Intraflagellar transport 20 cilia-dependent and cilia-independent signaling pathways in cell development and tissue homeostasis

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ABSTRACT **Intraflagellar transport (IFT) is an essential condition for ciliogenesis. The primary cilia protrude like antennae and act as chemical or mechanical sensory organelles that coordinate specific receptor localization and signal transduction. IFT20 is the smallest molecule in IFT complex B, which is located in both the cilia and the Golgi complex. Recent studies have shown that IFT20 is a key molecule in multiple signaling pathways. Importantly, in the function of IFT20, signal transduction is not restricted to cilia, but is also involved in non-ciliary functions. Here we summarize current knowledge regarding IFT20-mediated signaling pathways and their relationship with cell development and tissue homeostasis, and analyse the cilia-dependent and cilia-independent mechanisms of IFT20 coordinated signaling pathways and potential crosstalk between the mechanisms. This review provides a comprehensive perspective on IFT20 coordinates signaling mechanisms in cell development and tissue homeostasis.**

KEYWORDS: primary cilia, Intraflagellar transport (IFT)20, cilia-dependent signaling pathways, cilia-independent signaling pathway

Introduction

Cilia and flagella are microtubule (MT)-based and membrane-bound organelles that project from the cell surface and serve both motile and sensory functions. The core MT structures, called axonemes, originate in and grow from modified centrioles to form structures that become the ciliary basal body. The axonemes of microtubules are generally composed of one of two common patterns. The 9 + 2 MT structure consists of nine pairs of peripheral double MTs surrounded by a pair of central single MTs, and the 9 + 0 pattern lacks the central pair and thus only has the nine pairs of peripheral double MTs (Łysyganicz *et al.*, 2021). Mammalian cilia are typically classified into two types: motile cilia and primary cilia. The motile cilia tend to possess the 9 + 2 MT structure (Zhao *et al.*, 2020), and the primary cilia tend to have the 9 + 0 pattern (Fig. 1). Several exceptions to these patterns exist, as motile 9 + 0 cilia and immotile 9 + 2 cilia can be formed (Takeda and Narita, 2012). Moreover, recent studies have shown that the double microtubule structure of the 9 + 0 pattern is only present at the basal level of mammalian primary cilia; as the microtubule extends to the top, this structure gradually transforms into one consisting of actin

filaments associated with unstructured microtubules decorated with end-binding 1 protein (Kiesel *et al.*, 2020). This structure is clearly different from the more stable 9 + 2 MT structure of motile cilia. Motile cilia make cells move, for example in the case of sperm motility (Leung *et al.*, 2021), and they are involved in the movement of fluids through a tissue, such as in the clearance of mucus (Bustamante-Marin *et al.*, 2019), the flow of cerebrospinal fluid (Thouvenin *et al.*, 2020), and leftward flow in the embryonic node (Schweickert *et al.*, 2007). In addition, both motile cilia and primary cilia perform sensory functions (Pigino, 2021). Primary cilia in particular function as sensors of changes in the extracellular environment, and they transmit this information through signaling pathways to regulate cell development and other physiological processes (Cai *et al.*, 2017). Because of the diverse roles of primary cilia, defects in these structures are associated with multiple ciliopathies (Zhou *et al.*, 2020), including polycystic kidney disease (Ma *et al.*, 2013), Bardet-Biedl syndrome (Kanie and Jackson, 2021) and Meckel-Gruber syndrome (Zhang *et al.*, 2021).
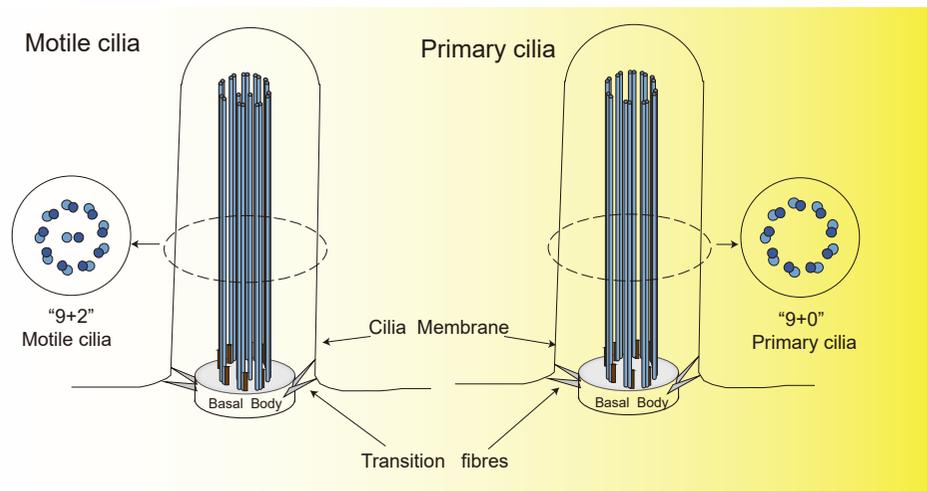
The biogenesis, function and structural maintenance of cilia rely on vesicular and IFT pathways. Pathways associated with vesicular trafficking mainly involve the transport of specific signaling mol-

Fig. 1. The structure of motile and primary cilia. (A) 9 + 2 motile cilia MT structure. **(B)** 9 + 0 primary cilia MT structure.

ecules or receptors from Golgi or endosomes to the ciliary base, which guides the early steps of ciliogenesis (Sung and Leroux, 2013). Because the cilia themselves cannot synthesize protein, the further assembly and maturation of cilia require specialized IFT pathways to transport building blocks and signaling molecules. Movement in IFT is powered by motor proteins that are directed both toward and away from the cilia. Kinesin-2 (KIF3 in mammals) (Engelke et al., 2019) and cytoplasmic dynein-2 (Toropova et al., 2019) drive anterograde and retrograde IFT movement, respectively, and the transport is mediated by two complexes, namely IFT-A and IFT-B (Wei et al., 2012). The IFT-A complex contains known 6 proteins. IFT-B can be further divided into two sub-complexes, IFT-B1 and IFT-B2, which contain 10 and 6 known proteins, respectively (Taschner et al., 2016). The structures that mediate IFT are often referred to as IFT trains. In anterograde IFT, these trains are assembled in the basal body of the cilia as the IFT complex interacts with cargoes and kinesin-2 (Zhu et al., 2021). These combined structures then traverse the transition zone (Scheidel and Blacque, 2018), a Y-type diffusion barrier between the microtubule doublets and ciliary membrane that controls the entrance and exit of ciliary proteins (Webb et al., 2020). The structure then moves to the top of the cilia along the B-tubule of microtubule doublets or the A-tubule of primary cilia distal singlet axonemal microtubules (Kiesel et al., 2020), up to the ciliated tip. At the tip, anterograde trains turn into retrograde trains that return to ciliary base along the A-tubule under the power of dynein-2 (Fig. 2) (Webb et al., 2020; Wingfield et al., 2021).

One protein in the IFT-B complex, IFT20, is not only located in the cilia and the centrosome pool, but is also found anchored to the Golgi complex by the Golgi microtubule-associated protein 210 (GMAP-210) (Follit et al., 2008). In ciliated cells, on the one hand, IFT20 located in the cilia participates in the transport of IFT trains. On the other hand, IFT20 located in the Golgi complex moves rapidly between the Golgi complex and the cilia, facilitating the trafficking of ciliary membrane proteins from the Golgi complex to the basal body of cilia and playing an important role in the assembly and function of cilia (Follit et al., 2006). IFT20 also possesses cilia-independent functions. For example, IFT20 mediates T cell antigen receptor (TCR) signaling in the activation of T cells in immune synapses (Galgano et al., 2017). It also influences tumor invasiveness via its regulation of Golgi structure and transport by mediating receptor

tyrosine kinase-like orphan receptors 2 (ROR2)-dependent signaling (Nishita et al., 2017). Increasing evidence indicates that cell type-specific of IFT20 emerges in different cell lines (Yang et al., 2021). This diverse functioning of IFT20 may help to explain the differential reception and transmission of signals in various cell types, and it allows IFT20 to mediate a variety of cell behaviors. This review summarizes current research on the mechanisms of IFT20 multiple signaling pathways in cell development and tissue homeostasis.

Hedgehog signaling

Hedgehog signaling plays a crucial role in the development of mammalian tissues and organs, homeostasis of internal environments, and repair and regeneration following injury (Rohatgi et al., 2007). In mammals, there are three hedgehog homologous (HH) genes that encode three HH proteins: sonic hedgehog (SHH); desert hedgehog (DHH); and Indian hedgehog (IHH). HH proteins are the ligands for two cell surface receptors, patched (PTCH1) and smoothened (SMO), which jointly control the activation and inactivation of the zinc finger transcription factor glioblastoma/cubitus interruptus (GLI/CI) (Russell et al., 2007; Hynes et al., 1997). The *GLI* gene family consists of *GLI1*, *GLI2* and *GLI3*. The product of the *GLI1* gene only acts as a transcriptional activator (Hynes et al., 1997), while the *GLI2* and *GLI3* gene products have both transcriptional activating and transcriptional repressing activity. When the three transcription factors are full-length, they all show transcriptional activation activity (Hui and Angers, 2011).

