REVIEW

Can faulty antennae increase adiposity? The link between cilia proteins and obesity

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Abstract

Primary cilia are sensory organelles that protrude from the surface of most mammalian cell types. In humans and mice, mutations in proteins required for normal cilia function have been identified as causing a class of disorders with overlapping phenotypes known as ciliopathies. Recent evidence has linked obesity in ciliopathies to both the regulation of energy

homeostasis in the hypothalamus and to adipogenesis. This article considers the role of cilia in these processes and whether cilia dysfunction may be relevant to more common forms of obesity.

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Introduction

In 2003, it was recognized that mutations in proteins essential for normal cilia function underlie Bardet–Biedl syndrome (BBS, Ansley *et al.* 2003; for details on the function of BBS proteins see Box 1). Subsequently, cilia dysfunction has been linked to further rare congenital multi-system disorders that have been termed ciliopathies (Table 1). These syndromes have some phenotypic overlap, for example retinal degeneration and kidney disease are common features, although penetrance is variable. The clinical features of two of these conditions, BBS and Alström's syndrome (ALS; Badano *et al.* 2006), incorporate a subset of endocrine phenotypes and in particular obesity. This review focuses on the potential cellular mechanisms by which disruption of ciliary protein function may lead to obesity. That variance in common obesity linked genes may impact upon cilia function is also considered.

What are primary cilia?

Primary cilia are small organelles, ~2–5 µm in length (up to 30 µm in some cell types) that extend from the surface of the majority of mammalian cells (Fig. 1; Praetorius & Spring 2005). For example, they are found throughout the brain including the hypothalamus (Bishop *et al.* 2007). They function as sensory antennae and are involved in the

regulation of a number of key cellular signaling pathways, including hedgehog signaling (Pazour & Witman 2003, Singla & Reiter 2006). Cilia consist of an axoneme and a basal body. The basal body is derived from a mother centriole that migrates to the plasma membrane after cell division. Structurally, the axoneme consists of nine microtubule doublets, originating from basal body triplet microtubules, covered by a ciliary membrane that is continuous with the plasma membrane. The formation of the axoneme from the basal body is dependent on the process of intraflagellar transport (IFT; Fig. 2). Axonemal synthesis occurs at the end distal to the basal body and IFT is necessary for structural proteins to be transported to this location. IFT is bidirectional with kinesin motor driven anterograde transport and dynein motor driven retrograde transport. The entry of proteins into the ciliary compartment and membrane is regulated and there is evidence for a protein quality control machinery at the basal body (Stephan *et al.* 2007).

Primary cilia are structurally different from motile cilia, for example those of the respiratory epithelium responsible for mucociliary clearance, as they normally lack a central microtubule pair and other structural features including radial spokes, inner dynein arms, and outer dynein arms. Thus, primary cilia have a 9+0 microtubule organization and motile cilia have a 9+2 composition. Generally, 9+0 cilia are not motile, though the nodal cilia, essential for the left and right axis development in early mammalian embryogenesis, are an exception (Nonaka *et al.* 1998). Likewise, not all 9+2

Box 1 Function of BBS proteins and ALMS1

Mutations in 12 genes have been identified as causative for BBS, with multiple protein–protein interactions occurring between the encoded proteins. A heptameric BBS protein complex containing BBS1, BBS2, BBS4, BBS5, BBS7, BBS8, and BBS9 has been identified (Nachury *et al.* 2007). This complex, known as the BBSome, localizes to both centriolar satellites (electron dense granules localized around the centrosome) and to the ciliary membrane. Depletion of BBSome proteins does not appear to affect centriolar satellites, but does cause a large reduction in ciliation. Other proteins were also reported to be associated with the BBSome including Rabin8, a guanosyl exchange factor (GEF) for the small GTPase Rab8. Rab8 functions in targeting post-golgi vesicles to polarized areas of the plasma membrane (Ang *et al.* 2003) and may promote docking and fusion of exocytotic vesicles to the base of the ciliary membrane (Nachury *et al.* 2007). Expression of a dominant negative, GDP-locked, Rab8 inhibits ciliation in cultured cells and has been shown to cause rhodopsin to accumulate at the base of the connecting cilium and cause cell death in *Xenopus laevis* photoreceptors (Moritz *et al.* 2001).

