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Review

Bardet–Biedl syndrome: Is it only cilia dysfunction?

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ABSTRACT

Bardet–Biedl syndrome (BBS) is a genetically heterogeneous, pleiotropic disorder, characterized by both congenital and late onset defects. From the analysis of the mutational burden in patients to the functional characterization of the BBS proteins, this syndrome has become a model for both understanding oligogenic patterns of inheritance and the biology of a particular cellular organelle: the primary cilium. Here we briefly review the genetics of BBS to then focus on the function of the BBS proteins, not only in the context of the cilium but also highlighting potential extra-ciliary roles that could be relevant to the etiology of the disorder. Finally, we provide an overview of how the study of this rare syndrome has contributed to the understanding of cilia biology and how this knowledge has informed on the cellular basis of different clinical manifestations that characterize BBS and the ciliopathies.

1. Introduction

Bardet–Biedl syndrome (BBS; MIM 209900) is a genetic pleiotropic condition characterized by retinal degeneration, obesity, postaxial polydactyly, mental retardation, hypogonadism and renal malformations, although patients can present a number of additional clinical manifestations including asthma, craniofacial defects, anosmia, hearing loss and diabetes [1]. Studies in humans, animal models, cells, and bioinformatics have shown that the cellular basis of BBS is intimately linked to the dysfunction of a particular cellular organelle, the primary cilium.

Cilia are evolutionary conserved, microtubule-based organelles that are organized from a modified centriole, the basal body, and that emanate from the plasma membrane of most cells in vertebrates. In a simplistic classification, two main types of cilia can be distinguished: motile and primary cilia whereby motile cilia are composed by an axoneme of 9 pairs of outer microtubule doublets surrounding a central pair (9 + 2) while primary cilia present a 9 + 0 structure. In addition, while cilia and flagella (same ultrastructure) are motile, primary cilia are generally immotile and present as a single structure on the apical surface of cells. A mechanism that is critical for building, maintaining and reabsorbing cilia is intraflagellar transport (IFT), the movement of material into and out of the cilium that is carried out by IFT particles linking their cargoes to microtubule based molecular motors. IFT-B particles are responsible for anterograde transport (toward the ciliary tip) whereas IFT-A directs retrograde movement (toward the cell body) in association with kinesin and dynein motors respectively (Fig. 1; reviewed in [2,3]).

A large body of work has shown that primary cilia participate in cell signaling, sensing and transducing a host of inputs ranging from mechanical cues to chemical and paracrine signaling including Hedgehog, Wnt and PDGF (Fig. 1; reviewed in [4–6]). Not surprisingly then, primary cilia play a critical role during development and in maintaining cellular and tissue homeostasis, a fact that is most clearly highlighted by the consequences of cilia dysfunction. While complete absence of cilia is incompatible with life, defective ciliary function has been associated with a number of clinical entities ranging from polycystic kidney disease (PKD) and nephronophthisis (NPHP) to pleiotropic conditions such as BBS, Alström syndrome (ALMS), Joubert syndrome (JBTS), and Meckel Gruber syndrome (MKS), all members of a novel human disease category: the ciliopathies [7,8]. The ciliopathies encompass a range of clinically distinct entities that share, to varying degrees, a common cellular basis. In this review, we will focus on a model ciliopathy, BBS, discussing the genetics of the syndrome and the known roles of the BBS proteins both in the context of the cilium but importantly also outside of the organelle.

2. The genetics of BBS

BBS is a genetically heterogeneous condition for which 19 BBS genes have been identified to date: *BBS1-12*, *BBS13/MKS1*,

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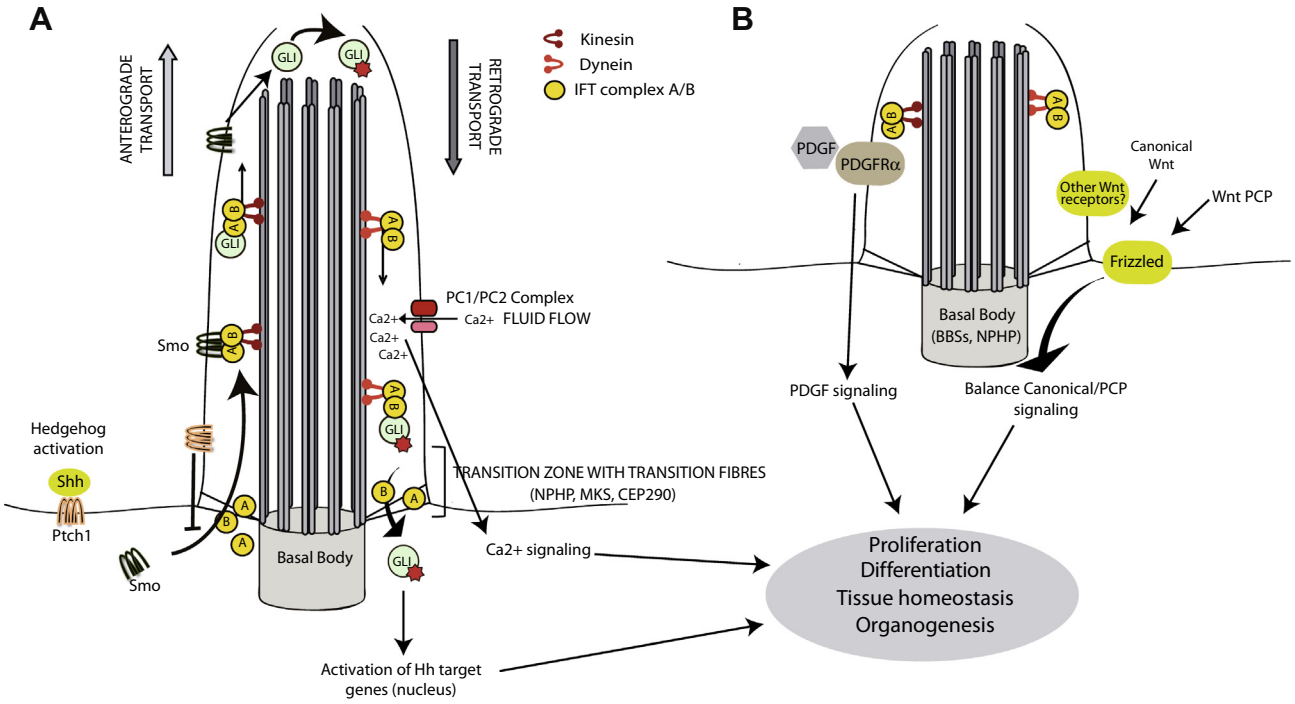

