docking onto the apical surface of membrane. At the base of cilia, the microtubule structure shifts to a doublet from the triplet after the transition fiber, and continues with necklace and Y-shaped structure which connects microtubule to the ciliary membrane. The doublet microtubule in proximal region to basal body between transition fiber and Y-shaped necklace are called the transition zone (TZ) which is the most important subdomain for ciliary gating control for cargoes and function. Recently, many protein complexes in transition fibers and TZ are identified as forming function module, and mutation in each complex gene shares identical phenotypes in animal model and humans, supporting the notion that they group together to participate in the specific function (14). TZ continues with the axoneme and the distal end of cilia tip which functions as the signaling center and is important for ciliary signaling flux. Human congenital disruption of ciliary structure or function

causes pleiotropic developmental disorders with a variable degree of spectrum, and collectively they are called ciliopathies. More than a dozen diseases, including Bardet-Biedl syndrome (BBS), nephronophthisis (NPHP), Senior-Løken syndrome (SNLS), Alström syndrome (ALMS), Meckel syndrome (MKS), Joubert syndrome (JBS), oral-facial-digital syndrome type I (OFD 1), Jeune asphyxiating thoracic dystrophy (JATD), Ellis-van Creveld syndrome (EVC), MORM syndrome and Leber congenital amaurosis (LCA), are attributed to cilia formation or function defects and affect most of the organs such as kidney, brain, limb, eye, ear, liver and bone (6). The distinct pathologic features of ciliopathy patient are cystic kidney, skeletal malformation, laterality and cerebral abnormalities. The unique characteristic entities of ciliopathies show wide phenotypic spectrums which are determined by degree of affected cilia and tissue specificity. The degree of ciliopathy symptoms is highly dependent on the identity of the affected gene and its role in ciliogenesis and ciliary function. Moreover, a certain group of ciliopathy genes forming the same ciliary subdomain module



**Fig. 1.** Ciliary genes associated with obesity. Primary cilia contain several compartments such as basal body, transition fiber (including subdistal appendage (SDA)), and distal appendage (DA), transition zone, and axoneme. Each compartment plays a specific function to regulate the import and export of cargoes and transport proteins such as IFT B and A. Currently, studies from the mouse model system and humans show that disruption of multiple ciliary genes (green) maintaining cilia structure and function manifest obesity phenotypes.

**Table 1.** List of proteins in animal model system or humans, showing obesity involved in ciliogenesis or ciliary function