A function for BBS proteins in intracellular transport is further suggested by the identification of an ADP-ribosylation factor-like (ARL) protein, ARL6 as BBS3 (Chiang *et al.* 2004). ARL proteins, along with ADP-ribosylation factor proteins, form a group of regulatory GTPases that function in the regulation of both microtubule dynamics and vesicle traffic (Kahn *et al.* 2005). The other BBS proteins are BBS11/TRIM32, which is an E3 ubiquitin ligase, and BBS6, BBS10 and BBS12 which have homology to the type II chaperonin family of molecular chaperones (Chiang *et al.* 2006, Stoetzel *et al.* 2007). Thus, it is plausible that BBS proteins that are not components of the BBSome may play a regulatory role for this complex (Nachury *et al.* 2007), such as mediating assembly/disassembly.

Importantly, BBS proteins do not function solely at cilia. Knockdown of Bbs proteins in zebrafish causes a defect in retrograde transport along microtubules of melanosomes (Yen *et al.* 2006), tissue-specific lysosome-related organelles in which melanins are synthesized and stored (Raposo & Marks 2007). Furthermore, BBS4 is an adapter protein of the p150^{glued} subunit of the dynein–dynactin microtubule motor complex recruiting pericentriolar material-1 and associated cargos to centriolar satellites (Kim *et al.* 2004). BBS4 knockdown disrupts both centrosomal and basal body function leading to a disruption of cellular microtubule organization (Kim *et al.* 2004).

ALMS1 is an extremely large protein (4169 amino acids) that localizes with centrosomes and basal bodies (Hearn *et al.* 2005). It contains 34 imperfect repeats of a 44 amino acid sequence and a short polyglutamine tract. Its knockdown in mice causes stunted cilia in kidney epithelial cells (Li *et al.* 2007). Details of ALMS1 function at the molecular level remain to be elucidated.

cilia are considered motile, e.g. the kinocilium of cochlear hair cells (Sobkowicz *et al.* 1995, Fliegauf *et al.* 2007).

Cilia have cell-type-specific functions that depend on the particular signaling machineries localized to them. For example, in olfactory sensory neurons, odorant receptors localize at the ciliary membrane, while in the primary cilia of kidney epithelial cells polycystin-2 (a transient receptor potential ion channel) functions as a mechanoreceptor detecting urine flow (Nauli *et al.* 2003). In some cells types, cilia are morphologically adapted to their specific function. This can clearly be seen in the photoreceptor outer segment which is part of a modified axoneme that is specialized for efficient light detection and phototransduction.

Cilia localization of receptors

The multiple components of ciliopathy phenotypes appear to result from disruption of signaling pathways that are cell-type-specific. It is therefore important to consider which cell

surface receptors are present at the ciliary membrane. For example, for GPCRs several cilia localization motifs have been identified. Rhodopsin has a C-terminal VxPx motif that binds the small GTPase ARF4, regulating assembly of a ciliary targeting complex at the trans-golgi network (Mazelova *et al.* 2009). A hydrophobic and basic residue motif, C-terminal to the last transmembrane segment of GPCRs, have also been identified as a ciliary localization motif (Dwyer *et al.* 2001). This motif is required for the cilia localization of the hedgehog signaling pathway by the smoothened protein (Corbit *et al.* 2005). The motif is found in somatostatin receptor 3 (SSTR3) and serotonin receptor 6 (HTR6), but is also in other, non-cilia localized, somatostatin and serotonin receptors. This suggests it may be necessary, yet not sufficient, for cilia localization (Berbari *et al.* 2008a). Subsequently, based upon the finding that a conserved sequence in the third intracellular loop of SSTR3 and HTR6 is required for their ciliary localization, the consensus sequence Ala X [Ser/Ala] X Glu (where X=any residue) was also derived as a cilia localization motif (Berbari *et al.* 2008a).