The mechanism by which PTCH1 regulates SMO remains poorly defined, but it is clear that the cilium is intimately involved. In the absence of HH, PTCH1 is localized in the primary cilia and inhibits the activity of SMO by preventing the accumulation of SMO. Upon phosphorylation of full-length GLI (GLI2/3-FL) by protein kinase A, glycogen synthase kinase 3 or casein kinase 1, proteasome-mediated hydrolysis of GLI2/3-FL leads to production of a repressor form of the protein (GLI2/3-R). GLI2/3-R then enters the nucleus and blocks the transcription of downstream target genes. HH binding to PTCH1 relieves the inhibition of SMO, and PTCH1 moves out of the primary cilia and SMO moves into the primary cilia through a process mediated by oxysterols (Rohatgi et al., 2007). KIF7, suppressor of fused (SUFU), and GLI also accumulates in

the primary cilia; activated SMO promotes the dissociation of the SUFU-GLI2/3-KIF7 complex and generates activated GLI (GLI-A). Activated GLI-A moves into the nucleus and induces the transcription of downstream target genes (Fig. 3) (Hu and Song, 2019).

The primary cilia represent the key location of reception and transmission of HH signaling. The effective activation of the SHH signaling pathway in particular depends on the normal functioning of IFT (Haycraft *et al.*, 2005). Knockdown of *IFT20* has been found to block HH signaling specifically by affecting ciliogenesis (Pampliega *et al.*, 2013; Clement *et al.*, 2009). In addition, decreased expression of *Ift20* was shown to result in the decreased expression of both *Smo* and *Gli1*, which reduced the proliferation and dedifferentiation potential of rat Müller cells mediated by SHH (Ferraro *et al.*, 2015).

In condylar cartilage, IFT20-assembled primary cilia also mediate the ability of the HH pathway to signal for the production of collagen type X, which is essential for the maturation of chondrocytes. The expression levels of *GLI1* and *PTCH1* were found to be significantly decreased, and there was no SMO accumulation in primary cilia from which *IFT20* was deleted in a chondrogenic cell line. Consistent with these *in vitro* results, cilia-dependent HH signal transduction was found to be severely attenuated in the pleomorphic, flat and hypertrophic layers of *Ift20* conditional knockout mice, while it was abundantly present in the condylar cartilage of control mice (Kitami *et al.*, 2019).

Primary cilia assembled by IFT20 are the venue of receiving and transmitting HH signaling in astrocytes. When astrocytes were stimulated by SMO agonist (SAG), the HH signaling pathway was also found to be activated, and this co-activation improved the survival rate of astrocytes under stress conditions. Conversely, when *IFT20* was knocked down, the effect of SAG on cell survival disappeared (Yoshimura *et al.*, 2011). In analysis of Down Syndrome, the disruption of IFT20 trafficking from the Golgi to the centrosome and cilia by elevated pericentrin was found to lead to fewer and shorter cilia, accompanied by the failure of SMO transport to the cilia (Fig. 3). These processes reduced ciliary SHH signaling, which may underlie a series of cardiovascular, musculoskeletal
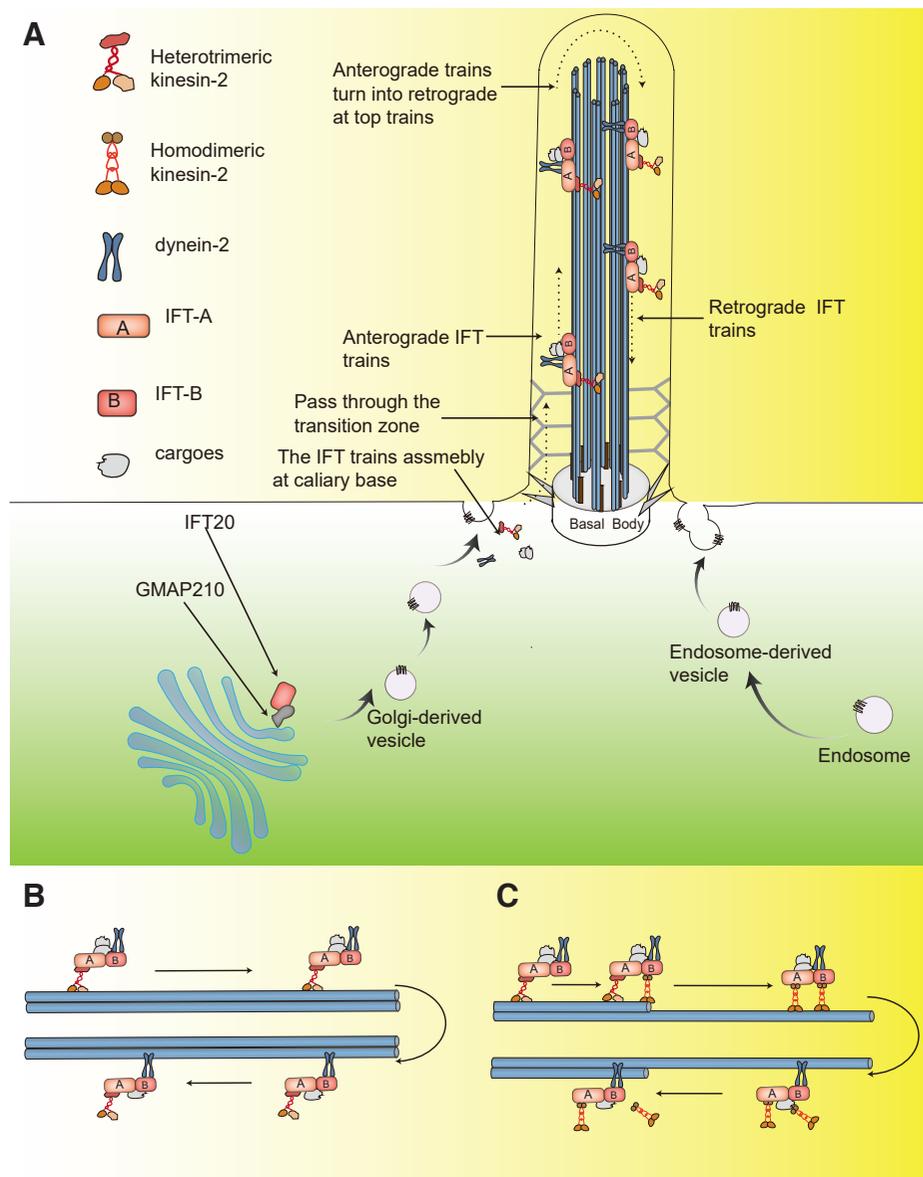
Fig. 2. Overview of primary cilia, IFT20 and IFT trains. (A) IFT20 anchored to the Golgi complex by GMAP210, where it regulates trafficking of ciliary membrane proteins from the Golgi complex to the cilia. IFT trains assembled in the basal body of cilia by the IFT complex interact with cargoes and kinesin-2, then pass through the transition zone. They move to the top of the cilia along the B-tubule of microtubule doublets or A-tubule of primary cilia distal singlet axonemal microtubules, up to the tip of the cilia. Anterograde trains then turn into retrograde trains that return to the ciliary base along the A-tubule under the power of dynein-2; **(B)** In IFT trains, heterotrimeric kinesin-2 and dynein-2 drive anterograde and retrograde movement, respectively, in most organisms, such as *Chlamydomonas*; **(C)** IFT is driven by two different types of kinesin-2 motors in *Caenorhabditis elegans*: heterotrimeric kinesin-2 and homodimeric kinesin-2. Heterotrimeric kinesin-2 drives IFT trains through the transition zone and proximal cilia, then they are gradually replaced by homodimeric kinesin-2, which drives the trains along the distal segment to the top of the cilia, while dynein-2 drives retrograde IFT transport.
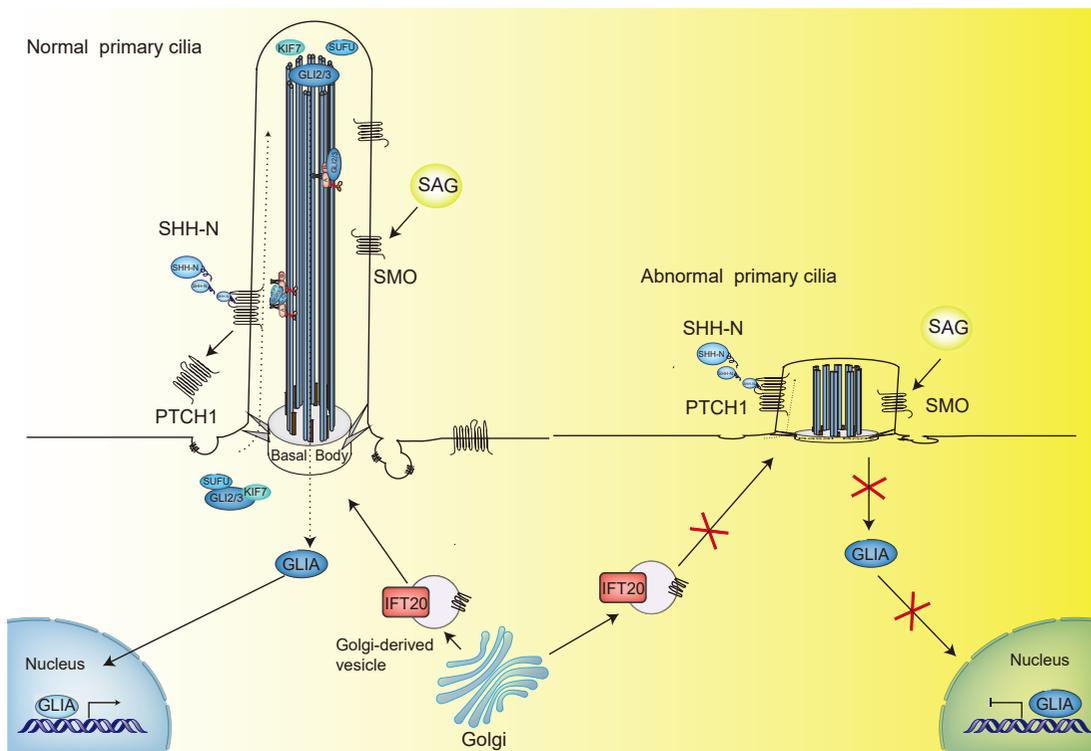
Fig. 3. IFT20-dependent HH signaling. IFT20-assembled primary cilia mediate the HH signaling pathway. Upon binding of the SHH ligand to PTCH1, the inhibition of SMO by PTCH1 is relieved, leading to movement of PTCH1 out of the primary cilia and of SMO into the primary cilia. KIF7, SUFU, and GLI also accumulate in the primary cilia, and activated SMO promotes the dissociation of the SUFU-GLI2/3-KIF7 complex and generates activated GLI(GLI-A). The activated GLI-A moves into the nucleus and induces the transcription of downstream target genes; Mutation or disruption of IFT20 blocks trafficking from the Golgi apparatus to the cilia, resulting in shorter and fewer cilia. Accompanying the failure of SMO transport to cilia is inhibition of cilia-dependent SHH signaling.