Gene	Murine mutation	Murine phenotype	Human phenotype	Ciliary localization
ALMS1	Alms1 <sup>foz</sup>	Retinal dysfunction, hearing loss, obesity, hyperinsulinemia, male-specific hyperglycemia, hypogonadism	Short stature, wide feet, retinal degeneration, hearing loss, mental retardation, hypothyroidism, truncal obesity, t2dm, insulin resistance, hepatic dysfunction, hyperlipidemia, hypogonadism	Transition zone
BBS1	Bbs1 <sup>tm1Vcs</sup>	Polydactyly, abnormal olfactory sensation, hydrocephalus, obesity, polycystic kidney	Polydactyly, retinopathy, hypogenitalism, mental retardation, congenital heart disease, obesity, diabetes mellitus, hypertension, renal malformation	Axoneme, Basal body
BBS2	Bbs2 <sup>tm1Vcs</sup>	Abnormal social interaction, polydactyly, abnormal brain neuroanatomy, mislocalization of rhodopsin, obesity, absent sperm flagellar	Developmental delay, polydactyly, retinitis pigmentosa, obesity, renal gonadal malformation	Axoneme, Basal body
BBS3	Arl6 <sup>tm1Vcs</sup>	Polydactyly, retinal degeneration, hydrocephalus, obesity, absent sperm flagellar	Obesity, renal anomalies, reproductive dysfunction	Axoneme
BBS4	Bbs4 <sup>tm1Vcs</sup>	Embryonic lethality, retinal degeneration, impaired olfaction, obesity, polyphagia, renal abnormalities, male infertility	Polydactyly, retinal dystrophy, chronic nasal congestion, genitourinary malformations, learning disabilities, obesity, renal anomalies	Basal body, pericentriolar
BBS5	Bbs5 <sup>tm1blEUCOMMIWsi</sup>	Skeleton dysplasia, retina dysplasia, obesity, thrombocytopenia	Polydactyly, retinal dystrophy, learning difficulties, congenital heart disease, obesity, renal anomalies	Axoneme, Basal body, Membrane
BBS6	Mkks <sup>tm1Vcs</sup>	Decreased aggression, hypoactivity, retinal degeneration, impaired olfaction, hypertension, obesity, hyperphagia, absence of flagella	Polydactyly, congenital heart disease, hydrometrocolpos	Centrosome, Basal body, Cytoplasm
BBS7	Bbs7 <sup>tm1Vcs</sup>	Retinal degeneration, ventriculomegaly, obesity, polycystic kidney, lack of spermatozoa flagella	Polydactyly, retinal dystrophy, hypogenitalism, learning difficulties, obesity, renal abnormalities	Basal body, Cytoplasm, Nucleus
BBS8	Ttc8 <sup>tm1Reed</sup>	Retinal degeneration, impaired olfaction, obesity, renal tubule dilation	Cognitive impairment, polydactyly, retinitis pigmentosa, situs inversus, obesity	Basal body, Cytoplasm, Focal adhesion
BBS9	None	None	Polydactyly, retinal dystrophy, mental retardation, obesity, renal dysfunction	Basal body
BBS10	Bbs10 <sup>-/-</sup>	Retinal degeneration, obesity, hyperphagia, hyperleptinemia, renal abnormalities	Polydactyly, retinal dystrophy, intellectual disability, obesity, renal dysfunction, hypogonadism	Basal body
BBS12	Bbs12 <sup>tm1.1Vmar</sup>	Obesity, increased insulin sensitivity, increased glucose usage, decreased inflammatory response	Myopia, astigmatism, night blindness, retinitis pigmentosa, hypodontia, obesity	Basal body, Cytoplasm
BBS17 (LZTFL1)	None	None	Polydactyly, retinal degeneration, polyuria, polydypsia, obesity, polycystic kidney, hypogonadism	Cytoplasm
BBS18 (BBIP10)	Bbip10 <sup>tm1.1Gne</sup>	Postnatal lethality, retinal degeneration, obesity, hyperphagia, male infertility	Behavioral dysfunction, brachydactyly, visual impairment, learning difficulties, obesity	Axoneme
BBS19 (IFT27)	Ift27 <sup>null1</sup>	Polydactyly, abnormal flexure of the wrists, micrognathia, hypotelorism, omphaloceles, cyanosis, cardiac malformation, lung isomerisms	Atopy, polydactyly, retinitis pigmentosa, hypogenitalism, congenital heart disease, obesity, fatty liver, renal hypoplasia	Axoneme
Arl13b	Arl13b <sup>hnn</sup>	Left-right randomization, defects of neural patterning	Retinal anomalies, molar tooth sign, superior vermian dysgenesis, elongated cerebellar peduncles, obesity	Membrane
Cep19	Cep19 <sup>tm2.1Mgi</sup>	Obesity, hyperphagia, glucose intolerant, insulin resistant	Intellectual disability, coronary artery disease, myocardial infarctions, congestive heart failure, obesity, t2dm, decreased sperm counts.	Distal appendage
IFT88	Tg737 <sup>loxP</sup> ; CAGG-Cre <sup>ER</sup>	Obesity, hyperphagia, hyperglycemia, hyperinsulinemia, hyperleptinemia, cystic kidney	None	Axoneme
INPP5E	Inpp5e <sup>tm1Ssch</sup>	Bilateral anophthalmos, bifid sternum, cleft palate, hexadactyly, anencephaly or exencephaly, cystic kidneys	Retinal dystrophy, molar tooth sign, mental retardation, truncal obesity, micropenis syndrome	Membrane
Kif3A	Kif3a <sup>loxP</sup> ; CAGG-Cre <sup>ER</sup> or POMC-Cre	Obesity, hyperphagia, hyperglycemia, hyperinsulinemia, hyperleptinemia, cystic kidney	None	Axoneme
Rab23	Rab23 <sup>opb</sup>	Embryonic lethal, polydactyly, open brain	Craniosynostosis, polydactyly, obesity	Axoneme
RPGRIP1L	Rpgrip1l <sup>tm1alEUCOMMIWsi</sup>	Obesity, hyperphagia	None	Transition zone
Tubby	Tub <sup>tub</sup>	Retinal degeneration, hearing loss, obesity, hyperinsulinemia	Night blindness, decreased visual acuity, obesity	Axoneme(?)