Table 1 Genetic syndromes associated with primary cilia dysfunction

Key phenotypic features	Mutated gene/protein	Protein function	References
Ciliopathy Alstrom syndrome OMIM: 203800	ALMS1	Centrosome and basal body localization. Large (> 4000 amino acid) protein of unknown function	Hearn <i>et al.</i> (2005)
Bardet-Biedl syndrome OMIM: 20990	BBS1	BBSome component, β propeller repeat protein	Kim <i>et al.</i> (2004), Nachury <i>et al.</i> (2007) and Stoetzel <i>et al.</i> (2007)
	BBS2	BBSome component, β propeller repeat protein	
	BBS3/ARL6 BBS4	ARF family GTP-binding proteins BBSome component. Interacts with PCM-1 and p150 ^{Glued}	
	BBS5	BBSome component	
	BBS6/MKKS BBS7	Homology with type II chaperonins BBSome component, β propeller repeat protein	
	BBS8	BBSome component. Interacts with PCM-1	
	BBS9	BBSome component	
	BBS10	Homology with type II chaperonins	
	BBS11/TRIM32	Ubiquitin E3 ligase	
	BBS12	Homology with type II chaperonins	
Joubert syndrome OMIM: 213300	JBTS3/AHI1/joubertin	Contains WD40 domain and SH3 domains	Dixon-Salazar <i>et al.</i> (2004), Fliegauf <i>et al.</i> (2006), Sayer <i>et al.</i> (2006), Valente <i>et al.</i> (2006), Delouis <i>et al.</i> (2007) and Kim <i>et al.</i> (2008)
	JBTS4/NPHP1/nephrocystin JBTS5/CEP290/MKS4/ nephrocystin 6	Cilia transition zone localization Interacts with PCM1, modulates the activity of the transcription factor ATF4. Also mutated in MKS4 and LCA	
	JBTS6/MKS3/meckelin	Transmembrane protein. Mutated in Meckel syndrome type 3	
	JBTS7/RPGRIPTL	Localized to primary cilia and centrosomes. Mutated in Meckel syndrome type 5	Beales <i>et al.</i> (2007)
Jeune syndrome/asphyxiating thoracic dystrophy (X-linked) OMIM: 208500	IFT80	IFT complex B component	
Orofaciodigital syndrome type 1 OMIM: 311200	OFD1	Centrosome and basal body localization	Romio <i>et al.</i> (2004)
Meckel-Gruber syndrome OMIM: 249000	MKS1	MKS1 and meckelin interact	Valente <i>et al.</i> (2006), Dawe <i>et al.</i> (2007), Delouis <i>et al.</i> (2007)
	MKS3/JBTS6/meckelin MKS4/JBTS5/CEP290/ nephrocystin 6	Meckelin and MKS1 interact Interacts with PCM1, also mutated in JBTS5 and LCA	Kim <i>et al.</i> (2008)

(continued)

Table 1 Continued

Key phenotypic features	Mutated gene/protein	Protein function	References
Senior-Loken syndrome OMIM: 266900	MKS5/JBTS7/RPGRIPL	Localized to primary cilia and centrosomes. Mutated in Joubert syndrome type 7	Otto <i>et al.</i> (2005), Roepman <i>et al.</i> (2005), Fliegauf <i>et al.</i> (2006) and Bergmann <i>et al.</i> (2008)
	MKS6/CC2D2A	Cilia function. Contains calcium binding domain	
	NPHP1/nephrocystin	Cilia transition zone localization	
	NPHP3/nephrocystin 3 NPHP4/nephrocystin 4 NPHP5/IQCB1	Possible role in regulation of Wnt signaling Centrosome and basal body localization. Interacts with the LCA protein RPGRIPL Interacts with the cilia localized retinal degeneration protein RPGR	

OMIM: www.ncbi.nlm.nih.gov/sites/entrez?db=omim. LCA, lebers congenital amaurosis, an inherited retinal degeneration. For a comprehensive reviews of ciliopathies see Ref. Badano *et al.* (2006).

