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Asma Boukhalfa, Caterina Miceli, Yenniffer Ávalos, Etienne Morel, Nicolas Dupont

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1 **Interplay between Primary cilia, Ubiquitin-Proteasome system and Autophagy**

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4 Asma Boukhalfa<sup>1,2\*</sup>, Caterina Miceli<sup>1,2\*</sup>, Yenniffer Ávalos<sup>3,4</sup>, Etienne Morel<sup>1,2#</sup>, Nicolas

5 Dupont<sup>1,2#</sup>

6

7 <sup>1</sup>Institut Necker-Enfants Malades (INEM), INSERM U1151-CNRS UMR 8253, <sup>2</sup>Université Paris

8 Descartes-Sorbonne Paris Cité, F-75993, Paris, France.

9 <sup>3</sup>Departamento de Fisiología, Facultad Ciencias Biológicas, Pontificia Universidad Católica de  
10 Chile, 7820436 Santiago, Chile.

11 <sup>4</sup>Departamento de Biología, Facultad de Química y Biología, Universidad de Santiago de Chile,  
12 8350709 Santiago, Chile.

13

14 \* These authors contribute equally to this work

15

16 # Corresponding Author:

17 Nicolas Dupont, [nicolas.dupont@inserm.fr](mailto:nicolas.dupont@inserm.fr)

18 Etienne Morel, [etienne.morel@inserm.fr](mailto:etienne.morel@inserm.fr)

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28 **Abstract**

29 Cilia are microtubule-based organelles located at the cell surface of many eukaryotic cell types.  
30 Cilia control different cellular functions ranging from motility (for motile cilia) to signal  
31 transduction pathways (for primary cilia). A variety of signaling pathways are coordinated by  
32 this organelle during development, cell migration and cell differentiation. Interestingly, aberrant  
33 ciliogenesis or altered cilium signaling has been associated with human diseases, notably in  
34 cancer. Disruption of cilia through mutation of genes encoding cilia proteins has been also linked  
35 to multiple human disorders referred as ciliopathies. Recent studies highlight the interplay  
36 between cilia and proteostasis. Here we review findings regarding the crosstalk between cilia and  
37 two proteolytic systems, the ubiquitin proteasome system and the autophagy-lysosomal system  
38 and discuss the potential implications in human disease including ciliopathies.

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## 42 **1. Cilia: from structure to function**

43

44 Cilia are tiny cellular membrane protrusions that emanate from the surface of different cell types.  
45 The cilia are composed of a microtubule-based core structure (the axoneme) which nucleates  
46 from a basal body (BB) that is derived from one centriole of the centrosome (the older one for  
47 primary cilia) [1,2]. The axoneme is separated from the rest of the intracellular compartments by  
48 the transition zone (TZ) which is a ciliary subdomain highly organized with a molecular structure  
49 resembling that of the nuclear pore. It functions as a ciliary gate that strictly controls the  
50 molecular composition of the ciliary compartment. Conventionally, cilia are classified as motile  
51 and non-motile according to their microtubule pattern and associated motility in the organism.  
52 Motile cilium (MC) is formed by an axoneme of 9 outer microtubule doublets and 2 single  
53 central microtubules whereas the primary cilium (PC), a solitary non-motile cilium, lacks the 2  
54 single central microtubules and dynein (molecular motors) arms, needed for motility. Cilia are  
55 very dynamic organelles since cilia formation and disassembly occur in synchrony with the cell  
56 cycle. Ciliogenesis takes place in quiescent cells when cell enter the G0 phase whereas cilia are  
57 disassembled as cell progress towards S phase. Due to the fact that no protein synthesis occurs in  
58 cilia, cilia growth is maintained by specific bidirectional trafficking system, coordinated by the  
59 IFT proteins (Intraflagellar Transport). More specifically, two well conserved IFT protein  
60 machineries are known to traffic along the polarized microtubules of the axoneme, through the  
61 action of two motor protein families (kinesins and dyneins) termed IFT-A (Retrograde) and IFT-  
62 B (Anterograde) with tip-to-base and base-to-tip cargo direction, respectively. Maintenance of  
63 the cilia also depends on the Bardet–Biedl syndrome (BBSome) proteins complex (consisting of  
64 eight BBS proteins) which recognize ciliary targeting sequence on specific proteins (for example  
65 RVxP (where x is any amino acid) in the N- terminus of polycystin-2 ciliary protein) that need to  
66 be targeted to the cilium. Readers can refer to excellent reviews for more detailed information on  
67 the regulation of the dynamic process of the cilia formation and disassembly [3].