share common clinical features, indicating dedicated biological roles for the each set of ciliary structural modules (15). For example, NPHP module and JBTS module proteins localized in TZ and mutations of these have phenotypically overlapping entities such as cystic kidney disease. However, NPHP primarily manifests in the renal cyst, but JBTS is in retinal degeneration, brain malformation and skeletal defect (16). Interestingly, two subtypes of ciliopathies, BBS and ALMS, are distinctively associated with morbid obesity and type II diabetes in humans (5). These human genetic links of the two types of ciliopathies to metabolic disorders, implicate that the cellular function of cilia might intersect with the energy balance system but lack of possible molecular mechanisms, and a limited type of ciliopathies casts a doubt for the ciliary role for obesity. Multiple lines of evidence have indicated mutations of multiple ciliary subdomain genes in the mouse model system and other human study results in obesity; these results corroborate the ciliary role of obesity, as shown in Fig. 1. Currently, studies on ciliopathies and related mouse model system confirms that disruption of ~20 cilia-related genes leads to obesity (Table 1) (8). Based on the type, we could subdivide the genes as a group identified in well characterized ciliopathies or a group related to the structure and function of cilia.

### CILIOPATHIES RELATED TO OBESITY: BBS AND ALMS

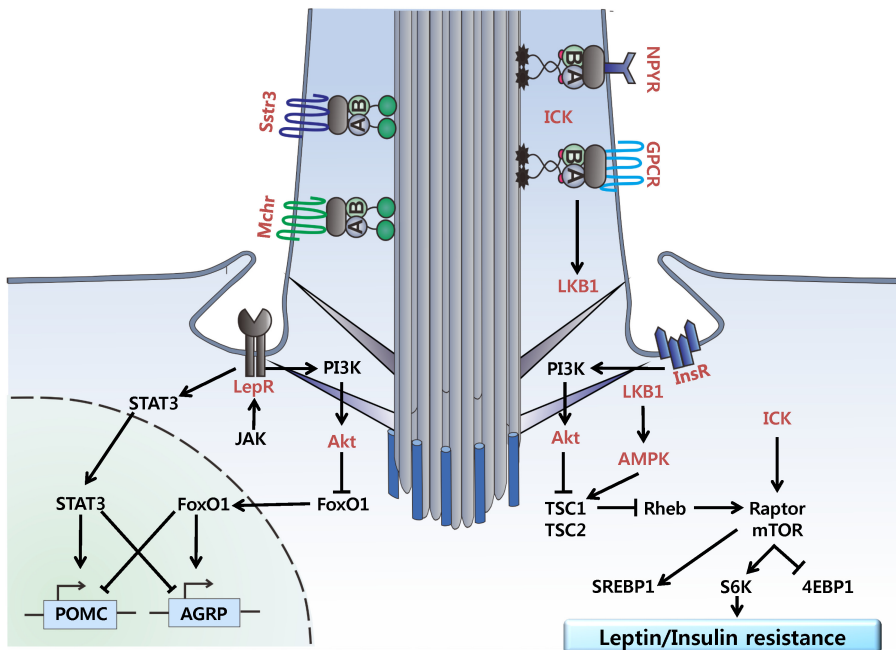
Bardet-Biedle syndrome (BBS) is a recessive rare genetic disorder (~1 in 13,500-160,000) which was first reported in 1866 by Laurence and Moon, and later by Bardet and Biedl (17). The clinical phenotype of affected patients commonly displayed obesity, retinal degeneration, polydactyly, cystic kidney, hypogonadism and mental retardation. The genetic basis of BBS is a consequence of ciliary dysfunctions, which are the first examples of the fundamental role of cilia in obesity; 14 genes (BBS1-12, MKS1 and CEP290) have been identified until now (18). The first molecular link of BBS to cilia dysfunction was hinted by a BBS8 patient who had defects in the left-right axis (*situs inversus*) which is a cardinal feature of ciliopathies. Recently, it has been shown that BBS is known to localize to the basal body (19). Most of the BBS proteins localize to basal bodies or cilia, but mutations in BBS genes do not affect ciliogenesis. Recent progress suggests that BBS proteins form a complex and associate with RAB8 for ciliary membrane growth by trafficking of vesicles to the cilia (20). Direct evidence linking BBS to obesity is coming from studies on mouse model system of BBS 2, 4 and 6 which show increased levels of leptin with unreduced food intake in response to leptin (21). In addition, studies from cultured cells demonstrate that depletion of BBS1 affects leptin receptor trafficking (22). These results indicate that defects in leptin signaling might contribute to obesity in BBS. In contrast, conflicting results regarding role of cilia in leptin signaling have been reported from the Yoder group (23). Although they observed leptin resistance after obese state in BBS4 mutant mice, they interestingly showed