Obesity in BBS and ALS

Obesity may be considered an energy balance disorder in which energy intake exceeds energy expenditure, resulting in storage of the excess energy in adipose tissue (Box 2). Nearly all ALS patients have been reported to be obese while more than 70% of BBS patients are reported to be overweight (Beales *et al.* 1999, Marshall *et al.* 2005). In both syndromes, truncal obesity develops in childhood and has been suggested to be linked to hyperphagia. In ALS, endocrine phenotypes of hyperinsulinemia, insulin resistance, and type 2 diabetes mellitus are common, while diabetes is also a secondary feature of BBS (Beales *et al.* 1999, Marshall *et al.* 2005).

Fat Aussie mice that have a spontaneous mutation in the ortholog of the gene responsible for ALS in humans, have a normal birth weight but exhibit hyperphagia and become severely obese. These mice also develop insulin resistance, diabetes, with morphological changes in pancreatic islets, and features of metabolic syndrome (Arsov *et al.* 2006). BBS knockout mice are again obese and hyperphagic, and furthermore, compared with wild-type littermates, they exhibit reduced locomotor activity (Rahmouni *et al.* 2008).

Primary cilia play a role in satiety signaling in the hypothalamus

These mouse models and others have been used to elucidate the pathophysiological pathway by which the mutations in cilia associated proteins result in obesity. IFT has been targeted using conditional tamoxifen-inducible knockouts of the heterotrimeric kinesin-2 motor component gene *Kif3a* and the IFT gene *Tg737* (also known as *Ift88/polaris*; Davenport *et al.* 2007). Conditional knockouts were necessary because disruption of IFT is embryonic lethal. After four weeks of tamoxifen administration both *Kif3a* and *Tg737* knockout mice were significantly fatter than untreated controls and went on to develop obesity with elevated plasma levels of glucose, insulin, and leptin. Pair feeding studies revealed this weight gain was due to hyperphagia. Unlike BBS knockout mice reduced locomotor activity was not reported for *Kif3a* and *Tg737* conditional knockouts. Thus, abnormal regulation of feeding behavior was strongly implicated in causing the phenotype observed in these IFT impaired mice. To further investigate this, Davenport *et al.* created central nervous system (CNS) specific knockouts by crossing the cilia mutant mice with synapsin-1-cre mice. The obesity phenotype was recapitulated in this model and, subsequently, pro-opiomelanocortin (POMC) expressing neurons of the hypothalamus were identified as the affected neuronal population, by specifically disrupting *Kif3a* using a *POMC-cre* deleter line. Cilia were lost from the POMC expressing neurons in the knockout

Figure 1 Primary cilia protrude from the surface of mammalian cells and localize components of key signal transduction pathways. Confocal microscope images of primary cilia in NIH3T3 (A) and IMCD3 cells (B–F). Ciliary axonemes and basal bodies were detected with antibodies against acetylated tubulin and pericentrin respectively. (C) Z-section. (D–F) The sonic hedgehog signaling pathway protein patched-1 localizes to primary cilia. Nuclei are stained with DAPI (blue). Scale bar=10 μ m.

mice, leading the authors to conclude neuronal cilia function in a pathway regulating the satiety response (Davenport *et al.* 2007).