68

69

70 MC is a beating organelle which generates fluid flow on the surface of epithelial cells lining the  
71 airways and the reproductive tract as well as of the ependyma. Motility of the MC in these  
72 epithelial cells is essential for mucociliary clearance and ependymal flow. PC is a sensory non-  
73 motile organelle that clusters receptors and signaling molecules and thus PC is recognized as  
74 signaling hubs. The ciliary membrane is enriched in signaling receptors such as components of  
75 the Hedgehog (Hh) pathway [4], Wnt signaling pathway [5], PDGF alpha receptors and calcium

76 channels among others [6]. The unique localization of the PC allows the activation of these  
77 pathways in response to extracellular changes. PC is therefore an organelle critical for vertebrate  
78 development, tissue homeostasis, cell migration and differentiation, cell cycle and apoptosis. The  
79 importance of cilia in pathophysiology is highlighted by the presence of a group of diseases  
80 known as ciliopathies (human disorders associated to abnormalities of cilia structure or/and  
81 function). Ciliopathies can affect many organs (including brain, eyes, liver, kidney, skeleton and  
82 limbs) with phenotypically variable and overlapping disease manifestations. Despite the fact that  
83 more than 50 genes have been linked to ciliopathies, much less is known about the specific  
84 molecular mechanisms which could explain the phenotypic characterization of this broad range  
85 of disorders. These genes encode for proteins mainly localized at the axoneme or at the transition  
86 zone. For example, polycystic kidney disease (PKD), such as autosomal dominant polycystic  
87 kidney disease (ADPKD), results from mutations in genes (*PKD1* and *PKD2*) encoding ciliary  
88 associated mechanosensitive calcium channels (polycystins proteins). We can cite also the  
89 Meckel-Gruber syndrome (MKS) or Bardet-Biedl syndrome (BBS) which are characterized by  
90 mutations affecting genes (at least 13 genes for MKS: *B9D1*, *B9D2*, *CC2D2A*, *CEP290*, *MKS1*,  
91 *RPGRIP1L*, *TCTN2*, *TCTN3*, *TMEM67*, *TMEM107*, *TMEM216*, *TMEM231*, *TMEM237* genes  
92 and more than 20 for BBS: *BBS1*, *BBS2*, *ARL6 (BBS3)*, *BBS4*, *BBS5*, *MKKS (BBS6)*, *BBS7*,  
93 *TTC8 (BBS8)*, *BBS9*, *BBS10*, *TRIM32 (BBS11)*, *BBS12*, *MKS1 (BBS13)*, *CEP290 (BBS14)*,  
94 *WDPCP (BBS15)*, *SDCCAG8 (BBS16)*, *LZTFL1 (BBS17)*, *BBIP1 (BBS18)*, *IFT27 (BBS19)*,  
95 *IFT72 (BBS20)*, and *C8ORF37(BBS21)*) coding for proteins associated with the transition zone  
96 or with the BBSome. Finally, cilium is not only associated to monogenic inherited disorders but  
97 also to many complex human diseases such as chronic obstructive pulmonary disease (COPD) or  
98 cancer. Significant cilia shortening is observed in COPD patients which leads to an impairment  
99 of mucociliary clearance interfering with the protection of airways from infection. The relation  
100 between cilia and cancer seems to be more complex. Indeed, oncogenic signaling pathways (such  
101 as Hh pathway) have been shown to be mediated by PC whereas cilia are also known to be lost in  
102 some types of cancer.

103

## 104 **2. Ubiquitin-Proteasome System (UPS)**

105

106 Two main intracellular protein degradation systems exist in vertebrates, the Ubiquitin-  
107 Proteasome System (UPS) and the autophagic-lysosomal pathway. Along with machineries  
108 involved in protein biogenesis, folding and trafficking, these two proteolytic systems play an  
109 important role in proteostasis [7,8]. Proteostasis is a crucial cellular homeostatic process that

110 allows cells to regulate protein general abundance according to functional need but also to  
111 recognize and remove damaged protein. Thus, proteostasis imbalance leads to the accumulation  
112 of misfolded proteins or excessive protein degradation and is associated, directly or indirectly,  
113 with many human diseases such as Alzheimer, Parkinson and Prion diseases.

