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Interplay Between Primary Cilia and Autophagy and Its Controversial Roles in Cancer

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Abstract

Primary cilia and autophagy are two distinct nutrient-sensing machineries required for maintaining intracellular energy homeostasis, either via signal transduction or recycling of macromolecules from cargo breakdown, respectively. Potential correlations between primary cilia and autophagy have been recently suggested and their relationship may increase our understanding of the pathogenesis of human diseases, including ciliopathies and cancer. In this review, we cover the current issues concerning the bidirectional interaction between primary cilia and autophagy and discuss its role in cancer with cilia defect.

Key Words: Cilia, Autophagy, Ciliopathy, Cancer

INTRODUCTION

Primary cilia are nonmotile, antenna-like organelles derived from the centrioles after cell division, and are therefore closely related to cell cycle control. These structure sense extracellular stimuli, including growth factors and mechanical stress, via multiple receptors clustered along the ciliary membrane. They are also known to contribute to metabolic regulation (Delaine-Smith *et al*., 2014). Autophagy is an intracellular process required for maintaining energy homeostasis, whereby damaged proteins are removed and recycled. This process is generally inhibited by the energy-sensing mTORC1 (mammalian target of rapamycin complex 1) under fed conditions, and is triggered by cellular stresses, including serum deprivation (Glick *et al*., 2010).

Potential correlations between primary cilia and autophagy have been recently suggested and an increasing number of studies are attempting to identify its specific molecular mechanisms (Cloonan *et al*., 2014; Pampliega and Cuervo, 2016; Avalos *et al*., 2017). Herein, we summarize the current issues regarding the bidirectional interplay between ciliogenesis and autophagy, and discuss its pathophysiological implications.

PRIMARY CILIA

Primary cilia are finger-like organelles protruding from the apical membrane of many mammalian cells. Non-motile primary cilia were considered to be ancient cellular organelles that lack a specific biological function. However, recent studies have reported that various signaling proteins and channels are localized to ciliary membranes and respond to diverse stimuli such as mechanical stress (Delaine-Smith *et al*., 2014; Battle *et al*., 2015) and various signaling molecules from the extracellular environment (Malicki and Johnson, 2017; Song *et al*., 2018). The biological significance of primary cilia is exemplified by the fact that functional or structural defects in the primary cilia in mice results in pathological phenotypes known as ciliopathies, such as cystic disease (Jonassen *et al*., 2008, 2012), cancer (Menzl *et al*., 2014; Jenks *et al*., 2018; Higgins *et al*., 2019), obesity (Volta and Gerdes, 2017; Ritter *et al*., 2018), blindness (Servattalab *et al*., 2012; Wheway *et al*., 2014), polydactyly (Taylor *et al*., 2015; Agbu *et al*., 2018), left-right asymmetry defects (Okada *et al*., 1999; Dasgupta and Amack, 2016), skeletal abnormalities (Xiao and Quarles, 2010), and neurological impairment (Youn and Han, 2018). Based on this evidence, primary cilia have emerged as signaling hubs involved in the regulation of diverse cell signaling.

Primary cilia consist of dynamic microtubule-based axoneme regulated by a precise mechanism called ciliogenesis (Taschner *et al*., 2012). Key proteins during ciliogenesis are the intraflagellar transport (IFT) particles, which are protein complexes that move bidirectionally along the ciliary axoneme (Taschner *et al*., 2012; Lechtreck, 2015). In addition to IFT

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complexes, cell cycle regulators are involved in ciliogenesis (Pugacheva *et al*., 2007; Plotnikova *et al*., 2012), with primary cilia typically assembling in response to quiescence (G1/G0 phase) and disassembling upon cell cycle re-entry (Plotnikova *et al*., 2009; Basten and Giles, 2013). Interestingly, multiple lines of research have revealed that autophagy (Tang *et al*., 2013), the ubiquitin-proteasome system (Kasahara *et al*., 2014), actin remodeling factors such as LIM kinase 2 (LIMK2), testicular protein kinase (TESK1) (Kim *et al*., 2015b), and serine/threonine kinases such as intestinal cell kinase (ICK) (Chaya *et al*., 2014; Moon *et al*., 2014) are critical for the maintenance and function of primary cilia. More recently, among these various regulators of ciliogenesis or ciliary function, interest in the bidirectional interaction between primary cilia and autophagy is increasing (Pampliega and Cuervo, 2016; Wiegering *et al*., 2019). Indeed, it has been reported that cells with defective cilia show reduced autophagy (Pampliega *et al*., 2013) and dysfunction of ICK known as ciliary protein leads to perturbation of ciliary signaling and autophagy (Tong *et al*., 2017), which suggests that there is a close relationship between primary cilia and autophagy.