Leptin receptor signaling is impaired in BBS

Rahmouni *et al.* (2008) showed that BBS mice have high levels of plasma leptin and increased leptin resistance. The possibility that BBS mutations may inhibit transport of leptin across the blood–brain barrier was excluded by i.c.v. administration of leptin. Hypothalamic leptin acts to alter expression of the downstream energy homeostasis neuropeptides POMC, agouti-related protein (AGRP) and neuropeptide Y (NPY). In *Bbs*^{−/−} mice, *Pomc* mRNA levels are reduced and levels of the other neuropeptides

unchanged, compared with *Bbs*^{+/+} mice (Rahmouni *et al.* 2008). As with IFT mutant mice, these findings point towards BBS mice having a defect in POMC neurons that accounts for the obesity phenotype.

As hyperleptinemia and leptin resistance may be secondary to obesity, the same group went on to examine the effects of exogenous leptin administrations in *Bbs*^{−/−} mice where calorific restriction had been used to normalize weight and serum leptin levels to that of control animals (Seo *et al.* 2009). In these *Bbs*^{−/−} mice, with normal weight and endogenous leptin levels, exogenous leptin did not cause weight loss or reduced food intake. In this study, Seo *et al.* (2009) also demonstrated that targeting melanocortin receptors (MCRs), by i.c.v. administration of agonist, resulted in reduced food intake and weight in BBS mice.

Figure 2 Schematic representation of primary cilia, showing microtubule-dependent trafficking to and from the basal body, as well as IFT of cargos within the axoneme.

In the hypothalamus, binding of leptin to the leptin receptor isoform LRb causes phosphorylation of signal transducer and activator of transcription-3 (STAT3), which then activates POMC transcription (Bates *et al.* 2003). In BBS mice normalized for weight and serum leptin levels, exogenous leptin administration has a reduced ability to activate this signaling pathway, as evidenced by reduced STAT3 phosphorylation (Seo *et al.* 2009). LRb has also been shown to interact with BBS1 by co-immunoprecipitation. BBS1 was not reported to precipitate other leptin receptor isoforms. Furthermore, LRb does not appear to interact directly with other BBS proteins (Seo *et al.* 2009), although BBS1 does form a stable complex with them (see Box 1; Nachury *et al.* 2007). Knockdown of BBS proteins in cultured cells exogenously expressing LRb has been shown to cause a change in localization of the receptor that is suggestive of a defect in trafficking from the golgi (Seo *et al.* 2009).

LRb has not been reported to be localized to the cilia of POMC neurons, although it has been reported to be

enriched in the ciliary membranes of olfactory sensory neurons (Baly *et al.* 2007). Therefore, both a failure of LRb transport from the golgi, possible to the basal body, and/or transport within the ciliary membrane may cause obesity.

Interestingly, melanin-concentrating hormone receptor 1 (MCHR1) contains the Ala X [Ser/Ala] X Glu motif and has been localized to primary cilia. This localization is disrupted in BBS mice (Berbari *et al.* 2008b). This is relevant because MCH is a hypothalamic neuropeptide, involved in the regulation of energy homeostasis, that is believed to act downstream of leptin (Shimada *et al.* 1998, Ludwig *et al.* 2001, Chen *et al.* 2002, Segal-Lieberman *et al.* 2003). However, disruption of MCHR1 results in obesity resistance in mice (Chen *et al.* 2002), while mice lacking MCH are lean and hypophagic (Shimada *et al.* 1998). It is unknown if other GPCRs, more directly involved in the hypothalamic regulation of energy homeostasis, such as MC3R and MC4R, are ever associated with cilia.

Box 2 Obesity and regulation of energy homeostasis

Energy homeostasis is regulated by multiple peripheral signals that are integrated in the CNS and in particular the hypothalamus (for recent reviews see: (Coll *et al.* 2007, Crowley 2008, Woods & D'Alessio 2008)). Monogenic causes of human obesity have highlighted the critical role of the leptin–melanocortin system in the control of food intake. Leptin is a peptide, secreted by adipose tissue, which normally circulates at levels proportional to body fat. Leptin attenuates appetite and increases thermogenesis in mice, with its deficiency resulting in obesity in mice and humans (Zhang *et al.* 1994, Montague *et al.* 1997). Leptin crosses the blood–brain barrier and, at the hypothalamic arcuate nucleus, modulates neuropeptide expression in cocaine and amphetamine regulated/POMC neurons and AGRP/NPY neurons. POMC and AGRP neurons also project to a number of second order neurons, which express neuropeptides involved in regulating energy balance. The expression of POMC is increased in response to leptin and decreased in leptin deficiency and fasting states. POMC is cleaved into peptides, including α - and β -MSH, which are ligands for the MCRs, downstream regulators of energy homeostasis.

