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The Roles of Lysosomal Exocytosis in Regulated Myelination

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ABSTRACT

The myelin sheath wraps axons is an intricate process required for rapid conduction of nerve impulses, which is formed by two kinds of glial cells, oligodendrocytes in the central nervous system and Schwann cells in the peripheral nervous system. Myelin biogenesis is a complex and finely regulated process and accumulating evidence suggests that myelin protein synthesis, storage and transportation are key elements of myelination, however the mechanisms of regulating myelin protein trafficking are still not very clear. Recently, the evidences of lysosomal exocytosis in oligodendrocytes and Schwann cells are involved in regulated myelination have emerged. In this paper, we briefly summarize how the major myelin-resident protein, as proteolipid protein in the central nervous system and P0 in the peripheral nervous system, transport from lysosome to cell surface to form myelin sheath and focus on the possible mechanisms involved in these processes. Advances in our understanding of glia, as well as new tools engineering, will further improve the knowing of myelin biogenesis.

Introduction

Myelin is a specialized membrane structure generated by oligodendrocytes and Schwann cells, which offers electrical insulation around the axon and involves in mutual communication with neurons and the outside environment[1]. Myelin biogenesis is a complex and finely regulated process and accumulating evidence suggests that myelin protein synthesis, storage and transportation are key elements of myelination[1]. However, the mechanisms of regulating myelin protein trafficking still remain poorly understood.

Lysosomes are acidic organelles and generally considered to be responsible for the degradation of endocytic and autophagic substrates. Interestingly, some cells used their lysosomes as secretory compartment. Compared to conventional lysosomes, this kind of lysosomes serve dual functions – for degradation of proteins and for storage of newly synthesized secretory proteins, were named as secretory lysosomes[2]. Lysosomal exocytosis is defined as a process that a lysosome responds to extracellular stimuli, docks at the interior of the cell surface and fuses with the plasma membrane to their contents[2,3]. In nervous system Ca^{2+}-dependent lysosomal exocytosis is already proved as a new pathway for gliotransmitter secreted from astrocytes[4-6] meanwhile the lysosome exocytic process was also found in microglia[7,8], oligodendrocyte[9] and Schwann cells[10,11].

Recently, the roles of lysosomal exocytosis in myelin formation

were investigated. It was discovered that some neuronal signals can induce proteolipid protein (PLP), the major myelin-resident protein in CNS (about 50% of the total protein component) and myelin protein P0, the major myelin protein in PNS (about 50% of the total protein component), release from late endosomes/lysosomes membrane stores to plasma membrane during myelination[9,11]. Consistent with these findings, myelin abnormalities are very common phenomenon in many lysosomal storage diseases (LSDs), a group of inherited and acquired diseases that are characterized by an accumulation of undigested material inside the lysosome as a result of one or more specific lysosomal enzymes deficiencies[12], including Niemann-Pick disease, Gaucher disease, metachromatic leukodystrophy, multiple sulfatase deficiency and globoid cell leukodystrophy [12-15].

Owing to the critical cellular role of lysosomes in the myelination, mounting studies focus on the mechanisms underlying exocytosis of lysosome in nervous system has emerged. In this paper, we briefly introduce the recent advances in this respect.

Roles of Lysosomal Exocytosis in Regulated Myelination in CNS

As an integral membrane protein, proteolipid protein (PLP) is the most prominently component of myelin-specific proteins in CNS[16,17]. PLP is major expressed in oligodendrocytes and it is synthesized in the rough ER then transported to the Golgi and plasma membrane via vesicles, followed to form the myelin sheath with neuronal signals or internalized and stored into late endosomal/lysosome without neuronal signals. The process of PLP transportation is carefully regulated by intracellular and extracellular signal. PLP localized in late endosomal/lysosome is particularly evident during active myelinogenesis in the brain[18]. The mechanisms of regulation of the trafficking of PLP from late endosomal/lysosome membrane stores to plasma membrane, thereby promoting the formation and maintenance of myelin are still not very clear[19-21]. Feldmann et al. found that the vesicle-soluble N-ethylmaleimide-sensitive factor attachment protein receptors (v-SNAREs) protein VAMP7 mediates trafficking of PLP from late endosomal/lysosome to plasma membrane and is involved in myelin formation[9]. Stx3 and SNAP23 serve as putative target SNAREs in the VAMP7-dependent pathway[9]. However, AP3-δ mutant mocha mice, with a defect in lysosomal exocytosis caused by VAMP7 missorting, exhibit normal levels of myelination which may due to the functional redundancy[9]. On the other hand, some members of the Rab family have been indicated to regulate membrane transport process in the late endosomes - lysosomes system, including Rab3[22,23], Rab7[24,25], Rab9[26,27], Rab27[23], Rab26[28] and Rab14[29]. For example, overexpression of rab3A and PLP promoted PLP surface transport in oligodendrocytes, indicating rab3A may regulate the membrane trafficking of PLP-containing transport vesicles[30]. Our recent study demonstrated that another small GTPase Rab27b is primarily expressed in lysosomes of mature oligodendrocytes and co-localized with PLP[31]. Downregulation of Rab27b in cultured mature oligodendrocytes by specific siRNA transfection strongly reduces lysosomal exocytosis and inhibits PLP transport from lysosome to plasma membrane. Furthermore, downregulation of Rab27b also affects the formation of myelin-like membranes in vitro analysis using oligodendrocyte–neuron co-culture system. This is the first demonstration that Rab27b is implicated in myelin protein PLP trafficking in oligodendrocytes via regulates lysosomal exocytosis and contributes to myelin formation[31]. Above all, these results strongly suggest that lysosomal exocytosis in oligodendrocytes contributes to myelin protein PLP trafficking and plays an important role in myelination in CNS.

