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Review

The role of PI3P phosphatases in the regulation of autophagy

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ABSTRACT

Autophagy initiation is strictly dependent on phosphatidylinositol 3-phosphate (PI3P) synthesis. PI3P production is under tight control of PI3Kinase, hVps34, in complex with Beclin-1. Mammalian cells express several PI3P phosphatases that belong to the myotubularin family. Even though some of them have been linked to serious human diseases, their cellular function is largely unknown. Two recent studies indicate that PI3P metabolism involved in autophagy initiation is further regulated by the PI3P phosphatases Jumpy and MTMR3. Additional pools of PI3P, upstream of mTOR and on the endocytic pathway, may modulate autophagy indirectly, suggesting that other PI3P phosphatases might be involved in this process. This review sums up our knowledge on PI3P phosphatases and discusses the recent progress on their role in autophagy.

1. Introduction

PI3P synthesis has long been recognized as one of the key events in the initiation of the autophagic process [1]. The phosphorylation of phosphatidylinositol is catalyzed by the well known, type III phosphatidylinositol 3-kinase, hVps34, in complex with the autophagy proteins, Beclin-1 (Atg6) and Atg14 [2–4] (Fig. 1). This highly regulated complex (see chapter in this issue), conserved from yeast to humans, allows spatio-temporal control of autophagy initiation [5]. Besides, and in contrast, to this proximal action at the early stage of autophagy, PI3P may also regulate autophagy upstream of mTOR, a negative regulator autophagy. Amino-acids have been shown to stimulate mTOR activity via hVps34 activation [6–7], therefore, this pool of PI3P could potentially inhibit autophagy, even though at the moment, evidence is lacking to support this model. Finally, PI3P plays a major role in the endocytic pathway where it promotes fusion of endosomes and receptor degradation [8]. Since autophagic and endocytic pathways merge, it is likely that this third pool of PI3P modulates either directly or indirectly the last stages of autophagy [9,10].

Although, the synthesis of PI3P and its regulation have been well studied, how PI3P is turned-over and how autophagy is turned-off once PI3P is produced, remained to be elucidated. The PI3P phosphatases were one of the likely candidates as it is known that the phosphoinositide, PI3,4,5P_3 and its signaling can be down-regulated by PI3,4,5P_3 phosphatase, PTEN. In this review we will summarize briefly the structure and functions of PI3P phosphatases (for reviews see, [11–13]) culminating in a discussion of the recently developing role of PI3P phosphatases in autophagy.

2. Structure and expression of PI3P phosphatases

In mammalian cells PI3P phosphatases belong to the myotubularin family [11–13]. This subgroup of phosphatases contains 15 members in humans of which all have a characteristic phosphatase domain with a CX5R motif. Only nine of them, MTM1 (also called myotubularin), MTMR1, MTMR2, MTMR3, MTMR4, MTMR6, MTMR7, MTMR8 and Jumpy (also known as MTMR14), possess an active phosphatase domain, that specifically dephosphorylates PI3P and phosphatidylinositol (3,5)-bisphosphate (PI3,5P_2) at position 3 on inositol ring. However, MTMR7 seems to have preference for inositol (1,3)-bisphosphate as a soluble substrate [14]. The six remaining myotubularins are inactive pseudophosphatases due to a substitution of Cys and Arg residues in their catalytic site. Besides the catalytic domain, all myotubularins, with the exception of MTMR14, contain two other protein domains, PH-GRAM (Pleckstrin Homology-Glucosyl transferases, Rab-like GTPase activators and myotubularins) and coiled-coil, that are believed to be important for lipid–protein or protein–protein interactions. Subgroups of myotubularins present additional domains such as PH and FYVE

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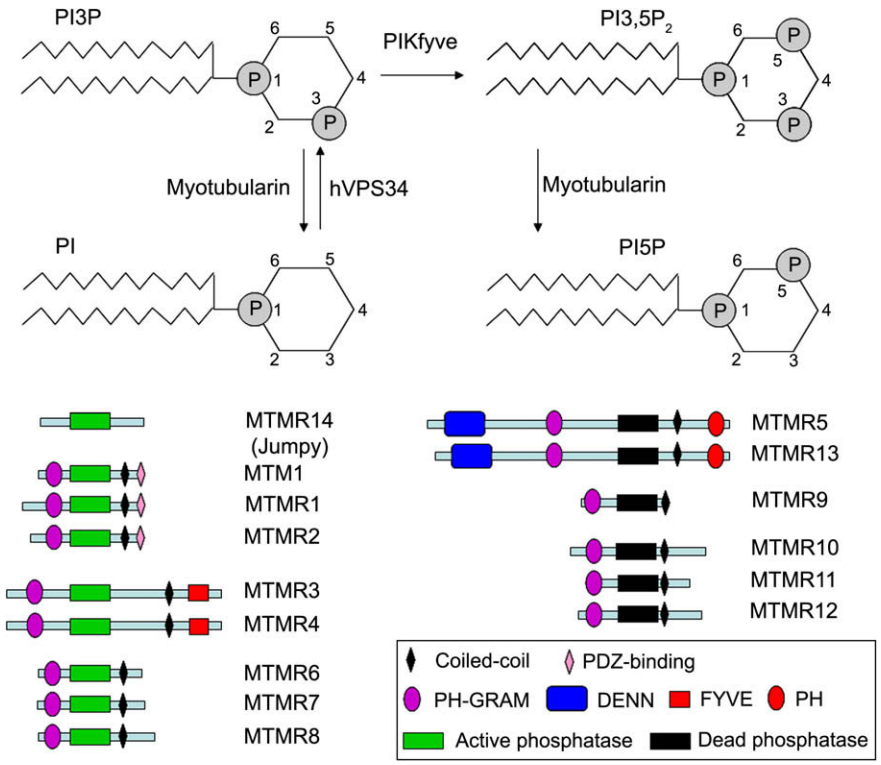