Cilia and adipocytes

Adipocytes originate from mesenchymal precursor cells that differentiate into preadipocytes. Preadipocytes may remain dormant or undergo further adipogenesis to become adipocytes. The master adipogenic regulator of this process is the transcription factor peroxisome proliferator-activated receptor γ (PPARG). Wnt signaling inhibits PPARG and CCAAT-enhancer-binding proteins (CEBPA, -B), which are also adipogenic (Ross *et al.* 2000). Hedgehog signaling also affects PPARG and CEBPA causing a reduction in expression of these proteins in 3T3-L1 adipogenic cells (Suh *et al.* 2006). Thus, both hedgehog and Wnt signaling are anti-adipogenic (Cousin *et al.* 2007, King *et al.* 2008, Christodoulides *et al.* 2009). In mouse models, reduced white fat mass has been observed in mice where the inhibitor of smoothened, patched, is truncated and hedgehog signaling is activated (Li *et al.* 2008), while expression of *Wnt10b*, under the control of an adipose-specific promoter (*Fabp4*), resulted in transgenic mice that had a $\sim 50\%$ reduction in total body fat and resistance to expansion of adipose tissue when fed a high fat diet (Longo *et al.* 2004). As cilia function/IFT is essential for normal hedgehog signaling in mammalian cells (Huangfu *et al.* 2003, Haycraft *et al.* 2005,

Huangfu & Anderson 2005), and is also implicated in the modulation of canonical, β -catenin-dependent, Wnt signaling (Gerdes *et al.* 2007, Corbit *et al.* 2008), it is possible that the obesity phenotype of ciliopathies may also be linked to disruption of these pathways.

A recent study from Marion *et al.* (2009) has reported that cilia are present on differentiating human white preadipocytes, yet are absent from both proliferating preadipocytes and mature adipocytes. These differentiating preadipocyte cilia have a 9+2 microtubule organization and localize hedgehog and Wnt signaling components at the axoneme. Furthermore, reduction of BBS10 and BBS12 expression was shown to reduce preadipocyte cilia incidence and affects key regulators of adipogenesis (Marion *et al.* 2009). In particular, levels of PPARG and activated glycogen synthase kinase 3 β (GSK3B) were reported to be elevated in adipocytes where BBS10 and BBS12 were knocked down, indicating promotion of adipogenic pathways (Marion *et al.* 2009). In canonical Wnt signaling, GSK3 is inactivated resulting in dephosphorylation of β -catenin and its nuclear accumulation, while in hedgehog signaling inhibition of GSK3 promotes stabilization of the *Gli2* and *Gli3* transcription factors leading to transcription of target genes. The Marion *et al.* (2009) study also reports that adipocytes derived from BBS patients had higher triglyceride content and increased levels of leptin secretion compared with controls.

Furthermore, the ALS protein, ALMS1, has been reported to be expressed at high levels in preadipocyte 3T3-L1 cells, with expression reducing in preadipocyte to adipocyte differentiation (Romano *et al.* 2008).

In contrast to disruption of the hypothalamic regulation of energy balance, defects in normal adipocyte differentiation have not been strongly implicated in the development of obesity. However, Marion *et al.* (2009) highlighted a recent study which reported that adipose tissue uses lipokines to regulate systemic metabolic homeostasis (Cao *et al.* 2008) and went on to suggest that adipogenesis may directly participate in the pathogenesis of obesity. For BBS, this would imply obesity results from two different routes.

