Mitophagy, the selective removal of dysfunctional mitochondria by autophagic machinery, is a highly conserved cellular process ranging from eukaryotes to mammals. Mitophagy plays a critical role in maintaining cellular homeostasis. Current evidence has mainly focused on the role of outer mitochondrial membrane (OMM) components in mitophagy. Mitochondrial kinase PINK1 activates E3 ligase Parkin, leading to the ubiquitination of several OMM proteins upon mitochondrial damage. Subsequently, the ubiquitination of these OMM proteins binding to autophagy receptors such as optineurin or p62/SQSTM promotes autophagosome formation via OMM proteins binding to autophagy receptors such as optineurin or p62/SQSTM, promotes autophagosome formation via LC3-interacting region (LIR) domain to trigger mitophagy [1,2]. In addition, OMM proteins including BH3-only protein BNIP3, NIX, and FUNDC1 molecular adaptors also directly interact with autophagosome membrane bound LC3 family members LC3/GABARAP/GATE-16 to mediate mitophagy [3]. Hence, cells execute mitophagy through several different mechanisms in the maintenance of mitochondrial integrity. Prohibitin 2 (PHB2) is extensively present in the inner mitochondrial membrane (IMM). PHB2 attenuates mitochondria fission program and induces mitochondrial fusion machinery, which exerts the regulatory function of mitochondrial dynamics regulation [4,5]. However, it remains uncertain about the properties of IMM protein PHB2 during mitophagy.

Recently, Wei et al. [6] published a report in Cell which revealed that PHB2 is a novel mitophagy receptor for the mitophagic machinery in mammals. Strikingly, PHB2 also participates in the paternal mitochondrial DNA (mtDNA) elimination in Caenorhabditis elegans. Upon mitochondrial depolarization, the autophagosome-associated protein LC3 directly binds to PHB2 or indirectly incorporates with PHB2-binding partner PHB1. Moreover, proteasome-dependent OMM rupture is responsible for PHB2 interaction with LC3. In mammals, the LIR domain of PHB2 is required for Parkin-induced mitophagy by targeting damaged or unwanted mitochondria. Thus, IMM component PHB2 acts as a mitophagy receptor and plays a vital role in Parkin-mediated mitophagy (Fig. 1). Additionally, PHB2 plays a conserved role in the clearance of paternal mtDNA after embryonic fertilization in C. elegans. In contrast, paternal knockdown of PHB2 significantly blocks sperm-derived mitochondrial degradation. Their findings illustrate that IMM component PHB2 is a novel mitophagy receptor which further mediates the process of Parkin-dependent mitophagy by selective autophagic machinery in mammals. The highly conserved protein PHB2 also eliminates paternal mitochondria after embryonic fertilization in C. elegans. The precise regulation and mechanism of PHB2 in Parkin-independent mitophagy warrants further investigation. Surprisingly, the presence of PHB2 may be correlated with mitophagy and mitochondria dynamics in regulating mtDNA. Therefore, in future studies, attention should be paid to how PHB2 interacts with mitochondrial functions. In addition, the roles of PHBs and other IMM molecules in mitochondrial functions should also be explored.

Mitochondria are highly dynamic organelles that play a central role in mitochondrial biogenesis. The removal of impaired mitochondria by mitophagy has a protective effect against mitochondrial dysfunction. Accordingly, mitochondrial dysfunctions due to mitophagy deficiency are implicated in human diseases, such as cardiovascular disease, obesity, cerebral ischemia-reperfusion injury, diabetes, tumorigenesis, and liver disease. In particularly, mitochondrial diseases are mainly characterized by defects in oxidative phosphorylation and are caused by mtDNA mutation. The proper removal of superfluous mitochondria by mitophagy may be important for the prevention of mtDNA damage [7]. In a review article,
Villanueva et al. [8] proposed that mitophagy may play a protective role in mitochondrial diseases.

In 2013, Supale et al. [9] reported that PHB2 significantly enhances inheritance mtDNA copy number, improves mitochondrial activity and assembles the oxidative phosphorylation system. Ablation of PHB2 impairs respiratory chain, leading to mitochondrial morphological and physiological abnormalities. Therefore, mitophagy induced by mitophagy receptor PHB2 may emerge as a potential therapeutic target for mitochondrial diseases. PHB2 may be a promising candidate for drug screening. In the future, the identification of mitophagy inducers is essential for the design of potential therapeutic agents for mitochondrial diseases.

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**References**