AUTOPHAGY

Autophagy is a highly conserved intracellular process in which misfolded or damaged proteins are sequestered into double membrane-bound vesicles named autophagosomes. More than 30 autophagy-related (*Atg*) genes are sequentially involved in autophagosome formation, and once formed, these vesicles fuse with lysosomes so that their engulfed cargo can be degraded by hydrolytic enzymes. Autophagy eliminates harmful intracellular proteins and recycles the functional macromolecular components, helping to ensure the maintenance of cellular homeostasis (Glick *et al*., 2010).

The stepwise process of autophagy is divided into four stages: initiation, vesicle nucleation, elongation of autophagosome, and fusion with a lysosome (Mizushima *et al*., 2011; Stanley *et al*., 2014). It initially starts with the accumulation of the ULK1/2 (Unc-51 like autophagy activating kinase 1/2) complex (ULK1/2-ATG13-FIP200), which is normally inhibited by the energy-sensing mTORC1 under fed conditions. mTORC1 inactivation, under autophagy-related stimuli including nutrient deprivation, in turn de-phosphorylates ULK1/2 and ATG13 and enhances the interaction between them. The active ULK1/2 complex translocates to cytosolic membrane structures where the phagophore membrane is possibly derived (Alers *et al*., 2012). Beclin 1, which is phosphorylated by ULK1, is one of the core proteins that initiate vesicle nucleation. It forms a complex with VPS34 (phosphatidylinositol 3-kinase catalytic subunit type 3) and subsequently interacts with co-activators (i.e., Vps15, UVRAG (UV radiation resistance associated gene) and Bif-1 (SH3 domain containing GRB2 like, endophilin B1)) to generate phosphatidylinositol-3-phosphate (PtdIns3P), which recruits other ATG proteins to grow the autophagosomal membrane from the phagophore (Kihara *et al*., 2001). During vesicle elongation, the microtubule-associated protein 1A/1B-light chain 3 (LC3) is processed to an active lipid-conjugated form, which allows for its incorporation into the autophagosomal membrane. Specific ATG proteins including ATG3, ATG4, the ATG5/ATG12/ATG16L complex, and ATG7 are sequentially involved in this stage (Nakatogawa *et al*., 2007). As the autophagosome becomes enclosed and completely matured, it fuses with lysosomes, which then allows for the proteolytic degradation of engulfed cargo proteins (Zhao and Zhang, 2019).

INTERPLAY BETWEEN AUTOPHAGY AND PRIMARY CILIA

Autophagy and ciliogenesis occur concurrently under serum deprivation and both are involved in maintaining intracellular energy balance, which suggests that the two might be linked. The first two studies identifying interplay between autophagy and ciliogenesis were published in 2013. One study found that autophagy regulated a cilia-related protein Oral-facial-digital syndrome 1 protein (OFD1, centriole and centriolar satellite protein). The authors identified that a centriolar satellite protein OFD1 negatively regulates ciliogenesis, and under fasted conditions, autophagy eliminates it (Tang *et al*., 2013) (Fig. 1A). The second study showed that impaired autophagic flux as well as reduced ciliogenesis occurred following serum withdrawal in cilia-defect models. In addition, a large number of ATG proteins turned out to be localized either to the basal body, where a cilium is primarily nucleated, or along the ciliary axoneme, suggesting a potential cilia-mediated autophagy initiation mechanism (Pampliega *et al*., 2013). Studies to further identify the functional relationship between autophagy and ciliogenesis are currently underway.