and neurological abnormalities (Galati *et al*., 2018). In summary, IFT20-deficient cells have multiple defects in signaling-dependent transport of a variety of HH components, including PTCH-1, SMO and GLI, and these defects are primarily related to the function of IFT20 in the biogenesis and structure maintenance of cilia.

WNT signaling

WNT signaling plays critical roles in cell proliferation, differentiation and tissue development. In mammals, 19 WNT ligands and 10 families of its receptor, frizzled (FZD), have been identified. WNT ligands induce the activation of canonical and non-canonical WNT/β-catenin signaling pathways through cross reactions with FZD receptors and the co-receptors low-density lipoprotein-related receptor proteins 5 and 6 (LRP5/6) (Janda *et al*., 2017).

Canonical WNT/β-catenin signaling

β-catenin is a key protein in canonical WNT signaling. The degradation and production of β-catenin determines the initiation and termination of WNT signaling. In the absence of WNT, cytoplasmic β-catenin is phosphorylated by a "destruction complex" to promote its degradation. The destruction complex consists of four proteins, including scaffolding proteins AXIN, adenomatous polyposis coli (APC), casein kinase 1α (CK1α), and glycogen synthase kinase 3β (GSK-3β) (Nong *et al*., 2021). Phosphorylated β-catenin is ubiquitinated by E3 ubiquitin ligase β-transducin-repeat-containing protein (β-TRCP) and is subsequently degraded by the proteasome (Ci *et al*., 2018). As a result, the level of β-catenin is kept low in the absence of WNT, and T cell factor (TCF) is able to bind to the repressor Groucho and is in its inactive state in the nucleus (Fig. 4A) (Li *et al*., 2020).

Non-canonical, β-catenin-independent WNT signaling

Non-canonical signaling downstream of WNT includes WNT/planar cell polarity (PCP) signaling and WNT/Ca^{2+} signaling. There are six core proteins in the PCP pathway, which mediates cellular polarization. These proteins include the four-pass transmembrane proteins Van Gogh and striabismus, the seven-pass transmembrane proteins FZD and cadherin Flamingo, and the cytoplasmic proteins Prickle, Diego and disheveled(DVL) (Harrison *et al*., 2020). The interactions of these core proteins in neighboring cells can promote cytoskeleton reorganization via the action of small GTPases and Rho-associated kinase, and can also induce transcription via C-Jun N-terminal kinase (JNK) activation (Strutt *et al*., 2019; Wang *et al*., 2019).

In WNT/Ca^{2+} signaling, when WNT proteins bind to FZD receptors, two pathways are mediated by heterotrimeric G proteins. One pathway involves activation of phosphodiesterase (PDE) and the decrease of cGMP concentrations. The other pathway involves activation of phospholipase C (PLC), which produces inositol 1,4,5-trisphosphate (IP$_3$) and diacylglycerol (DAG), leading to the release of intracellular Ca^{2+} and the activation of protein kinase C (PKC), respectively (Sheldahl *et al*., 1999). Both of these pathways affect the activity of transcription factors (Zhen *et al*., 2020; Wang and Malbon, 2003).

Relationship between IFT20 and the WNT pathway and disease

Although primary cilia have been demonstrated to play a negative regulatory role in WNT signaling (Kawata *et al*.,2021), the links the between primary cilia and canonical WNT/β−catenin or WNT/PCP pathways remain controversial. One of the links between
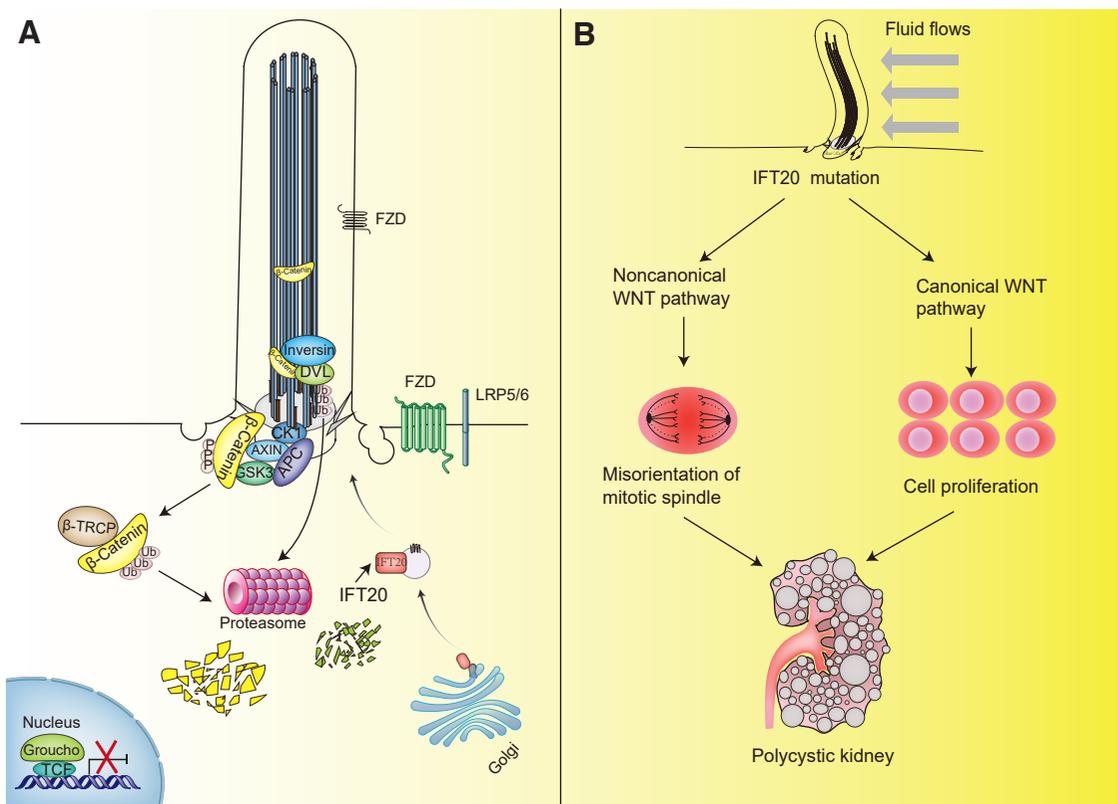
Fig. 4. IFT20 modulation of WNT signaling. (A) IFT20-assembled primary cilia mediate the actions of the ciliary protein Inversin, which inhibits the canonical WNT pathway through degradation of cytoplasmic β-catenin and DVL by proteasome recruitment; **(B)** When fluid flows through the nephron, IFT20 mutations in the collecting ducts of kidney lead to alterations in non-canonical and canonical WNT signaling, causing misorientation of the mitotic spindle and increased proliferation of duct cystic epithelium, respectively. Eventually, cyst formation occurs.