that preobese BBS4 mutant mice show normal leptin signaling as well as another cilia mutant, *lft88* (23). These results suggest that cilia involved in leptin resistance and signaling defects might not be the primary cause of obesity in BBS mutants. The precise molecular mechanisms underlying BBS mediated leptin signaling in obesity have not been fully elucidated, and further investigations are needed to resolve the conflicting issue.

Alström syndrome (ALMS) is the second most well studied type of ciliopathy involved in obesity and reported in 1959 by Alstrom (24). ALMS is a very rare recessive monogenic disorder (~1 in 10,000-1,000,000) manifesting retinal degeneration, hearing loss, cardiomyopathy, childhood obesity and type II diabetes. Although ALMS has many similarities to BBS, it does not manifest mental retardation, polydactyly, and hypogonadism, as seen in BBS. The mutation in ALMS is caused by mutations in the novel gene *ALMS1*, and the mouse model recapitulated pathologic features in ALMS patients (25, 26). *ALMS1* is a ubiquitously expressed 461-kDa protein of unknown function and contains novel tandem repeats and putative leucine zipper domain. Phenotypic similarities to BBS suggest that *ALMS1* might be related to ciliopathies, and studies from cultured cells show that *ALMS1* localizes to basal bodies without affecting ciliogenesis (27). Recent data have been shown that *ALMS1* regulates cell migration and endosomal trafficking, but the molecular mechanism of *ALMS1* in obesity and cilia remains to be revealed (28).

### CILIARY GENES LINK TO OBESITY

Mice lacking key ciliary genes such as *lft88* and *Kif3a*, which are key transport proteins for ciliogenesis, show embryonic lethality attributing to multiple defects in developmental signaling (29). Due to lack of studies regarding role for cilia in adult stage, the idea of ciliary role in obesity had been challenged. However, well-designed mouse genetic model studies from bona fide ciliary genes, *lft88* and *Kif3a*, uphold that idea (30). Using two conditional alleles of *Kif3a* and *lft88* with neuron or hypothalamic pro-opiomelanocortin-expressing neuronal cells in specific Cre lines, the Yoder group examined the direct effects of adult stage ciliary loss on weight gain without developmental defects (30). Interestingly, they observed that both of the alleles show increasing levels of leptin as well as insulin, with reduced responses. They further showed that the ciliary effect on obesity and type II diabetes are caused by hyperphagic behavior of affected mice rather than secondary effects. These studies indicate that cilia might play a role in the energy balance by affecting the central regulator in the hypothalamus. Growing evidence further provides the possible link of cilia in central energy metabolism regulation with ciliary localization of many G protein-coupled receptors (GPCRs) to regulate GPCR signaling, including melanin-concentrating hormone receptor 1 (MCHR1) and somatostatin receptor 3 (SSTR3) which are well-known for appetite regulation (31). The *tubby* mouse was originally introduced as a naturally identified obesity ani-



**Fig. 2.** Energy balance signaling, leptin and insulin interaction with possible ciliary genes. Leptin and insulin ligand binding to their receptors (LepR and InsR) signaling share the PI3K-AKT pathways. LepR activation specifically increases the expression of Pomc through JAK-STAT3 activation, and PI3K-AKT pathway mediated FoxO1 inhibition. Insulin receptor activation shares PI3K-AKT pathway and further regulates mTOR-S6K pathway. S6K inhibition by genetic or pharmacological intervention causes insulin resistance. Primary cilia related downstream signal transduction mediators of leptin and insulin are highlighted with red color.