114

115 The UPS starts with the ubiquitylation of target proteins. Ubiquitin is a small (8 kDa) and highly  
116 conserved protein and expressed in all eukaryotic cells. The C-terminal glycine of this protein  
117 can be covalently attached to lysine residues of substrate proteins, which is the process by which  
118 target proteins are tagged for degradation. This post-translational modification involves the  
119 hierarchical action of three general families of ubiquitin enzymes. An E1 (Ub-activating) enzyme  
120 must first activate ubiquitin (Ub). Then, the activated Ub is transferred to E2 (Ub-conjugating)  
121 and E3 (Ub Ligase) enzyme which transfer it to the target protein. The E3 Ub ligase dictates  
122 substrate specificity. Conversely, ubiquitin tags can be removed from protein substrates by  
123 deubiquitinases (DUBs). The human genome encodes two E1s, more than 30 E2 enzymes,  
124 nearly 600 E3s and 100 DUBs. There are several types of ubiquitination: fixation of one Ub  
125 protein on one lysine residue of the protein substrate (monoubiquitylation, monoUb), fixation of  
126 one Ub on several lysines of the same substrate (multi-monoubiquitylation, multimonoUb) and  
127 fixation of multiple Ub chains (polyubiquitylation, polyUb) on the same lysine residue [9,10].  
128 Since ubiquitin itself contains seven lysines residues (K6, K11, K27, K29, K33, K48 and K63)  
129 that can be targeted in recurrent rounds of enzymatic cascade, a great variety of distinct  
130 polyubiquitylations can be generated. These different types of ubiquitination are associated with  
131 distinct cellular mechanisms including endosomal pathway (for MultimonoUb or polyUb K63),  
132 post-Golgi trafficking (for polyUb K33), NF- $\kappa$ B signaling (for polyUb K63), proteasomal  
133 degradation (for polyUb K48, K11 and K29) and autophagic degradation (see dedicated section  
134 for details on autophagic pathway). For example, K48-linked polyubiquitins have been shown to  
135 be mainly destined for proteasomal degradation whereas nondegrading K63-linked polyubiquitin  
136 or mono and multi-monoubiquitylation are mostly associated with endo-lysosomal trafficking  
137 and signal transduction regulation. To achieve its cellular function, the Ub tag added on a  
138 substrate needs to be properly decoded by the eukaryotic cells. This step is completed through  
139 ubiquitin receptors which possess one or more Ub-binding domains (UBDs)[11]. For example,  
140 Rpn10 (Proteasome Regulatory Subunit 10), which belongs to the 19S regulatory subunits of the  
141 proteasome, is known to possess ubiquitin-binding domains and function as receptor for  
142 ubiquitinated substrates destined for proteasomal degradation. Once target proteins are  
143 recognized, proteins are then degraded thanks to the macromolecular protease activity of the 26S

144 proteasome, a large multi-protein complex of about 1700 kDa which consists of a 20S catalytic  
145 subunit (also called core particle, CP), flanked by two 19S regulatory subunits (also called  
146 regulatory particle, RP)[12]. It is important to notice that proteasome is not only required for  
147 degradation of cytosolic protein but also membrane bound proteins. For example, newly  
148 synthesized misfolded membrane proteins are known to be recognized by specific UPS system  
149 called ERAD (for ER-associated degradation)[13]. These proteins are ubiquitinated,  
150 retrotranslocated/dislocated from ER and degraded by the proteasome. Since UPS is a  
151 fundamental cellular process involved in proteostasis, the regulation of its dedicated molecular  
152 machinery and activity are tightly controlled. First, different factors induce the expression of  
153 genes encoding enzymes (involved in different steps of ubiquitylation) or structural proteasomal  
154 components. Second, another layer of regulation is added by different kinds of posttranslational  
155 modifications (such as ubiquitination, phosphorylation) of proteasomal subunits regulating the  
156 assembly, the degradative capacity but also the localization of 26S proteasomes. Finally,  
157 proteasomal activity has been shown to be compromised in age related-human diseases. For  
158 example, this defect leads to an accumulation of aberrant proteins such as the tau protein in  
159 tauopathy. Here, after reviewing the interplay between cilia and UPS, we will discuss the  
160 potential implications of this relationship in ciliopathies.

161

162

### 163 **3.Crosstalk between Cilia and UPS**

164

165 The first piece of evidence showing the interplay between cilia and UPS came from proteomic  
166 analysis of cilia (figure 1) [14] [15]. In these studies, authors have identified several UPS  
167 proteins associated with cilia proteome. Among them, E1 activating enzymes (including UBA1,  
168 UBA6), Ub E3 ligase (such as MYCBP2 and NEDD4L) and chaperones involved in Ub  
169 signaling quality control (such as VCP (also known as p97)). Interestingly, functional analyses  
170 through genome-wide RNAi screens have also been performed and lead to propose that UPS-  
171 mediated protein degradation is crucial for regulating cilia formation and disassembly [16,17].  
172 Thus, these studies have identified several UPS components as positive or negative regulators of  
173 ciliogenesis. Most of them were validated by complementary and dedicated studies [18–20]. For  
174 example, UBR5, an E3 ubiquitin ligase frequently misregulated in tumors, is known to  
175 ubiquitylate a centrosomal protein called CSPP1 (Centrosome And Spindle Pole Associated  
176 Protein 1) required for cilia formation [21]. Others E3 ligase such as SCF (Skp1-Cul1-F box  
177 protein), FBW7, Mib1 (Mindbomb1), KCTD17 and KCTD10 were all also identified to regulate