Interestingly, RAB23, which is a negative regulator of hedgehog signaling, has been identified as mutated in Carpenter's syndrome, a congenital disorder which has obesity as part of the phenotype (Jenkins *et al.* 2007). RAB23 functions in regulation of vesicular transport, possible in cilia, (Huangfu & Anderson 2006). However, the obesity phenotype observed in Carpenter's syndrome may not be directly related to a defect in the hedgehog signaling pathway, but could represent a consequence of impaired vesicular transport of another, unknown, protein.

BBS gene variants associated with common obesity

Heterozygous carriers of BBS mutations have been reported to be more likely to be obese than control individuals (Croft *et al.* 1995). Single nucleotide polymorphisms (SNPs) have

subsequently been identified in BBS genes and non-coding variants in *BBS2*, *BBS4*, and *BBS6*, but not *BBS1*, suggested to be associated with obesity in a French–Caucasian population (Benzinou *et al.* 2006). Interestingly, the SNPs in *BBS4* and *BBS6* were shown to be associated with childhood and adult obesity, while an intronic SNP in *BBS2* was only associated with adult obesity. Another study in a Danish population failed to link variants in *BBS6* to obesity (Andersen *et al.* 2005), however, this study examined coding polymorphisms. These coding changes were not associated with obesity in the French–Caucasian population either (Benzinou *et al.* 2006). The importance of variance in BBS genes, towards common obesity, is unclear as genome-wide association studies (GWAS) have not reported association.

Possible association of the ciliary gene *RPGRIP1L* with obesity?

GWAS have identified common variants in the fat mass and obesity-associated (*FTO*) gene that predispose towards elevated body mass index (BMI) and obesity (Dina *et al.* 2007, Frayling *et al.* 2007, Scuteri *et al.* 2007, Thorleifsson *et al.* 2009). SNPs at the *FTO* locus are the variants most strongly associated with high BMI and weight in people of European ancestry. The region of *FTO* that contains obesity associated SNPs is up to 47 kb and contains parts of intron 1 and 2, as well as exon 2, of this gene. Intriguingly, another gene, *RPGRIP1L* (also known as *FTM*) which is cilia associated, lies in the opposite orientation and has its transcriptional start ~3.4 kb upstream of *FTO*, leading to the possibility that either *FTO*, *RPGRIP1L* or both could account for the association of variance in this genetic interval with obesity (Frayling *et al.* 2007, Stratigopoulos *et al.* 2008). However, obesity is not a feature of Joubert syndrome (cerebello–oculo–renal syndrome), an autosomal recessive ciliopathy caused by mutations in *RPGRIP* (Delous *et al.* 2007). Moreover, in *FTO* deleted mice, where *FTM* expression is unaltered, a significant reduction in body weight, adipose tissue and adipocyte size has been reported (Fischer *et al.* 2009).

Conclusions

There is strong evidence for defects in the hypothalamic regulation of energy homeostasis, in particular regulation of feeding, in mouse models where cilia protein function has been deleted. Loss of cilia protein function most likely affects leptin receptor signaling. There is also evidence that differentiating preadipocytes are ciliated, BBS proteins are needed for cilia maintenance in these cells, and loss of cilia may release repression of adipogenesis by hedgehog and Wnt signaling. However, it remains unclear if cilia mediated defects in adipocyte differentiation are directly linked to the development of obesity. Importantly, some cilia proteins also

function in processes not directly related to cilia (see Box 1). For example, specific cilia proteins play a role in intracellular transport (for e.g. vesicular transport along microtubules), beyond the cilium. Thus, it cannot categorically be concluded that cilia function is directly required for normal maintenance of body weight. Furthermore, although cilia proteins can be mechanistically linked to obesity in genetic syndromes and it is also unclear if cilia/cilia proteins are important in common forms of obesity.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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