Early approaches attempted to determine whether the two processes were concurrently triggered following a common stimulus, and whether they influenced each other. Bidirectional regulation between autophagy and cilia was indeed observed, with impaired autophagic flux in cells with cilia defects as well as shorter cilia led by autophagy inhibition (Wang *et al*., 2015). Several studies also demonstrated either genetic or chemical inhibition of autophagy attenuated cilia growth that was stimulated by chemicals including Sertraline, BIX01294, and Mefloquine in retinal pigment epithelium (RPE) cells (Kim *et al*., 2015a; Shin *et al*., 2015a, 2015b). These studies demonstrated positive correlations between autophagy and cilia growth; however, other studies have made contradictory findings. Using mouse embryo fibroblast 3T3-L1 cells, cilia were shortened by histone deacetylase 6 (HDAC6)-mediated autophagy via decreasing the expression of ciliary proteins such as IFTs and KIF3a (kinesin family member 3A) (Xu *et al*., 2016). Similarly, downregulation of the HDAC6-autophagy pathway was involved in cilia growth promoted by type I collagen, which provides mechanical strength to modulate cellular morphology or shape (Xu *et al*., 2018). More recently, studies to identify specific mediators regulating the autophagy-ciliogenesis axis were attempted. PPARA (peroxisome proliferator activated receptor alpha) was identified as one of these potential meditators, as it was found to positively regulate ciliogenesis, which was changed by drugs or genetic manipulations that targeted autophagy. *In vivo* data showing impaired autophagy as well as kidney damage, commonly observed in ciliopathies, in *Ppara*$^{-/-}$ mice was further evidence for the involvement of autophagy in ciliogenesis (Liu *et al*., 2018). In addition, another group suggested Gli2 as a link between primary cilia-dependent cell cycle control and autophagy, in which Gli2 repressed Ofd1-eliminating autophagy under serum deprivation (Hsiao *et al*., 2018).

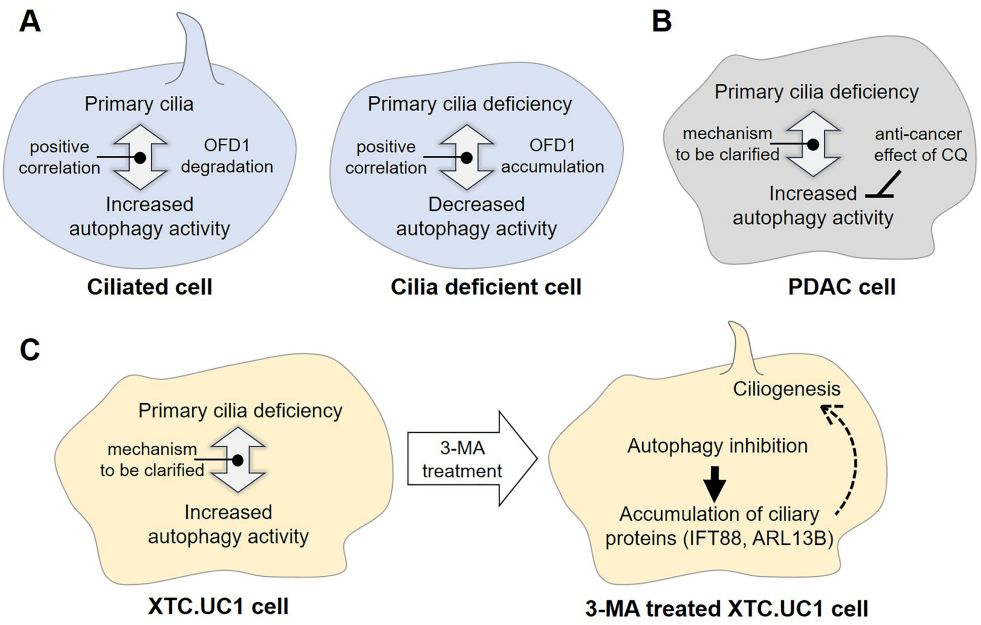

Fig. 1. Controversial interplay between primary cilia and autophagy and effect of autophagy inhibitors in cancer cells. (A) Proposed model for the positive correlation between primary cilia and autophagy involving OFD1 protein in normal cells (B) Pancreatic ductal adenocarcinoma (PDAC) cells with increased autophagy activity despite absence of primary cilia. In this cancer cell, the autophagy inhibitor, chloroquine (CQ), shows therapeutic effect. (C) XTC.UC1 cells derived from thyroid Hürthle cell carcinoma with increased autophagy activity despite decreased frequency of ciliated cells. In this cancer cell, the autophagy inhibitor, 3-MA, increases frequency of ciliated XTC.UC1 cells via accumulation of ciliary proteins, such as IFT88 and ARL13B.