178 the stability of different centrosomal proteins (CP110, NDE1, Talpid3, Trichoplein, CEP97  
179 respectively) which is crucial for ciliary axoneme extension [22–24][25]. Others UPS  
180 components including DUBs were also identified as a positive regulator of ciliogenesis. The  
181 deubiquitylation of Cep70 by the tumor suppressor CYLD (cylindromatosis) favors the cilia  
182 assembly [26]. It is important to highlight that UPS consequences on ciliogenesis is not restricted  
183 to primary cilia since the DUB activity of CYLD has been shown to contribute to the assembly of  
184 both primary and motile cilia in multiple organs [26]. Others ubiquitin-like proteins such as E2  
185 SUMO-conjugating enzyme called UBE2I/UBC-9 have also been shown to be a regulator of  
186 ciliogenesis in mammalian cells [16]. UBE1/UBC9 sumoylates a small GTPase ARL-13 and this  
187 sumoylation is required for the ciliary entry of polycystin-2, the protein mutated in autosomal  
188 dominant polycystic kidney disease [27]. Others studies are needed to better investigate the  
189 interplay between ubiquitin-like proteins and cilia. One should also better clarify whether cilia  
190 homeostasis is also interconnected with other aspects of proteostasis including UPR (Unfolded  
191 Protein Response) and proteasome-dependent ERAD (ER-associated degradation system)  
192 pathways. During ERAD, as mentioned before, misfolded proteins are recognized and  
193 ubiquitinated at ER surface and subsequently retro-translocated/dislocated from ER to the 26S  
194 proteasome in the cytosol for proteolytic elimination. Interestingly, polycystin-2 (PC2), a ciliary  
195 calcium channel which is mutated in autosomal dominant polycystic kidney disease (ADPKD)  
196 has been shown to be degraded by ERAD [28] thus highlighting that UPS not only regulate  
197 ciliogenesis but also primary cilia dependent-signal transduction pathways.

198 The interplay between UPS and cilia homeostasis is not restricted to the effect of UPS on  
199 ciliogenesis: this relationship being indeed bilateral (figure 1). Different ciliary proteins  
200 (including BBS4, OFD1 and RPGRIP1L) have been shown to directly interact with different  
201 proteasomal components (such as RPT6 from the 19S subunit) leading to a reduction of  
202 proteasomal activity [29,30]. The presence of specific cilia-(or centrosomal)-associated  
203 proteasomal activity regulated by ciliary proteins was even suggested [31,32]. However, it is still  
204 unclear whether cilia are able to relocalize the proteasome complex itself at basal body since a  
205 subpopulation of proteasomes, with different subunits composition, possibly exists at the ciliary  
206 base. Finally and more interestingly, reduction of UPS activity has been observed in mouse  
207 models of ciliopathies. For example, Gerhardt and co-authors have highlighted a specific  
208 disruption of proteasomal activity in mouse embryos invalidated for the gene *Rpgrip1l* encoding  
209 the RPGRIP1L proteins which is mutated in different ciliopathies including the Joubert  
210 Syndrome [33]. The most intriguing question that remains to be answered is to what extent this  
211 UPS deregulation corresponds to the effect of ciliary protein on UPS. Knowing the fact that this



212 proteasomal activity disruption seems to occur specifically and exclusively at the ciliary base  
213 [33], targeting proteasome appears to be an attractive therapeutic strategy to cure human ciliary  
214 disorders.