mal model with spontaneous loss of function of the tubby gene, displaying retinal degeneration, hearing loss and late-onset obesity. Recently the molecular basis of it highly links it to ciliary function like GPCR trafficking (Table 1 and Fig. 2) (32). The tubby gene family also includes tubby-like protein 1, 2 and 3 (Tulp1, 2 and 3), and they share the phosphodiesterase binding C-terminal tubby domain. Although Tulp mutant mice do not show obesity, they are involved in the GPCR ciliary trafficking and regulate ciliary signaling. Moreover, specific distribution of phosphoinositide in the ciliary membrane is important for proper protein trafficking in cilia and disruption of its distribution by mutations in inositol polyphosphate 5-phosphatase E (INPP5E), causing ciliary dysfunction and obesity in humans (Table 1) (33). These findings highlight that the ciliary role of GPCR trafficking and signal transduction in cilia might be related to energy homeostasis. Several lines of human genetic studies consolidate the ciliary role in obesity. Evidences from Arl13b and Rab23 mutation in humans demonstrated that they display canonical phenotypes of ciliopathies with obesity (34, 35). CEP19 is a novel centrosomal protein, and mutations in human and mouse model systems cause morbid obesity and resistance to insulin (36). Although Cep19 mainly localizes in the basal bodies, implicating a ciliary role, Cep19 KO mice do not show any noticeable structural abnormality of cilia and common phenotypic features of ciliopathy except obesity. Further studies revealing ciliary function and obesity of Cep19 remain to be revealed.

## ROLE OF PRIMARY CILIA IN ENERGY BALANCE SIGNALING: LEPTIN AND INSULIN

Leptin and insulin are peripheral energy metabolisms, controlling energy homeostatic neuropeptides, proopiomelanocortin (POMC) and agouti-related protein (AGRP) expression. They are secreted by white adipocyte tissues or pancreatic  $\beta$ -cells respectively, and their primary function is to induce anorexigenic effect (37). Leptin binding to its receptor (LepR-b) recruits and activates Janus kinase (JAK), leading to STAT3 phosphorylation and activation for Pomc and Agrp expression in the hypothalamus (Fig. 2). LepR-b also activates phosphatidylinositol-3-kinase (PI3K) signaling resulting in AKT activation, affecting many downstream targets such as Forkhead box protein O1 (FoxO1), AMP-dependent kinase (AMPK) and mammalian target of rapamycin (mTOR). Insulin signaling by insulin receptor substrate (IRS) also converges with the leptin signaling pathway at the step of activation of PI3K and AKT (Fig. 2). When the energy status changes to surplus, leptin and insulin activate mTOR pathway but inhibit the AMPK activation to suppress food intake.

Primary cilia have been established as the signaling center for processing multiple animal development and homeostasis signaling pathways, Hedgehog (Hh), Notch, Wnt, mTOR and Platelet-derived growth factor receptor  $\alpha$  (PDGFR $\alpha$ ) (38). Hh signaling has been extensively studied, and primary cilia are highly regarded as critical organelles in transmitting Hh signaling (39). Briefly, the secreted Sonic hedgehog (Shh) protein in mammals binds to the transmembrane receptor, Patched1

(Ptch1) to release its inhibition of the GPCR-like protein, Smoothed (Smo), leading to ciliary localization. Ciliary Smo subsequently activates the Gli transcription factors in primary cilia with unknown mechanisms, which turn on the Shh target gene expressions. Although the molecular logic of other signaling pathways are different and dependent on types of signaling, they share common theme with Hh signaling which key elements in signaling accumulate within the cilia to transduce signaling; for example Notch or PDGF receptors and downstream effectors, and loss of cilia, affects the extent of signal transduction.