Fig. 1. Myotubularin family: activity and different members with their domains. hVps34 catalyzes phosphatidylinositol (PI) phosphorylation at position 3 on inositol ring to form phosphatidylinositol 3-phosphate (PI3P). PI3P can be further phosphorylated by PIKfyve to generate PI3,5,P_2. Myotubularins remove 3-phosphate on PI3P and PI3,5P_2 resulting in generation of PI and PI5P, respectively. Nine active and six inactive phosphatases are present in humans. See text for domain description.

which are predicted to bind to phosphoinositides, PDZ-binding site likely to mediate protein–protein interaction and DENN in inactive myotubularins MTMR5 and MTMR13 (Fig. 1) [11,12]. Myotubularins are ubiquitously expressed, however, they can be enriched in certain tissues. For instance, MTM1 and Jumpy are highly expressed in skeletal muscles whereas MTMR2 is abundant in neurons and Schwann cells [15–19].

Saccharomyces. cerevisiae genome encodes only one myotubularin, Ymr1p. However, yeast expresses two additional unrelated phosphatases, members of the synaptojanin-like family, Sjl2p and Sjl3p that account also for PI3P dephosphorylation [20]. Only *ymr1Δ sjl3Δ* and *ymr1Δ sjl3Δ* double mutants show a significant increase in PI3P level, suggesting that these phosphatases may have redundant function in yeast [20].

3. PI3P phosphatases and diseases

Four of the fifteen PI3P phosphatases present in mammals have been linked to serious human diseases. MTM1 defects cause X-linked myotubular myopathy (XLMTM) also known as centronuclear myopathy, a severe congenital disorder affecting the physiology of skeletal muscle fibers and characterized by centrally localized nuclei and hypotonia [12,13]. More than two hundred different mutations, truncations and missenses, in *MTM1* have been reported in XLMTM patients that result in loss or decrease of MTM1 level [21]. A severe case of centronuclear myopathy was observed in one patient with an inactive MTM1 suggesting that XLMTM is likely due to defect in PI3P metabolism [21]. MTM1 knockout mice studies indicate that myotubularin is essential for muscle growth and maintenance but not for myogenesis [22]. Histopathological analyses of MTM1-deficient mice reveal skeletal hypotrophic myofibers with numerous vacuoles [22]. However, ultrastructural analyses show that these vacuoles do not seem to contain cellular debris [22].

Recently, another gene encoding for a PI3P phosphatase, *jumpy*, has been identified as mutated in some patients with centronuclear myopathy [15]. The mutations lead to a reduced or total loss of phosphatase activity and they are likely the basis for the disease as observed for MTM1 [15]. Indeed, a recent study reports that MTMR14$^{-/-}$ mice display muscle weakness and fatigue similar to patients with centronuclear myopathy [16].

MTMR2 and MTMR13 have been found mutated in two forms of Charcot–Marie–Tooth (CMT) Type 4B disease, an autosomal recessive disorder of the peripheral nervous system characterized by nerve demyelination and myelin outfoldings [13,21]. CMT type 4B1 is caused by missense or deletion mutations in *MTMR2* gene that result in MTMR2 loss of function. In addition to CMT4B1, one patient manifests azoospermia suggesting that MTMR2 also plays a role in testis. MTMR2-deficient mice develop CMT4B1-like neuropathy and azoospermia [21]. Interesting, inactive myotubularin MTMR5, which interacts with MTMR2, has been shown to be essential for spermatogenesis in mice [13]. Cell type-specific gene knockout indicates that loss of MTMR2 in Schwann cells but not in neurons leads to CMT4B1-like neuropathy. CMT type 4B2 is due to mutations in *MTMR13* gene which encodes a pseudophosphatase [12,13]. MTMR13-deficient mice manifest myelin outfoldings in peripheral nerves very similar to ones found in CMT4B2 [13]. It has been suggested that MTMR2 might form two complexes, one with MTMR5, in Sertoli or germ cells, involved in spermatogenesis and a second one with MTMR13, in Schwann cells, important in myelin homeostasis [13].

4. Regulation and cellular functions of PI3P phosphatases

One important feature of myotubularins is their ability to form homo- and heterodimers [23] (Table 1). These interactions often lead to an enhancement of phosphatase activity or to regulation of myotubularin intracellular localization. For instance, MTMR9,