215

### 216 **3. Autophagy pathway**

217

218 Autophagy is a lysosomal degradation and recycling pathway that controls the quality and  
219 quantity of cytoplasmic material [34,35]. Autophagy mobilizes nutrient stores such as glycogen,  
220 lipid droplets, proteins and organelles and provide nutrients, essential amino acids, fatty acids,  
221 glucose allowing cell survival during starvation. It is now widely accepted that autophagy plays  
222 crucial roles in cellular and tissue homeostasis as well as metabolism, development, and, through  
223 pathogen clearance, immunity. Dysfunctional autophagy, defective or excessive, has been  
224 associated to human pathologies ranging from neurodegenerative diseases to cancer and  
225 infectious diseases. Growing list of mutations in genes encoding the autophagy-related  
226 proteins (ATG) was also identified in various human diseases. In translational terms, autophagy  
227 is now recognized as an attractive target for the development of new treatments for human  
228 diseases. To this date, three major types of autophagy have been described in mammals:  
229 chaperone-mediated autophagy, microautophagy and macroautophagy. During chaperone-  
230 mediated autophagy, a subset of cytosolic proteins with KFERQ motifs are recognized by the  
231 Hsc70 chaperone and degraded selectively in lysosome. In the case of microautophagy, the  
232 cytoplasmic content is directly engulfed by the lysosome by the invagination of the lysosomal  
233 membrane itself. The process of macroautophagy (hereafter referred simply to as “autophagy”)  
234 requires the formation of a double-membrane vacuole called the autophagosome that sequesters  
235 proteins and other cytoplasmic components to be delivered into the lysosome (figure 2).  
236 Autophagosome biogenesis is mostly orchestrated by autophagy-related proteins (ATGs) and  
237 initiated by a complex that is composed of the kinase ULK1/2 and ATG13, FIP200, and  
238 ATG101. The activity of this complex is under the control of the mTOR complex 1 (MTORC1),  
239 which integrates a variety of signals such as amino acids, glucose, and growth factors. The  
240 subsequent step of autophagosome formation relies on VPS34/PIK3C3, a class III  
241 phosphatidylinositol kinase responsible for phosphatidylinositol-3-phosphate (PI3P) synthesis,  
242 which forms a complex with ATG14L, Beclin1, VPS15, and then with the subsequent, and PI3P-  
243 dependent, ATG12—ATG5-ATG16L1 complex. This complex allows the lipidation of LC3-I  
244 (ATG8) to form LC3-II which favors maturation of the autophagosome. Finally, fully formed  
245 autophagosome will fuse with a lysosome (autolysosome step) to allow the proper breakdown

246 and recycling of the engulfed cargoes by specific lysosomal enzymes. Several trafficking  
247 regulators, including Rab small GTPases, SNAREs, and VPS proteins have been shown to be  
248 crucial for the last stage of autophagosome maturation for fusion with lysosome. (figure 2).

249  
250

251 Autophagy takes place at basal levels in all eukaryotic cells. However, autophagy is mostly a  
252 stress-response catabolic process that is induced by many different physiological stimuli  
253 (among which nutrient starvation, growth factor withdrawal, drug treatment, radiotherapy,  
254 oxidative and mechanical stress) and pathophysiological situations. Although in general  
255 autophagy is a bulk process, it can also be highly selective. Selective autophagic responses are  
256 named according to the type of cellular material targeted: aggregated proteins (aggrephagy),  
257 mitochondria (mitophagy), peroxisomes (pexophagy), lipid droplets (lipophagy), ribosomes  
258 (ribophagy), endoplasmic reticulum (reticulophagy), lysosomes (lysophagy), glycogen  
259 (glycophagy), intracellular pathogens (xenophagy) or proteasome components (proteaphagy).  
260 Many efforts have been made in understanding certain aspects of selective autophagy  
261 especially how cargo(es) is (are) sequestered into autophagosome. Two different cellular  
262 pathways (ubiquitin-independent and ubiquitin-dependent) have been shown to recognize  
263 signals on cargoes to deliver them into the autophagosome [36]. The ubiquitin independent  
264 pathway requires receptors (including NIX for mitophagy or FAM134B for reticulophagy) that  
265 bind directly certain substrates and target them for autophagic degradation by interacting with  
266 LC3. The ubiquitin dependent pathway involves adaptor proteins (such as p62/SQSTM1,  
267 NBR1 or NPD52) which also recognize LC3 and cargoes, however, its ubiquitination is  
268 required for its own recognition. As mentioned before, ubiquitination is therefore not only  
269 important for substrate degradation by proteasome but also for selective autophagy. The precise  
270 mechanism that governs the choice between these two proteolytic systems is still unclear. The  
271 lysine residue position, as well as the length and nature of ubiquitin chains have been suggested  
272 to be required to pathway selection. Indeed, K48-linked chains lead to proteasomal degradation  
273 of the substrates while K63-linked chains or phosphorylated ubiquitin are likely more involved  
274 in xenophagy and mitophagy respectively.