primary cilia and WNT signaling resulted from evidence that the ciliary protein Inversin, which is localized to the primary cilium of tubular epithelial cells, inhibits the canonical WNT pathway through degradation of cytoplasmic β-catenin and DVL by the recruitment of the proteasome (Christian Wigley *et al*., 1999). Here, Inversin and DVL interact to form a protein complex that increases DVL ubiquitination resulting in proteasome-dependent degradation (Fig. 4A). Accordingly, mutations of the *Inversin* gene that occur during embryonic development lead to cystic kidney disease (Simons *et al*., 2005). Another link was indicated by the finding that the loss of primary cilia in mice via the deletion of the ciliogenesis genes *Kif3a*, *Ift88* and Orofacial digital type I syndrome (*Ofd1*) increases the activation of the canonical WNT pathway (Corbit *et al*., 2008).

However, some researchers believe that there is no substantial link between primary cilia and WNT signaling. In mouse embryos with mutations in *Ift88*, *Ift72*, and *Kif3a* and the gene encoding dynein-2 (*Dync2h1*), the activities of the WNT target *Axin-2* gene and a transgenic reporter of canonical WNT signaling were both normal. The conversion from canonical WNT signaling to non-canonical WNT signaling has also been found to be normal in embryonic fibroblasts from mice with an IFT mutation (Ocbina *et al*., 2009).

Research has indicated that IFT20 is also related to WNT signaling regulation. For example, generation of dysfunction of primary cilia by the deletion of *Ift20* or *Itf88* leads to increased canonical WNT signaling and decreased HH signaling, which decreases branching morphogenesis of mammary glands and other organs (McDermott *et al*., 2010). Notably, non-canonical WNT pathways control the orientation of the mitotic division (Gong *et al*., 2004), while the canonical WNT/β-catenin pathway regulates

cell proliferation (Aulicino *et al*., 2020), and one of the functions of primary cilia is to regulate the conversion between canonical and non-canonical WNT signaling when fluid flows through the nephron (Simons *et al*., 2005). Accordingly, deletion of *Ift20* in the collecting ducts of the kidney lead to elevate dephosphorylation of β-catenin and increased expression of genes in the WNT pathway, including those coding for WNT ligands (*Wnt7a/b, Wnt10a, Wnt9a, Wnt6, Wnt 4, and Wnt2*), WNT-binding proteins (*Frz6 and Frzb*) and WNT targets (*Myc, JNK, Tcf3 and Tcf7*). Under these conditions, the expression of both the canonical and non-canonical WNT signaling components increased, eventually causing misorientation of the mitotic spindle and increased proliferation of duct cystic epithelial cells and cyst formation (Fig. 4B) (Jonassen *et al*., 2008). However, because IFT20 also has important extraciliary functions, the specific mechanisms of cross-reaction between canonical and non-canonical WNT signaling and ciliary or non-ciliary functions of IFT20 merits further study.

Platelet-derived growth factor signaling

Platelet-derived growth factor (PDGF) signaling plays an important role in embryonic development and tissue homeostasis. The monomer forms of PDGF are inactive, and these monomers include four different polypeptide chains (PDGF-A, PDGF-B, PDGF-C and PDGF-D). PDGF-A and -B are secreted as active peptides linked by disulfide bonds to form homodimers (PDGF-AA or PDGF-BB) and heterodimers (PDGF-AB), while PDGF-C and -D are secreted as latent homodimers (PDGF-CC or PDGF-DD) (Fredriksson *et al*., 2004). The PDGF isoforms perform their biological effects by binding to

and dimerizing two structurally related tyrosine kinase receptors, PDGFR-α and PDGFR-β(Pahara *et al*., 2010; Li and Schlessinger, 1991). The receptor interactions lead to autophosphorylation and activation of intracellular tyrosine kinase domains (Kazlauskas and Cooper, 1989).

The autophosphorylation serves two important functions. On the one hand, this phosphorylation releases the inhibitory effect of the carboxy-terminal tail of the conserved tyrosine residue and juxtamembrane domain that were folded over the kinase domain; on the other hand, the phosphorylated tyrosines serve as docking sites for containing Src homology 2 (SH2) domains signal transduction molecules (Songyang and Cantley, 1995). Various SH2-domains signal transduction molecules have been reported to be involved in the connection of the docking sites of PDGFR. Some of the SH2-domain molecules act as enzymes, including PLC, the Src family of tyrosine kinases, a GTPase activating protein (GAP) for RAS, phosphatidylinositol 3-kinase and the tyrosine phosphatase
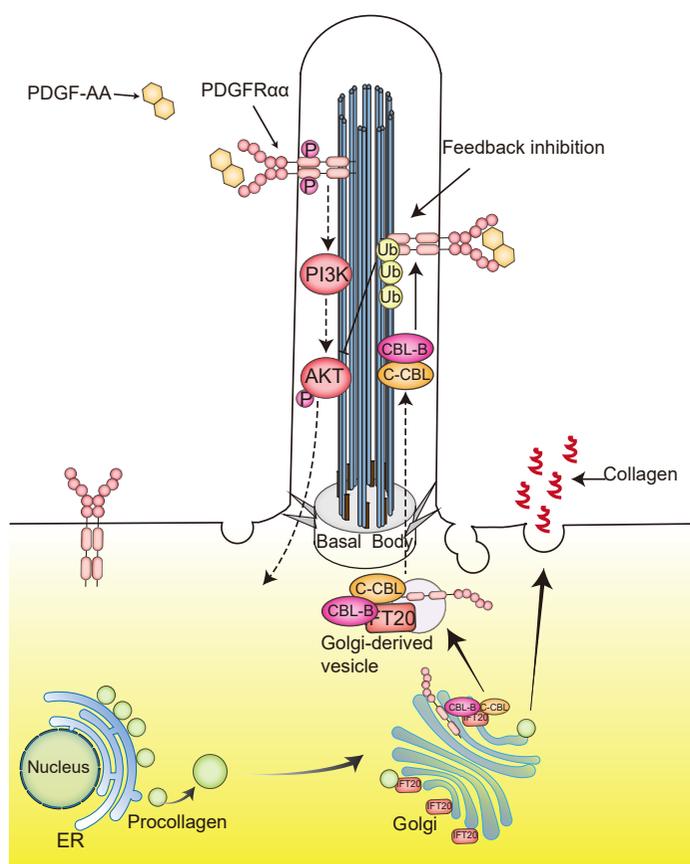
Fig. 5. IFT20 modulation of PDGF signaling. A complex containing IFT20 and C-CBL and CBL-B transports PDGFRα to cilia, where it forms homodimer receptors when stimulated by PDGF-AA. The PDGFR dimer leads to autophosphorylation of intracellular tyrosine kinase domains that provides docking sites for signal transduction molecules. An important effect is the activation of the PI3K-AKT signaling pathway, which promotes osteoblastic differentiation and fracture healing. In addition, the interaction of IFT20 with CBL promotes formation of stable CBL homo- or hetero-dimers that mediate ubiquitination and internalization of PDGFRα for feedback inhibition of receptor signaling. IFT20 also trafficks procollagen from the ER to the Golgi in osteoblasts.

SHP-2, while other SH2-domain molecules act as adaptor proteins, including growth factor receptor-bound protein (GRB)2, GRB7 and CRK (Noguchi *et al*., 2017; Heldin and Lennartsson, 2013). Upon PDGF receptor activation, various SH2 domain-containing molecules initiate a series of signaling transduction pathways, leading to different cellular responses.

PDGFRα is predominantly localized to the primary cilium, and primary cilium formation is correlated with increases of PDGFRα expression. The signaling mediated by PDGFRα depends on its ciliary localization, while PDGFRβ is primarily localized to the cell surface (Schneider *et al*., 2005). One connection between the cilia and PDGF signaling involves PDGF-mediated initiation of signaling through phosphatidylinositol 3-kinase (PI3K) and protein kinase B (PKB/AKT), which promotes osteoblastic differentiation and healing of bone fractures (Zhu *et al*., 2020). IFT20 plays a vital role in craniofacial skeletal development by regulating ciliogenesis and collagen intracellular trafficking PDGFRα activation, and the resulting AKT phosphorylation is mediated through the primary cilia in the regulation of osteogenic proliferation and cell survival. Disruption of IFT20 and the resulting absence of primary cilia decreases PDGFRα localization to the primary cilia. While this receptor is still present on the cell surface under these conditions, osteogenic proliferation was found to have decreased and cell death to have increased. In addition, IFT20 is also indispensable for regulation of secretion of type I collagen by controlling the transport of procollagen from the endoplasmic reticulum (ER) to the Golgi apparatus during skull development (Fig. 5) (Noda *et al*., 2016). These results indicate that IFT20 mediates the localization of PDGFRα in primary cilia and regulates the activation of PI3K -Akt signaling.