Recently, several lines of indirect evidences suggest a possible crosstalk between ciliary signaling and energy balance signaling. First, energy homeostatic neuropeptides or neurotransmitter receptors, for example insulin growth factor receptor (IGFR), melanin-concentrating hormone receptor (Mchr) and neuropeptide Y receptor (NPYR), localize to the cilia and require ciliogenesis machinery such as BBS and cilia function to properly transmit signaling (31). The *Bbs* or *Ift* mutant mice show reduced *Pomc* expression with leptin resistance, and *LepR* interacts with BBS to translocate to the cilia (22). These findings indicate that primary cilia are required for leptin signaling by properly trafficking *LepR*. However, studies from tamoxifen inducible ablation of *Ift88* mice, argues against the contribution of leptin resistance to obesity (23). These observations are not consistent with BBS mutant mice results and need further experiments to clarify them. Second, GPCR signaling cascade in cilia, such as somatostatin receptor 3 (*Sstr3*), and *Mchr* increase the levels of cyclic AMP and  $Ca^{2+}$ , which in turn, activate various downstream targets; for example LKB1 and AMP-activated protein kinase (AMPK) (31, 40). Ciliary localized IGFR also activates the kinase cascade including PI3K-Akt, which could activate the mTOR pathway (37). Absence of cilia might affect the PI3K-Akt axis, resulting in down-regulation of anorexic *Agpr* expression or suppression of S6 kinase (S6K), causing hyperphagic obesity and leptin/insulin resistance. Third, protein kinases regulating ciliogenesis might involve energy balance signaling through mTOR pathways. Though it happens in kidney tissue culture cells, liver kinase B1 (LKB1) localizes in the cilium, and bending of cilia activates the LKB1 to phosphorylate AMPK at the basal body (41). AMPK pathway has been well known as an energy state sensor, and regulates the metabolic enzymes and glucose uptake. AMPK activation by LKB1 might suppress mTOR pathway, leading to insulin resistance (42). In addition to this, intestinal cell kinase (ICK) is a key cilia length control kinase and localizes in cilia; kinase activity is required for proper ciliary localization (43). ICK has been shown to phosphorylate the mTOR effector Raptor, which activates S6K kinase (44). Collectively, multiple kinases regulating ciliogenesis are associated with the mTOR pathway, which are important for leptin/insulin resistance. Further conclusive studies are needed to dissect whether or not the abnormal ciliogenesis by ciliary kinase defects directly affects the mTOR signaling and metabolic disorders.

## CONCLUSION

Human monogenic obesity studies identify crucial genes underlying the molecular basis of obesity, such as leptin, leptin receptor, melanocortin 4-receptor, and pro-opiomelanocortin. Research on primary cilia have been focused on processing of intracellular signaling during animal development and disease in recent years (45). Given that obesity is the accompanying phenotype in ciliopathies, studying this disorder might further unravel the molecular complexities of metabolic disorders by integrating the signaling events derived from primary cilia. However, studies have just been initiated to link the importance of ciliary structure and function on regulating the energy balance of the body. Many unanswered questions remain to be solved, which would deepen our understanding of primary cilia and metabolic disorders. First, primary cilium is the sole organelle existing as one per cell, but pathogenic mutation of the core ciliary genes show variable phenotypes, including obesity, in multiple tissues and malformation of cilia. Intriguingly, only a small fraction of ciliogenesis genes manifest as obesity. The question arises as to why only certain types of ciliogenesis defects are associated with obesity. Ciliogenesis is a highly ordered, sequential event requiring multiple genes, and evidence reveals that some ciliary genes are also involved in cilia-independent events. It might be possible that obesity associated ciliary genes might have dual functions. In fact, the BBSome complex components, *Bbs4* and 6, have cilia independent roles in cell division (46, 47). *Bbs4* localizes to the spindle body in association with dynactin subunit, and depletion of *Bbs4* as well as *Bbs6* cause defects in cytokinesis and mitosis. Cell cycle protein, Cdk inhibitor p21 and p27, have been shown that they regulate adipogenesis, and mouse model systems develop obesity by an increase in adipocytes (48). Therefore, it might be possible that subset of ciliary genes involved in the cell cycle, might cause adipogenesis dependent obesity. Second, energy homeostasis are maintained under the control of the central nervous system and the another site of the metabolic regulating organ, the pancreas. Recent studies demonstrate that leptin and insulin resistance in BBS mouse model system contributes to obesity. In addition to this, insulin signaling is affected before the obese phenotype is developed in the pancreas. Primary cilia also regulate adipogenesis through Wnt and Hh signaling. Defects in cilia, as shown in *BBS12* KO mice, enhance adipogenesis leading to obesity (49). Controversially, cilia dependent obesity might be a secondary effect resulting from increase of food intake. Preobese *Bbs4* KO mice show normal leptin response, and leptin resistance developed after mice get obese (23). Overall, these results implicate that primary cilia in central and peripheral metabolic regulators differentially act on development of obesity. We would like to highlight that there are more implications of the role of primary cilia in obesity, and further expanded studies would clarify the role of this tiny cellular organelle in obesity.

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