275

276 Before reviewing data on the interplay between cilia and autophagy, it is important to underlie  
277 that autophagy and UPS pathways are tightly interconnected [37]. As mentioned before,  
278 autophagy directly regulates UPS by degrading the proteasome through a selective autophagy  
279 called proteaphagy. However, the relation between UPS, which is the primary proteolytic

280 pathway for short-lived proteins, and autophagy, more dedicated to the long-lived ones, is not  
281 restricted to the effect of autophagy on the regulation of proteasomal degradation. Upon  
282 proteasome impairment, autophagy is well known to be able to compensate the reduced cellular  
283 proteasomal degradative capacity [38]. Apart from this compensatory function of autophagy,  
284 both systems are interconnected by influencing each other through the degradation of key  
285 components. This is for example the case of several E3 ligases which control the proteasomal  
286 degradation of various autophagy effectors such as ULK1.

287

#### 288 **4. Crosstalk between Cilia and Autophagy**

289

290 The crosstalk between cilia and proteolytic systems is not restricted to UPS (figure 1). In fact,  
291 since 2013 several studies including ours have highlighted the existence of a specific interplay  
292 between primary cilia and autophagy (see previously published contributions [39] [40,41][42]).  
293 Here we will summarize and update this research area. Work by Tang and colleagues show that  
294 the autophagic degradation of the centriolar satellite protein oral-facial-digital syndrome 1  
295 (OFD1) is necessary for the serum starvation-induced ciliogenesis in mouse embryonic  
296 fibroblasts (MEFs)[43]. Accordingly, both ciliogenesis and degradation of OFD1 induced by  
297 serum deprivation are partially inhibited in *Atg5<sup>-/-</sup>* MEFs. Indeed, these cells show a lower  
298 percentage of ciliated cells and a diminished cilia length. Importantly, the knockdown of OFD1  
299 in autophagy-deficient cells restores the serum deprivation-induced ciliogenesis and cilia length,  
300 suggesting that the autophagic degradation of OFD1 is necessary for starvation-induced  
301 ciliogenesis [43]. At the same time, Pampliega and colleagues demonstrated a close interaction  
302 between PC-dependent signaling pathways, ciliogenesis and autophagy [44]. The authors used  
303 two cellular models of impaired ciliogenesis: the knockdown of the ciliary IFT20 protein in  
304 MEFs and mouse kidney epithelial cells (KECs) with a hypomorphic mutation of IFT88. In these  
305 models, both autophagic maturation and PC formation are significantly reduced in conditions of  
306 serum starvation suggesting that compromised ciliogenesis impairs autophagy induction  
307 following serum withdrawal. Interestingly, they show that the Hh signaling pathway is necessary  
308 for the up-regulation of PC-dependent autophagy following serum withdrawal since the  
309 pharmacological or genetic activation of the Hh pathway induces autophagy in wild type MEFs  
310 but not in IFT20(-) MEFs or IFT88<sup>-/-</sup> KECs [44]. This work also shows that autophagy-  
311 associated ATG16L1 protein re-localizes at the basal body of the primary cilium after serum  
312 starvation or when ciliary Hh signaling is increased. Interestingly, this protein seems to be  
313 associated with IFT20, participating in the proper trafficking of the latter from the Golgi to the

314 base of the PC in conditions of ciliogenesis. This study also demonstrates that IFT20 is degraded  
315 by basal autophagy, thus maintaining ciliogenesis to a minimum in nutrient rich conditions.  
316 Accordingly, in autophagy-deficient *Atg5<sup>-/-</sup>* MEFs the protein IFT20 is accumulated, thus  
317 promoting ciliogenesis and cilia growth [44].

318 Recently, it has been shown that the crosstalk between PC and autophagy involves the mTOR  
319 pathway and the ubiquitin-proteasome system [45]. In this work, Wang and colleagues, using  
320 epithelial kidney HK2 cells in which IFT88 was knocked down, and C13 cells (epithelial kidney  
321 cells with short cilia), demonstrated that both basal and starvation-induced autophagy are reduced  
322 in both paradigms of cilia-deficient cells. Interestingly, these cells show higher activation of the  
323 mTOR pathway and treatment with rapamycin restores autophagy in both cell types suggesting  
324 that the PC depletion inhibits autophagy through the activation of the mTOR signaling pathway  
325 [45]. In addition, autophagy induction significantly increases cilium length, while its inhibition  
326 reduces cilia length and frequency in IFT88-KD and *Atg7<sup>-/-</sup>* kidney proximal tubular cells,  
327 respectively. Interestingly, the pharmacological inhibition of proteasomal activity reverses the  
328 shortening of cilia in autophagy deficient cells, suggesting that the autophagy's inhibition  
329 promotes proteasomal degradation of an unknown protein that is necessary for ciliogenesis [45].