Further studies of the mechanism of interaction between IFT20 and PDGF/PDGFR signaling pathways have indicated that IFT20 stabilizes the Casitas B-lineage lymphoma (CBL) E3 ubiquitin ligases C-CBL and CBL-B, and this stabilization provides a negative feedback mechanism in PDGFRα signaling pathways. When cells are stimulated by PDGF-AA, C-CBL proteins become enriched in the primary cilia, and IFT20 interacts with C-CBL and CBL-B to promote the formation of stable CBL homo- or hetero-dimers (Schmid *et al*., 2018). Those dimers mediate ubiquitination and internalization of PDGFRα for feedback inhibition of receptor signaling (Fig. 5). In contrast, in the absence of IFT20, PDGFRα mislocalizes to the plasma membrane, where it promotes autoubiquitination and proteasomal degradation of CBL proteins, resulting in overactivation of PDGFRα after PDGF-AA stimulation (Schmid *et al*., 2018; Anvarian *et al*., 2019).

The mechanisms of interaction between IFT20 and C-CBL and CBL-B, which play critical negative regulatory roles in cell development, activation, and tolerance induction(Schmid *et al*., 2018), in the regulation of the localization of PDGFRα on cilia have not been completely clarified. GFP-labeled C-CBL was used to identify potential interaction sites of IFT20 and CBL proteins in Golgi complex and ciliary-base region (Schmid *et al*., 2018). Contrary to the effects of *IFT20* mutations, mutations to *IFT72* and *IFT88* led to decreased *PDGFRα* expression, and PDGFRα did not respond to PDGF-AA stimulation in these contexts (Schneider *et al*., 2005; Schmid *et al*., 2018; Umberger *et al*., 2015). Based on these results, a hypothetical model established that IFT20 coordinates CBL protein to mediate the relocalization of PDGFRα to the cilia from the Golgi apparatus (Fig. 5) (Schmid *et al*., 2018); however, the precise mechanisms require further study.

Fibroblast growth factor signaling

Signaling involving fibroblast growth factor (FGF) and its receptor (FGFR) play crucial roles in embryonic development, angiogenesis, tissue homeostasis, wound repair, and cancer in various biological models. 22 mammalian FGF proteins have been identified, 18 of which bind to FGF tyrosine kinase receptors and coreceptors. These signaling molecules are grouped into five paracrine subfamilies and one endocrine subfamily based on differences in sequence homology and phylogeny. Four of the FGFs comprise a subfamily of intracellular non-signaling proteins that serve as cofactors for voltage-gated sodium channels and other molecules (Xie *et al.*, 2020). FGFs exert their diverse effects by binding to and activating FGFRs and coreceptors at the cell surface. Coreceptors include heparan sulfate proteoglycans (HSPGs) for paracrine signaling (Jones *et al.*, 2000) and Klotho for endocrine signaling (Goetz *et al.*, 2007).

Activation of the FGFR promotes the phosphorylation of the TK domain, and phosphorylated tyrosines serve as docking sites for downstream signaling molecules, causing a series of signaling cascade reactions. In addition, the activated receptor also catalyzes the phosphorylation of FGFR substrate 2a (FRS2a) (Ong *et al.*, 2000), which activates signaling pathways involving RAS, mitogen-activated protein kinases (MAPKs) (Gotoh *et al.*, 2004), extracellular signal-regulated kinases (ERK), P38, JNKs and PI3K/AKT (Xie *et al.*, 2020; Sacco *et al.*, 2021). The receptor can also recruit and phosphorylate phospholipase Cγ (PLCγ), which activates signaling pathways involving IP_3, Ca^{2+}, and DAG and subsequent activation of PKC (Zeng *et al.*, 2020; Landgren *et al.*, 1995; Huang *et al.*, 2016).

Interactions between cilia and FGF signaling are manifest in part through a series of skeletal ciliopathies that occur due to defects in the biosynthesis or function of primary cilia (Zhang *et al.*, 2018). IFT20 is a key regulator of temporal space FGF signaling required for endochondral osteogenesis. Specific deletion of mice chondrocyte *Ift20* increased the expression of *Fgf18* in the perichondrium that maintained the expression of *Sox9*, thus inhibiting endochondral ossification. Inhibition of the enhancing of ERK1/2 activation through phosphorylation can partially rescue defective chondrogenesis in *Ift20* deleted cells (Yamaguchi *et al.*, 2022). In addition, continuous signaling caused by gain-of-function mutations of FGFR3 in both bone and cartilage results in shortening of the primary cilia and the induction of achondroplasia and thanatophoric dysplasia (Martin *et al.*, 2018). Constitutively active FGFR3 also affects the length of primary cilia by disrupting the trafficking of IFT20-enriched vesicles from the Golgi complex to the cilia-basal body, and partial depletion of *IFT20* resulted in the shortening of the primary cilia (Kim *et al.*, 2011; Stoetzel *et al.*, 2016).

Further research has shown that the molecular mechanisms of interaction may include the activation of TOR signaling pathways (Martin *et al.*, 2018). NIH3T3 fibroblasts transfected with GFP-tagged IFT20 were used to demonstrate that strong and constitutive sustained activation of FGF signaling slowed the speed of both anterograde and retrograde movement of IFT20-GFP, and this deceleration resulted in the shortening of primary cilia. On the contrary, a relatively low level of transient activation of FGF signaling accelerated IFT20-GFP, resulting in the extending of the primary cilia (Fig. 6). These findings indicate that the regulation of the speed of IFT20-mediated transport is a main process by which FGF affects the length of primary cilia (Kunova Bosakova
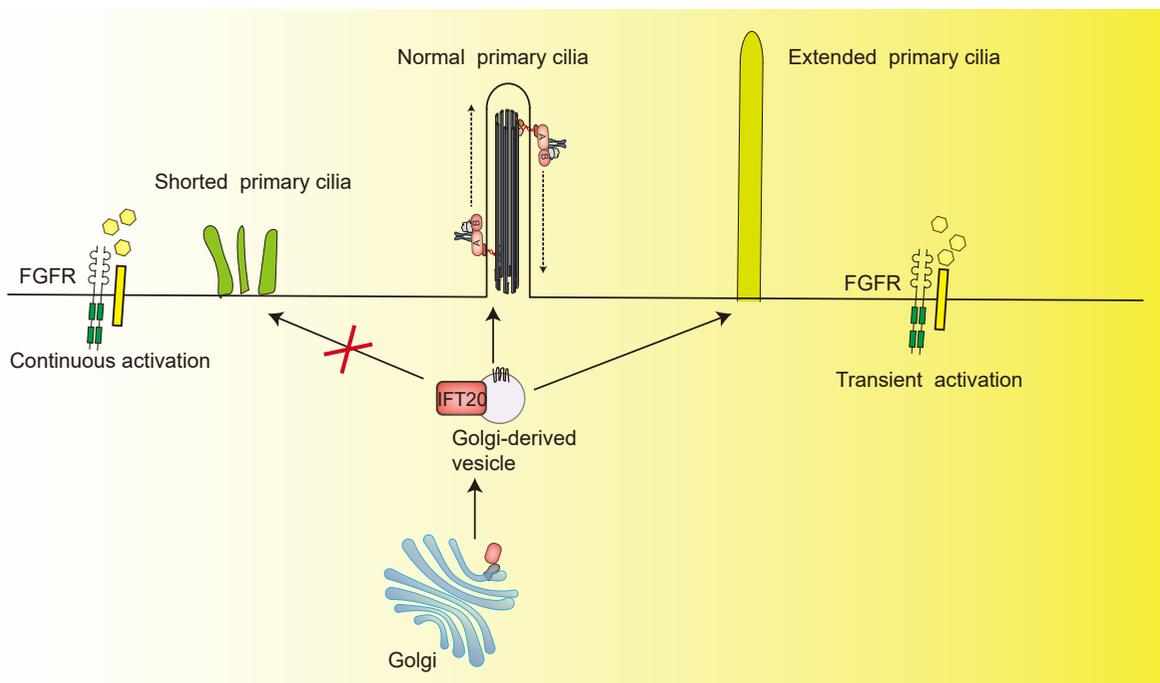
Fig. 6. IFT20 modulation of FGF signaling. Constitutive activation of FGFR3 by gain-of-function mutations results in disrupting the trafficking of IFT20-enriched vesicles from the Golgi complex to the cilia-basal body, and it slows both anterograde and retrograde IFT20-GFP movement, resulting in the shortening of primary cilia. On the contrary, transient (low level and time-restricted) activation of FGF signaling accelerated IFT20-GFP movement, resulting in extending of the primary cilia.
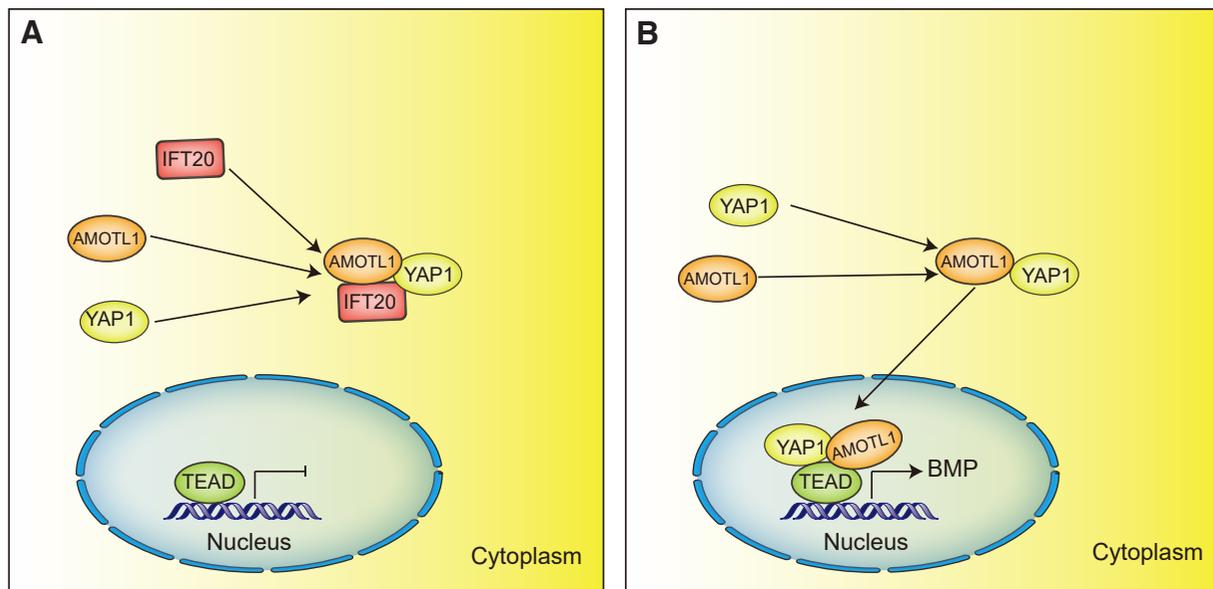
Fig. 7. IFT20 modulation of Hippo signaling. (A) IFT20, YAP1 and AMOTL1 interact in the cytoplasm to form regulatory complexes that limit nuclear YAP1-TEAD activity, which controls the size of the proepicardium; **(B)** In *Ift20* knockout mice, YAP1 and AMOTL1 interact with each other in the cytoplasm and transfer to the nucleus, activating BMP signaling and resulting in increased proepicardium size.