Roles of Lysosomal Exocytosis in Regulated Myelination in PNS

Compared to the CNS, peripheral nerves have a remarkable capacity to regenerate and remyelination allowing for functional recovery in affected body regions[32]. This regenerative ability to a great degree is dependent on and supported by Schwann cells, the myelin-forming glial cells of the PNS[33,34]. Schwann cells myelinating are regulated by extrinsic signals from the axon, and the extracellular matrix[35]. Peripheral nerve injury can induce Schwann cells transition from axon myelination to an immature Schwann cell - like stage, proliferate, supports neuronal survival which is followed by remyelination of newly-regenerated axons[36,37]. Therefore to find out the potential mechanisms of regulate myelin proteins trafficking in Schwann cells during this process is one of matters of cardinal significance. The role of lysosomal exocytosis in the PNS has been studied recently. It is believed that in the process of Wallerian degeneration lysosomal exocytosis is involved in Schwann cell demyelination, dedifferentiation, proliferation and remyelination[38]. Our previous results showed that lysosomal exocytosis in Schwann cells also contribute to myelination in PNS. We found that Rab27a, another small GTPase of Rab27 family, is required for secretory lysosome trafficking in Schwann cells and myelination in PNS[11]. The mechanism was dissected by several evidences. First, myelin protein P0 was stored in Schwann cell late endosomes/lysosomes. Second, Rab27a is also distributed in late endosomes/lysosomes and co-localized with P0 in Schwann cells. Third, the potent and selective calcium ionophore ionomycin, which acts as a motile Ca^{2+} carrier and enhances Ca^{2+} influx, induced lysosomal exocytosis in Schwann cells was significantly decreased in Rab27a downregulated Schwann cells, which were transfected with Rab27a shRNA plasmid. Finally, after sciatic nerve

injury, the remyelination of the injured axon was obviously impaired in Rab27a deficient ashen mice[11]. In addition, our unpublished data suggest that the downstream effector molecule of Rab27a also plays an important role in the formation of myelin-like membranes in vitro analysis using Schwann–neuron co-cultures. Although the exact regulating mechanisms of myelin biogenesis are unknown, our experiments suggest that the process of lysosomal exocytosis in Schwann cells is involved in myelination in PNS. Generally, compared to complex CNS, discover the molecular basis of myelination in PNS will not only help for promoting peripheral myelin in peripheral nerve diseases but also provide important conceptual insights into CNS myelination.

Demyelination Associated with Lysosomal Disorders

Lysosomal disorders are caused by deficiency of the specific lysosomal enzymes and/or lysosomal membrane proteins[12-15]. About two-thirds of all lysosomal disorders have a severe phenotype in nerve system, including neuronal dysfunction or death, axonal damage, and demyelination[12]. Primary demyelination of lysosomal disorders display a primary loss of myelin due to oligodendrocytes and/or the myelin sheath are selectively affected by different pathogenesis, which include multiple sulfatase deficiency, metachromatic leukodystrophy and globoid cell leukodystrophy[12-15]. Multiple mechanisms involved in primary demyelination of lysosomal disorders, such as defective lipid and protein transport from lysosome to plasma membrane results in abnormal biochemical composition and causes myelin sheaths instability, accumulating materials in lysosome causes cellular toxicity and anomalous response of neuroimmunomodulation.

Typically strategies for treating lysosomal disorders are focus on directly increase activity of the specific protein or enzyme defect. Interestingly, stimulation of lysosomal exocytosis has been determined as a new treatment for lysosomal disorders. In general, lysosomal exocytosis is a Ca^{2+} - dependent process. Recently, transcription factor EB (TFEB) was found can modulate this process[39,40]. Overexpression and activation of TFEB reduced lysosomal size, improved autophagosome processing, and enhanced clearance of substrates in lysosomes in cultured myoblasts from some lysosomal disorders murine model[39,40]. It is worth emphasizing that the effects of TFEB enhanced lysosomal exocytosis and induced cellular clearance of stored substrates may be repeated in all lysosomal disorders, independent of the different kinds of metabolic defects. There is a possibility that TFEB maybe also involved in myelination.

Concluding Remarks

Myelin biogenesis is a carefully regulated process as different myelin components are expressed at the right time and place, involved multiple transport pathways. Due to a lot of lysosomal diseases have a severe phenotype affect the nerve system, including neuronal dysfunction, axonal damage, and demyelination, there might be an interesting link between the functions of lysosome and myelin biogenesis. The role of lysosomal exocytosis in myelination has been to support by different research groups. These studies have shown that VAMP7 and Rab27b mediate PLP trafficking from late endosomes/lysosomes to plasma membrane and are implicated in myelin formation in CNS. We have also seen Rab27a as a molecule of vital significance in lysosomal transport of P0 in PNS. However, our understanding about the molecular mechanisms remains limited. Previous studies have shown that Rab27b is primarily expressed in the CNS and Rab27a is expressed outside the CNS[41]. Rab27 family, including Rab27a and Rab27b, and their multiple effectors are involved in the regulation of lysosome-related organelle exocytosis[41,42]. The challenge in the future will be to investigate and integrate the different signaling and trafficking pathways to get a comprehensive view of how myelination is regulated. Interdisciplinary methods based on different cell culture systems in vitro and animal models in vivo are required to identify the involved molecular mechanisms. For example, a drug called ambroxol more selectively induces lysosomal exocytosis via Ca^{2+} release from lysosomes[43] and that this drug promotes axonal growth after injury[44] and ameliorates biochemistry in lysosomal storage disease[45], all being consistent with the idea that ambroxol could be a useful tool in the future to investigate lysosomal exocytosis in regulated myelination. However, it is still a long way to go for us to find out the exact rules of myelin biogenesis.

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