Fig. 1. Schematic representation of the cilium and its role in signal transduction. The cilium is composed by a microtubule axoneme organized from a basal body. Alongside the microtubules, IFT particles and motors are in charge of transporting moieties in and out of the cilium. Different receptors localize to the ciliary membrane and rely on the cilium for signal transduction to control several biological processes (A and B). One of the best characterized is the Hedgehog signaling pathway (A). Upon binding of the activator (Shh) to its receptor Ptch1, the complex is translocated outside of the cilium and no longer inhibits the ciliary entry of Smo, which in turn facilitates Gli processing and activation. Activated Gli transcription factors (Gli-star) exit the cilium and enter the nucleus to drive gene transcription. (B) Basal body proteins, such as the BBSs and NPHPs, are involved in regulating Wnt signaling whereby depletion of BBSs results in increased canonical signaling and reduced PCP.

BBS14/CEP290, *BBS15/WDPCP/FRITZ*, *BBS16/SDCCAG8*, *BBS17/LZTFL1*, *BBS18/BBIP10/BBIP1* and *BBS19/IFT27*; ([9–14] and references within). This heterogeneity was originally thought to be the cause of the significant inter-familial variability that characterizes the syndrome. However, establishing genotype–phenotype correlations has been a challenge, likely due to the significant functional overlap between the BBS proteins that we will discuss in the following sections. Having said that, thorough analyzes of different BBS patient cohorts and animal models are demonstrating subtle differences in disease presentation that are likely due to specific functions of different BBS proteins. For example, studies suggest that mutations in *BBS2*, *BBS3* and *BBS4* are associated with characteristic ocular phenotypes [15,16] and patients bearing mutations in *BBS16/SDCCAG8* are characterized by highly penetrant renal disease but do not present with polydactyly [13]. Similarly, patients with mutations in *BBS6*, *BBS10* or *BBS12* present with a more severe renal phenotype [17]. Importantly, BBS6, BBS10 and BBS12 belong to a functionally distinguishable subgroup of BBS proteins, a fact that could provide a molecular explanation to this finding [18,19]. Studies in mice are also highlighting differences linked to the identity of the mutated gene. *Bbs3*$^{-/-}$ mice develop common features of *Bbs* mutants, such as increased body weight and retinal degeneration, but also distinct manifestations, such as severe hydrocephalus and increased blood pressure [20]. Likewise, *Bbs4*$^{-/-}$ and *Bbs6*$^{-/-}$ mice present differences in blood pressure compared to *Bbs2*$^{-/-}$ animals [21].

BBS is also characterized by significant intra-familial variability, a phenomenon not readily explained by genetic heterogeneity. Although BBS is largely inherited as an autosomal recessive trait, the screening of patient cohorts showed that in some families the disorder behaves as an oligogenic condition whereby mutant alleles in more than one BBS gene and other modifier *loci* interact to modulate the penetrance and expressivity of the syndrome [11,22–30]. Thus, differences in the total mutational load across different BBS associated genes likely contribute to the characteristic phenotypic variability in this syndrome [31,32].

The functional characterization of the BBS proteins has provided critical information to understand both the overall lack of genotype-phenotype correlations and the genetic interaction between different BBS genes. These proteins share biological functions and even work forming multi-protein complexes. Therefore, mutations in different BBS genes are likely to affect the same biological processes (i.e. the formation/function of the cilium) and thus correlations between mutations in specific BBS genes and subsets of phenotypes would not be expected and rather would only be explained by specific functions of individual BBS proteins. Likewise, the observation of oligogenic inheritance in BBS is likely a consequence of mutating different components of the same protein complex, where different subunits can at least partially compensate for the lack of another, or affecting the same biological pathway at more than one step, models that have been used to explain this type of genetic interactions (reviewed in [22,33]). Interestingly, oligogenicity is not restricted to BBS but appears to be relatively common among ciliopathies as examples have been documented or postulated for NPHP, MKS and Acrocallosal (ACLS) syndrome [34–36].

The ciliopathies encompass a range of human conditions that although clinically distinct, share significant aspects of both their phenotypic presentation and their cellular basis. In other words, mutations in genes associated with different disorders can result in similar phenotypes because they affect the same organelle. Thus, if all the ciliopathies are caused by cilia dysfunction, why are these disorders distinct clinical entities? The main factor is the identity of the mutated gene and the specific function of its encoded protein in the cilium. It is not the same to impair cilia formation than to affect a given ciliary channel or receptor. In

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