et al., 2018). In addition, the fact that activating FGFR3 mutations decreased both IFT20 speed and primary cilia length suggests that IFT20 plays a vital role in the pathologies of achondroplasia and thanatophoric dysplasia.

Hippo signaling

The Hippo pathway responds to various upstream stimuli, including biochemical and biomechanical cues; it is an important sensor of cells' physical environment and integrator of growth control signals. The Hippo pathway has multiple components. The most widely studied are mammalian transcriptional co-activator with a PDZ binding domain (TAZ), and yes-associated protein (YAP), which act as key downstream effectors of the Hippo pathway (Mia *et al.*, 2020). YAP and TAZ are transcriptional coactivators that lack DNA-binding domains and perform their effects through cognate transcription factors (Zhao *et al.*, 2008).

The Hippo kinase cascade is the main regulator of the activities of YAP and TAZ. This cascade inhibits the nuclear activity of the transcriptional coactivators by phosphorylation and thus inhibits the transcription mediated by the associated transcription factors (Zhao *et al.*, 2010). YAP and TAZ therefore serve as integrators of many important signaling pathways, such as Notch signaling, G-protein-coupled receptor signaling, transforming growth factor-β and Bone Morphogenetic Protein (BMP) signaling, and WNT signaling, and they play key roles in controlling cell fate and tissue regeneration (Piccolo *et al.*, 2014).

IFT20 regulates the Hippo effector YAP1 independently of its function in cilia signaling to restrict proepicardial and myocardial development in zebrafish and mice. IFT20, YAP1 and the protein angiomotin-like 1 (AMOTL1) form a cytoplasmic regulatory complex that limits the activity of nuclear YAP1 and its associated transcription factor TEA domain family member 1, which restricts the size of the proepicardium and myocardial development by modulating

BMP signaling activity (Fig. 7A). In *Ift20* knockout zebrafish and mice, YAP1 and AMOTL1 freely interact in the cytoplasm and translocate to the nucleus, where they activate BMP signaling (Fig. 7B). This uncontrolled signaling results in an increased size of the proepicardium. In contrast, overexpression of *Ift20* results in decreased nuclear YAP1 activity and restriction of the size of the proepicardium (Peralta *et al.*, 2020). In addition, IFT20 also mediates YAP cilia-dependent signaling during zebrafish kidney development. Joubert syndrome protein ADP ribosylation factor–like GTPase 13B (ARL13B) and IFT88 are both required for ciliogenesis (Seixas *et al.*, 2016; Singh *et al.*, 2020). Genetic analyses indicate that *Ift20*, *Ift88* and the gene encoding *Arl13b* genetically interact with *Yap* in pronephric cyst formation, knocking down *Yap* in zebrafish embryos combined with either knockdown of *Ift20*, *Ift88* or *Arl13b*, resulting in significant increases in the percentage of pronephric cysts (He *et al.*, 2015). These observations suggest that IFT20 can mediate cilia-dependent and cilia-independent Hippo signaling pathways in different cells and tissues.

T cell antigen receptor signaling

T cell antigen receptor (TCR) signaling plays a central role in the development, homeostasis, activation, and reactivation of T cells, as well as in the regulation of immune tolerance and immunity (Huang and August, 2015). TCR signaling is activated when TCR binds to peptides presented by major histocompatibility complex (MHC) class I or class II associated with antigen presenting cells. Upon activation, the SRC family protein tyrosine kinase LCK is recruited to the TCR/CD3 complex, where LCK phosphorylates immunoreceptor tyrosine-based activation motifs (ITAMs) in the cytoplasmic region of the TCR / CD3 complex. This phosphorylation results in the recruitment and activation of zeta chain of TCR-associated protein kinase 70 (ZAP70) (Wardenburg *et al.*, 1996), which phosphorylates linker for activation of T cells (LAT). The phosphorylation of LAT triggers
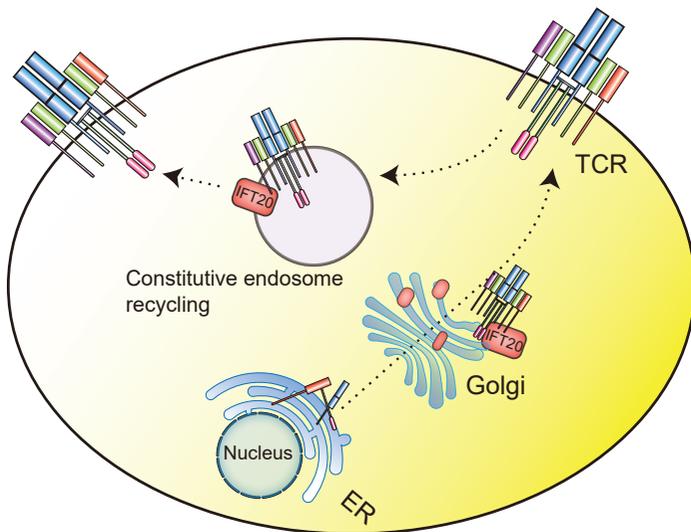
Fig. 8. ITF20 modulation constitutive endosome recycling. The TCR/CD3 complex is assembled in the ER and completed in the Golgi apparatus. Subsequently, IFT20 regulates the recycling of TCR/CD3 complexes via exocytosis to the surface through the constitutive recycling pathway in resting cells.

a series of signaling cascades, mainly involving calmodulin, MAPK and nuclear factor-κβ signaling pathways (Huang and August, 2015).

The immune synapse is a specialized structure formed at the site of contact between an antigen presenting cells and a T cell, and it plays an important role in signaling integration, fine-tuning and termination (Čemerski and Shaw, 2006). One indicator of the formation of the immune synapse is targeting of the TCR/CD3 complex to the locus of interaction between the antigen presenting cells and the T cell. This targeting occurs through a combination of lateral diffusion, cytoskeleton-driven movement and polarized

endosome recycling (Čemerski and Shaw, 2006; Das *et al.*, 2004). The assembly of the TCR/CD3 complex begins in the ER and is completed in the Golgi apparatus; subsequently, IFT20 regulates the exocytosis of the TCR/CD3 complex to the cell surface through a constitutive recycling pathway in resting cells (Fig. 8) (Finetti *et al.*, 2009).