330 Altogether, these results suggest that a PC of “normal length” is necessary for basal and  
331 starvation-induced autophagy and, conversely, autophagy is required for ciliogenesis and cilia  
332 length maintenance. On the other hand, it is known that the PC acts as a flow sensor that  
333 regulates kidney epithelial cell size through the liver kinase B1 (LKB1)-AMPK-mTOR pathway  
334 [46]. Interestingly, we have shown that physiological fluid flow induces autophagy and decreases  
335 cell volume in a cilium-dependent manner, suggesting that the PC is required for fluid flow-  
336 induced autophagy [47]. Unlike PC-induced autophagy following serum withdrawal, Hedgehog  
337 signaling pathway is not involved in this setting. So far, this flow-induced autophagy is  
338 characterized by the recruitment of ATG16L1 to the basal body of the PC as previously  
339 demonstrated by Pampliega and colleagues. These results suggest that ATG16L1 translocation  
340 might be one of the hallmarks of PC-dependent autophagy. Additionally, we evaluated the role of  
341 the PC *in vivo* in the regulation of autophagy and cell size in kidney epithelial cells. The specific  
342 depletion of *Kif3a* in tubular cells in mice impairs ciliogenesis, reduces autophagy, and enlarges  
343 tubular epithelial cells compared with control mice. Altogether, these results indicate that the PC-  
344 dependent flow-induced autophagy is required for the control of cell size *in vitro* and *in vivo*  
345 [47]. Recently, Park and colleagues studied the role of autophagy and cilia in the development of  
346 focal malformations of cortical development (FMCDs) which are a group of cortical  
347 abnormalities associated with epilepsy, intellectual disability and developmental delay. These

348 authors demonstrated that brain somatic activating mutations of mTOR decrease neuronal  
349 ciliogenesis due to impaired autophagy and the consequent accumulation of the protein OFD1  
350 [48]. Interestingly, the mouse model of the brain somatic mutation of mTOR (p.Cys1483Tyr)  
351 exhibits the same phenotype found in FMCDs patients such as cortical dyslamination, seizures,  
352 cytomegalic neurons and decreased ciliogenesis which can be rescued by rapamycin treatment or  
353 OFD1 knockdown. Altogether these results suggest that the accumulation of OFD1 induced by  
354 defective autophagy is responsible for reduced neuronal ciliogenesis. These results were  
355 confirmed through the analysis of brain tissues from FMCDs patients which exhibit lower  
356 percentage of ciliated neurons, decreased autophagy, and accumulation of OFD1 protein [48]. To  
357 date, most of recent data focus on the post-translational mechanisms that control the crosstalk  
358 between the PC and autophagy. However, the work of Liu and collaborators delve in the  
359 transcriptional control of the PC-autophagy interplay [49]. They indeed show that ciliogenesis is  
360 reciprocally controlled by PPARA (peroxisome proliferator activated receptor alpha) and  
361 NR1H4/FXR (nuclear receptor subfamily 1, group H, member 4). Specifically, pharmacological  
362 activation of PPARA promotes ciliogenesis, induces expression of autophagic genes, and  
363 activates autophagy in mammalian cells. Interestingly, ciliogenesis requires PPARA-mediated  
364 activation of autophagy since the rapamycin treatment prevents the impaired ciliogenesis in  
365 *Pppara*<sup>-/-</sup> MEFs, however knockdown of *Atg7* in *Pppara*<sup>-/-</sup> MEFs abrogates the effect of  
366 rapamycin. On the contrary, pharmacological activation of NR1H4 negatively regulates  
367 autophagy and ciliogenesis and, conversely, siRNA-mediated knockdown of NR1H4 induces  
368 cilia formation and autophagy. Indeed, activation of NR1H4 inhibits the PPARA-dependent  
369 ciliogenesis suggesting that ciliogenesis is reciprocally controlled by these two transcription  
370 factors [49].

371 Finally, defective autophagic activity has been linked to different mouse model of ciliopathies  
372 such as chronic obstructive pulmonary disease (COPD) or polycystic kidney disease (PKD)  
373 models. Thus, as mentioned before for UPS, we could wonder whether targeting autophagy is an  
374 attractive target for the development of new treatments for human ciliary disorders. Along this  
375 line, Lin and colleagues have recently demonstrated the beneficial effect of autophagy  
376 activation on preventing cystogenesis. In this study, authors have developed zebrafish model of  
377 PKD and shown that activating autophagy using mTOR-dependent (rapamycin) or mTOR-  
378 independent compounds (carbamazepine, minoxidil) reduces cystogenesis and restores renal  
379 function [50]. However, other *in vivo* experiments are needed to study the therapeutic (versus  
380 the renal and non-renal toxicity [51,52]) effect of several autophagic activators in PKD  
381 models.