Taken together, these studies indicate that there is a substantial link between autophagy and ciliogenesis, in which impaired autophagy leads to a ciliary defect and vice versa. However, further studies are still required to identify the specific molecular mechanisms.

CONTROVERSIAL INTERPLAY BETWEEN PRIMARY CILIA AND AUTOPHAGY IN CANCER

Multiple human cancers, including melanoma (Zingg *et al*., 2018), renal cell carcinoma (Basten *et al*., 2013), pancreatic cancer (Seeley *et al*., 2009a; Kobayashi and Itoh, 2017), and breast cancer (Menzl *et al*., 2014; Nobutani *et al*., 2014), are accompanied by primary ciliary defects (Yuan *et al*., 2010) and dysregulated autophagy (Wang *et al*., 2018). The relationship between primary cilia and autophagy still requires further studies; however, primary cilia are generally known to have a positive effect on autophagy regulation (Pampliega *et al*., 2013; Wang *et al*., 2015) (Fig. 1A). If this is true, how is autophagy regulated in cilia-deficient cancer models and what are the effects of autophagy regulators in cilia-defective cancer models?

It can be speculated that most cancer cells that do not have primary cilia have lower autophagic activity. Indeed, autophagy was suppressed in renal cell carcinoma (RCC) cell lines (Wang *et al*., 2018) with decreased ciliated frequency (Basten *et al*., 2013). However, many research groups have reported that autophagy has a dual function as both a tumor suppressor and tumor promoter, depending on the cancer subtype and development/progression stage (White, 2015; Zhi and Zhong, 2015). In this context, it is interesting that many cancer cells do not have primary cilia and yet they display differences in their autophagic activities, which indicates that the correlation between primary cilia and autophagy is still unclear in these cancer models. An example of this comes from a study where the effect of autophagy repression on cancer cells was investigated. In that study chloroquine (CQ), an inhibitor of late stage of autophagy (Mauthe *et al*., 2018), was used in various human cancer models. Among these cancers, the pancreatic ductal adenocarcinoma (PDAC) cell line and its primary tumor display increased autophagic activities (Yang *et al*., 2011) despite the absence of primary cilia (Fig. 1B) (Seeley *et al*., 2009b; Kobayashi and Itoh, 2017). Thus, even though primary cilia are suspected to have a positive effect on autophagy, the PDAC model indicates that there must be a cilia-independent mechanism for autophagy regulation (Fig. 1B). In the study with the PDAC cell lines, CQ treatment reduced growth and tumorigenesis (Yang *et al*., 2011), suggesting that even if cancer cells do not have primary cilia, autophagy inhibition can show some anti-cancer effects (Fig. 1B). In addition to study of PDAC model, there is another research showing this controversial interplay in thyroid cancer (Lee *et al*., 2016). XTC.UC1 cells derived from thyroid Hürthle cell carcinoma show higher activity of autophagy even though these cells display decreased frequency of ciliated cells compared with that in controls (Fig. 1C) (Lee *et al*., 2016). Interestingly, pharmacological inhibition of autophagosome formation of XTC.UC1 cells using 3-MA treatment increases ciliogenesis via restoring expression of ciliary proteins, IFT88 and ARL13B (Fig. 1C) (Lee *et al*., 2016). Likewise, cilia and autophagy seem to be related to each other in cancer, but may not be applied to cancer models with positive correlation observed in normal cells. Therefore, further studies are needed to reveal underlying regulatory mechanism between primary cilia and autophagy in

various cancer models.

CONCLUSIONS

In the last few years, the interplay between primary cilia and autophagy has been an active area of research (Hsiao *et al*., 2018; Struchtrup *et al*., 2018; Takahashi *et al*., 2018), and several studies have indicated that there is biological interaction between these two entities. Because primary cilia and autophagy have various cellular functions (Cao and Zhong, 2015), the interaction of these two regulatory mechanism will provide critical evidences to help understand disease pathogenesis. However, the functional significance of primary cilia on autophagy and vice versa remains controversial. There is a bidirectional interplay between primary cilia and autophagy, but more studies are needed to explain this complicated connection. This is especially true in more complex diseases models such as cancer, where the interplay between primary cilia and autophagy is not as clear. Further studies are needed to investigate the regulatory mechanism between primary cilia and autophagy in disease models, as they may provide new therapeutic approaches of ciliopathies, including cancer.

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