When the TCR binds to an MHC-bound peptide on the surface of an antigen presenting cell, IFT20 induces IFT88 and IFT57 to bind to the TCR/CD3 complex. This complex formation promotes TCR clustering at immune synapses through polarized endosome recycling, which is required to recruit the tyrosine kinase ZAP70 to activate the TCR signaling (Fig. 8) (Finetti *et al.*, 2009). Accordingly, *IFT20* knockdown in Jurkat T-cells resulted in an impairment of both TCR polarized recycling and constitutive recycling that prevented the TCR/CD3 complex from clustering at the immune synapse and the localization of the TCR/CD3 complex on cell surface, respectively (Finetti *et al.*, 2009; Finetti *et al.*, 2014). Moreover, in IFT20-dependent pathway of TCR recycling, IFT20 cooperates with RAB GTPase network proteins RAB5, RAB8, RAB11 and RAB29 to form complexes in Jurkat T cells to control polarized TCR recycling to immune synapses (Finetti *et al.*, 2014; Finetti *et al.*, 2015; Onnis *et al.*, 2015). IFT20 and RAB5 interact on early endosomes (Finetti *et al.*, 2014), and RAB8 regulates the final step of the TCR recycling (Fig. 8) (Finetti *et al.*, 2015).

The recycling pathway responsible for the transport of endosomal TCR to the immune synapse was studied via detailed investigation of five newly discovered binding partners of IFT20. These proteins included IFT54, GMAP-210, actin-related protein2/3 complex subunit-3 (ARPC3), constitutive photomorphogenesis 9 signalosome subunit-1 (CSN1; also known as G protein pathway suppressor 1 (GPS1)) and ER-Golgi intermediate compartment 53 kDa protein (ERGIC53; also known as lectin mannose-binding 1 (LMAN1)). Three of these proteins were found to be involved in the trafficking of the TCR to the immune synapse. Specifically, the
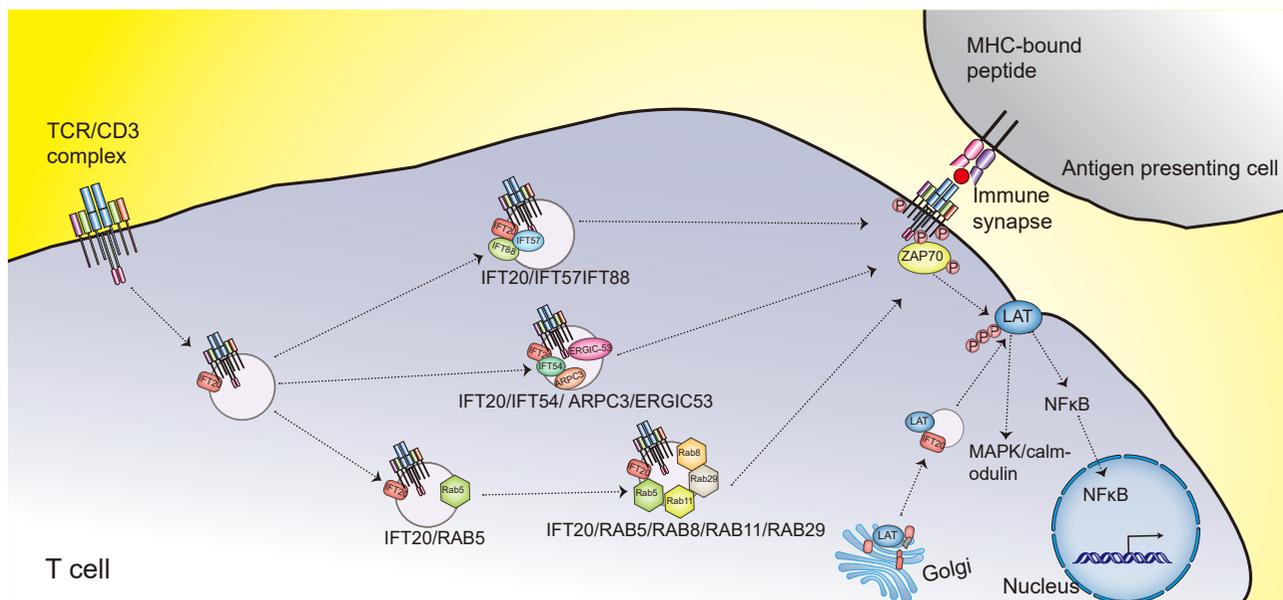
Fig. 9. IFT20 modulation of TCR signaling. When TCR binds to antigen presenting cells through an MHC-bound peptide on the surface, IFT20 promotes TCR clustering at immune synapses through recycling of polarized endosomes. In addition, IFT20 drives LAT vesicle transport and regulates the TCR signaling pathway by controlling the phosphorylation of LAT and ZAP70 and their recruitment at the immune synapse. The phosphorylation of LAT triggers a series of signaling cascades.

research found that IFT20 cooperates with IFT54, ARPC3, and ER-GIC53 to regulate polarized TCR and transferrin receptor recycling to the immune synapse (Fig. 8), while GMAP-210 and CSN1 were found to be independent of this process. Confocal microscopic analysis further showed that IFT54 and ERGIC53 could promote the accumulation of phosphorylated ZAP70 at the immune synapse, while ARPC3 had no effect on the accumulation, indicating that ARPC3 was involved in T cell activation downstream of TCR-proximal signal transduction (Galgano *et al.*, 2017). In *IFT20* knockout Jurkat T-cells, the basal level of ZAP70 and LAT phosphorylation decreased, and both tonic TCR signaling and mTOR activity were deficient, resulting in disordered autophagic clearance and accumulation of lipid droplets due to defects in the biogenesis and functioning of lysosomes (Finetti *et al.*, 2020).

In order to further clarify the effect of IFT20 on CD4+ T cells *in vitro* and *in vivo*, a mouse model with conditionally defective expression of IFT20 on T cells was established. Studies of model mice and of primary cells extracted from these mice showed that IFT20 regulates TCR signaling by controlling the phosphorylation and recruitment of ZAP70 and LAT at the immune synapse, suggesting that IFT20 is involved in the trafficking of vesicular LAT. Confocal imaging also showed that IFT20 and LAT vesicle pool colocalization in Jurkat T-cells (Fig. 8). In the absence of IFT20, recruitment of LAT at the activation sites of TCR was impaired, resulting in deficiencies of CD4+ T cell activation and proliferation. These cells cannot produce effective antigen-specific T cell responses, or induce colitis in the model of T-cell-adoptive transfer (Vivar *et al.*, 2016).

Receptor tyrosine kinase-like orphan receptors 2(ROR2) signaling

ROR2 is a member of the receptor tyrosine kinase (RTK) superfamily. Activation of ROR2 by WNT3A and WNT5A activates canonical WNT/β-catenin and non-canonical β-catenin-independent signaling pathways, respectively. This signaling plays vital roles in polarized cell migration, invasion, and tumor growth (Menck *et al.*, 2021). ROR2 is most typically involved in the activation of non-canonical WNT pathways by WNT5A in various contexts, and this pathway tends to regulate polarity and polarized cell movement of planar cells. WNT5A/ROR2 signaling has been shown to inhibit canonical WNT/β-catenin pathways at the TCF/LEF-mediated transcriptional level (Mikels and Nusse, 2006). The expression of ROR2 is upregulated in many tumors, such as osteosarcomas, renal cell carcinomas, melanomas, and breast cancers (Nishita *et al.*, 2017; Menck *et al.*, 2021).

Invasive tumor cells form actin-rich dynamic adhesive structures, called invadopodia, that can degrade the extracellular matrix (Cortesio *et al.*, 2008). The activity of these invadopodia is supported by constitutive activation of WNT5A/ROR2 signaling in osteosarcoma cell lines, as it induces matrix metalloproteinase 13 (MMP-13) expression in a cell-autonomous manner. MMP-13 secreted into the extracellular environment, where it has crucial roles in both invadopodia formation and extracellular matrix degradation (Enomoto *et al.*, 2009; Yamagata *et al.*, 2012). MMPs are targeted for transport to the invadopodia on the surfaces of tumor cells, which is the key site of attachment and degradation of the extracellular matrix. The invadopodia concentrate and target MMPs to specific sites of the extracellular matrix to promote tumor invasion (Kumar *et al.*, 2018). Thus, the polarized secretion of intracellular proteins to the cell surface is necessary for tumors to achieve invasion and migration. The Golgi plays a central role in this polarized secretion, which requires Golgi to use a ribbon-like structure (Fig. 10A) (Nishita *et al.*, 2017; Hurtado *et al.*, 2011).