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**5. Concluding remarks**

Here we focused on the interplay between cilia and two proteolytic systems: autophagy and UPS. Despite several reports that have identified bidirectional crosstalk between autophagy and the PC or UPS and the PC, only a limited number of data have directly focused on the interplay between autophagy, UPS and the PC in the control of cellular functions. It is known that cilium-dependent signaling pathways are necessary for autophagy induction in some cellular models (such as fibroblast and kidney epithelial cells), while both basal or starvation-induced autophagy regulate ciliogenesis and the PC length through the degradation of specific proteins that acts as positive or negative regulators of ciliogenesis. Despite exciting progresses in the understanding of the interplay between autophagy and cilia, many questions remain to be answered: is this interplay between autophagy and the PC also occurring in other cell types? Likewise, as the majority of the published articles show the effect of autophagy on ciliogenesis, or *vice versa*, under serum deprivation conditions, could other stimuli that modulate the autophagic pathway also control ciliogenesis or cilia length? On the other hand, are cilia associated structures and/or complexes also interconnected with other aspects of proteostasis including protein folding and protein synthesis? Is there a relationship between cilia and other forms of autophagy such as chaperone-mediated autophagy or microautophagy? Thus, future research needs to focus on better understanding the translational interplay that exists between autophagy, UPS and ciliogenesis in order to identify therapeutic targets that, through the modulation of these processes, might represent effective treatments for different ciliopathies or non-communicable diseases associated with cilia or proteostasis defects such as insulin resistance, type-2 diabetes, cancer, and neurodegenerative disorders.

409 **Conflicts of Interests**

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411 The authors declare that they have no conflict of interest.

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421

422 **Figure Legends:**

423 **Figure 1: Interplay between primary cilium (PC), ubiquitin proteasome system (UPS)**

424 **and autophagy.**

425 UPS-PC relationship is bilateral: PC can modulate UPS activity whereas UPS components are

426 able to control cilia formation and disassembly via different proteins (such as RPGRIP1L,

427 Tricho and NDE1). Autophagy and PC are also interconnected: PC is a positive modulator of

428 autophagic pathway since compromised ciliogenesis impairs basal autophagy whereas induced

429 autophagy is required for ciliogenesis and cilia length maintenance. Interplay between

430 autophagy and UPS pathways: autophagy directly regulates UPS by degrading the proteasomal

431 machinery through a selective process called proteaphagy. Several key proteins like OFD1,

432 BBS1, HDAC6 and others modulate specifically this UPS and autophagy crosstalk. In addition,

433 when the UPS is not efficient, autophagy can compensate the reduced proteasomal degradative

434 capacity. The two systems can also influence each other through the degradation of mutual key

435 components.

436

437 **Figure 2: The Autophagic pathway.**

438 The autophagic pathway requires three different steps: 1) Initiation in which the cytosolic

439 substrates are sequestered within a double membrane vesicle called phagophore or pre-

440 autophagosome 2) Maturation that is characterized by the elongation and the closure of

441 phagophore forming an « autophagosome » 3) Degradation that includes the fusion of

442 autophagosome-lysosome to form an autolysosome in which the cargo is degraded and  
443 recycled.

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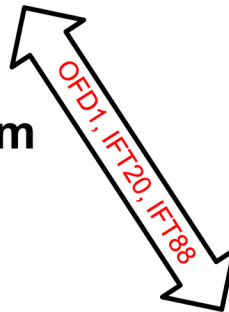
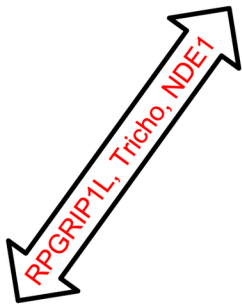
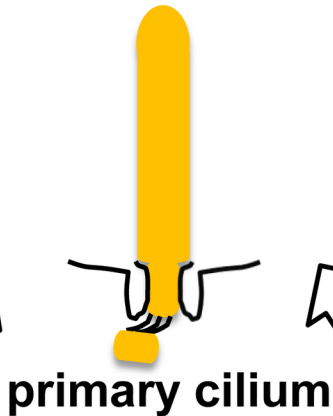
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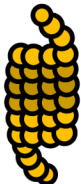
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ubiquitin proteasome system



autophagy