In ciliated cells, IFT20 located in the Golgi apparatus only associates with the transport of cargoes from to the cilia (Follit *et al.*, 2006), but some tumor cells lose cilia during transformation. In these non-ciliated tumor cells, IFT20 acquires new functions in the regulation of Golgi structure and transport. In particular, IFT20 promotes invasiveness of human osteosarcoma cells through
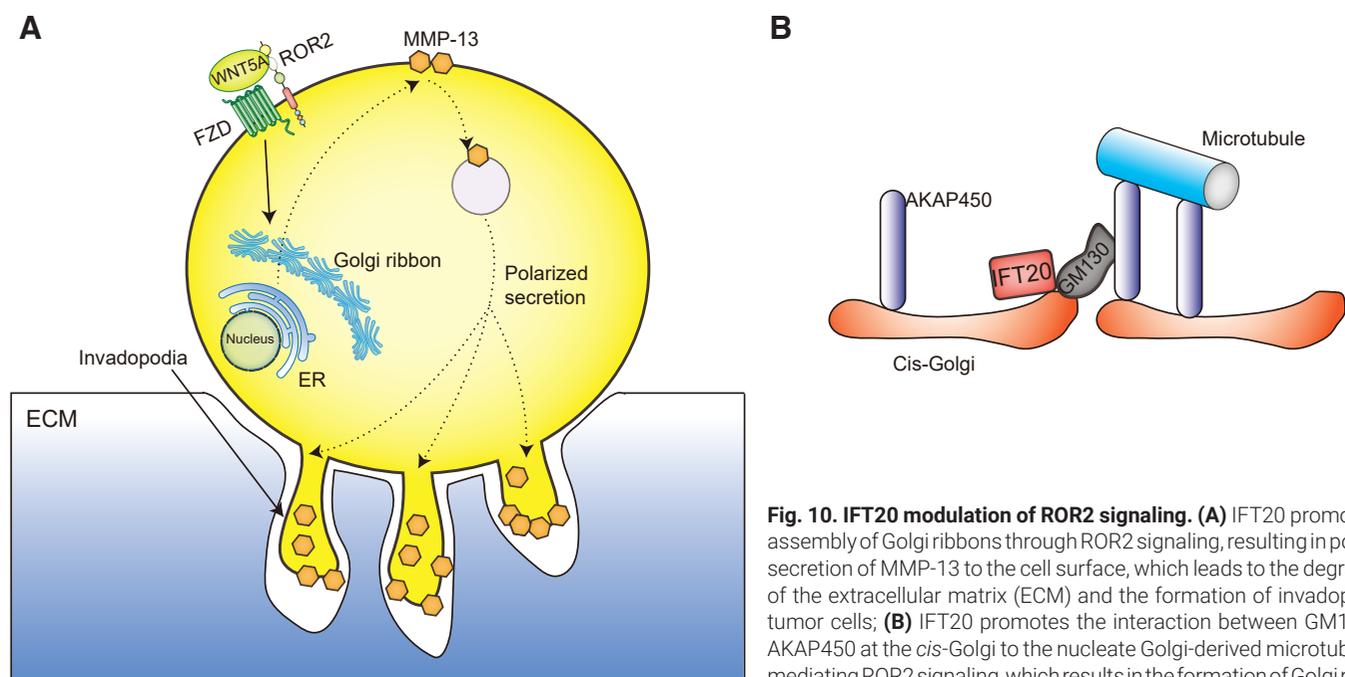
Fig. 10. IFT20 modulation of ROR2 signaling. (A) IFT20 promotes the assembly of Golgi ribbons through ROR2 signaling, resulting in polarized secretion of MMP-13 to the cell surface, which leads to the degradation of the extracellular matrix (ECM) and the formation of invadopodia in tumor cells; **(B)** IFT20 promotes the interaction between GM130 and AKAP450 at the *cis*-Golgi to the nucleate Golgi-derived microtubules by mediating ROR2 signaling, which results in the formation of Golgi ribbons.

constitutive activation ROR2 signaling. Further studies showed that the regulation of Golgi structure by IFT20-mediated ROR2 signaling is achieved by influencing the assembly of Golgi ribbon rather than the stacking of Golgi cisternae. In addition, through its mediation of ROR2 signaling, IFT20 also promotes the interactions between Golgi matrix protein 130 (GM130) and A kinase anchoring protein 450 (AKAP450) at the *cis*-Golgi that nucleate Golgi-derived microtubules (Fig. 10B). The formation of these microtubules results in the formation of the Golgi ribbon structure, thus achieving the polarized secretion necessary for cell migration and invasion (Nishita *et al.*, 2017). In colorectal cancer cells, IFT20 plays a vital role in collective invasion by regulating the organization of the direction of growth of Golgi-associated microtubules and polarization of the Golgi apparatus in leader cells. However, this function is independent of the status of expression and function of ROR2. Thus, the role of ROR2 signaling in the impact of IFT20 on invasion may be cancer cell line-dependent (Aoki *et al.*, 2019).

Conclusions and Perspectives

As a signal integrator, primary cilia can mediate and integrate various signal pathways to maintain cell development and tissue homeostasis. IFT20, as the only IFT-B complex protein localized to Golgi apparatus except cilia and centrosome, plays a primary cilia-dependent and primary cilia-independent role in signal transduction. Due to the functional specificity of IFT20, we summarized the mechanisms of IFT20 coordinates multiple signaling pathways in cell development and tissue homeostasis, discussed the cross-integration function of various signaling pathways mediated by IFT20, and illustrated the cell, tissue and organ specificity of IFT20 in signal transduction.

IFT20 mutations show a variety of phenotypic characteristics. Although great progress has been made in the study of IFT20-mediated signaling pathways in the manifestation of these phenotypic characteristics, many problems remain to be solved. The questions for continued study include the complete elucidation of the ways that IFT20 mediated signaling pathways in cell development and tissue homeostasis, identification of mechanisms of integration of multiple cilia signaling pathways, the crosstalk between different signaling pathways, and justification of cell, tissue and organ specificity in these pathways. Thus, further research regarding IFT20 is needed.

Compliance with ethics guidelines
This manuscript is a review article and does not involve a research protocol requiring approval by the relevant institutional review board or ethics committee.

Abbreviations used in this paper
AKAP450, A kinase anchoring protein 450; APC, adenomatous polyposis coli; AMOTL1, angiomotin-like 1; ARL13B, ADP ribosylation factor−like GTPase 13B; ARPC3, actin-related protein2/3 complex subunit-3; BMP, Bone Morphogenetic Protein CK1α casein kinase 1α; CBL, Casitas B-lineage lymphoma; CSN1, constitutive photomorphogenesis 9 signalosome subunit-1; DVL, disheveled; DHH, desert hedgehog; DAG, diacylglycerol; ERK, extracellular signal-regulated kinases; ERGIC53, ER-Golgi intermediate compartment 53 kDa protein; ER, endoplasmic reticulum; FGF, fibroblast growth factor; FGFR, fibroblast growth factor receptor; FRS2a, FGFR substrate 2a; GMAP-210, Golgi microtubule-associated protein 210; GLI/CI, glioblastoma/cubitus interruptus; GLI-F, full-length GLI; GAP, GTPase activating protein; GRB, growth factor receptor-bound protein; GM130, Golgi matrix protein 130; GSK-3β, glycogen synthase kinase 3β; HH, hedgehog homologous; HSPGs, heparan sulfate proteoglycans; IHH, Indian hedgehog; ITAMs, immunoreceptor tyrosine-based activation motifs; IP3, inositol 1,4,5-trisphosphate; IFT, Intraflagellar transport; JNK, C-Jun N-terminal kinase; LAT, linker for activation of T cells; LRP5/6, lipoprotein-related receptor proteins 5 and 6 MT microtubule; MAPKs, mitogen-activated protein kinases; MHC, major histocompatibility complex; MMP, matrix metalloproteinase; Ofd1, Orofacial digital type I syndrome; PTCH, patched; PLCγ, phosphorylate phospholipase Cγ; PDGF, Platelet-derived growth factor; PI3K, phosphatidylinositol 3-kinase; PKB/AKT, protein kinase B; PCP, planar cell polarity; PLC, phospholipase C; PKC, protein kinase C; β-TRCP, β-transducin-repeat-containing protein; RTK, receptor tyrosine kinase; ROR2, receptor tyrosine kinase-like orphan receptors 2; SH2, Src homology 2; SHH, sonic hedgehog; SMO, smoothened; SUFU, suppressor of fused; SAG, SMO agonist; TCR T, cell antigen receptor; TCF T, cell factor; TAZ, transcriptional co-activator with PDZ-binding motif; YAP, yes-associated protein; ZAP70, zeta chain of TCR-associated protein kinase 70.

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