www.jneurology.com



Mini Review Open Access

The Roles of Lysosomal Exocytosis in Regulated Myelination

Yun-Tian Shen¹, Ying Yuan^{1,2}, Wen-Feng Su¹, Yun Gu¹, Gang Chen¹

1 Jiangsu Key Laboratory of Neuroregeneration, Co-innovation Center of Neuroregeneration, Nantong University, Nantong, China 2 Affiliated Hospital of Nantong University, Nantong, China

Article Info

Article Notes

Received: June 02, 2016 Accepted: July 21, 2016

*Correspondence:

Dr. Gang Chen

Jiangsu Key Laboratory of Neuroregeneration Co-innovation Center of Neuroregeneration, Nantong University, Nantong, China. 226001, Tel: 86-513-85051805,

Email: chengang6626@ntu.edu.cn

© 2016 Chen G. This article is distributed under the terms of the Creative Commons Attribution 4.0 International License

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 environment¹. Myelin biogenesis is a complex and finely regulated process and accumulating evidence suggests that myelin protein synthesis, storage and transportation are key elements of myelination¹. 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 lysosomes². 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 Ca²⁺-dependent lysosomal exocytosis is already proved as a new pathway for gliotransmitter secreted from astrocytes⁴⁻⁶ meanwhile the lysosome exocytic process was also found in microglia^{7,8}, oligodendrocyte⁹ 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 deficiencies12, 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 myelinspecific 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 brain18. 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 formation9. Stx3 and SNAP23 serve as putative target SNAREs in the VAMP7-dependent pathway⁹. 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 redundancy9. 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 vesicles³⁰. Our recent study demonstrated that another small GTPase Rab27b is primarily expressed in lysosomes of mature oligodendrocytes and co-localized with PLP³¹. 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 formation³¹. 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

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 regions³². 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 matrix³⁵. 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 axons36,37. 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 demyelination, dedifferentiation, proliferation and remyelination³⁸. 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 PNS¹¹. 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 Ca²⁺ carrier and enhances Ca2+ 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 mice¹¹. 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 proteins¹²⁻¹⁵. About two-thirds of all lysosomal disorders have a severe phenotype in nerve system, including neuronal dysfunction or death, axonal damage, and demyelination¹². 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 leukodystrophy¹²⁻¹⁵. 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 Ca²⁺ - 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 CNS⁴¹. 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 Ca²⁺ release from lysosomes⁴³ and that this drug promotes axonal growth after injury44 and ameliorates biochemistry in lysosomal storage disease⁴⁵, 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.

Acknowledgements

This work was supported by the National Natural Science Foundation of China (31071251, 81471255, 81471259), the National Basic Research Development Program of China (2014CB542202), the Basic Research Program of the Department of Education, Jiangsu Province, China (14KJA310004), a Natural Science Research Project of Nantong Science and Technology Bureau, Jiangsu Province, China (HS2013014).

References

- Trapp BD. Cell Biology of Myelin Assembly Myelin Biology and Disorders. Myelin Biology & Disorders. 2004; 29-35.
- Blott EJ, Griffiths GM. Secretory lysosomes. Nat Rev Mol Cell Biol. 2002; 3(2): 122-131
- Hissa B, Pontes B, Roma PM, Alves AP, Rocha CD, Valverde TM. et al. Membrane cholesterol removal changes mechanical properties of cells and induces secretion of a specific pool of lysosomes. Plos One. 2013; 8(12): 1524-1528.
- Zhang Z, Chen G, Zhou W, Song A, Xu T, Luo Q. et al. Regulated ATP release from astrocytes through lysosome exocytosis. Nat Cell Biol. 2007; 9(8): 945-953.

- Li D, Ropert N, Koulakoff A, Giaume C, Oheim M. et al. Lysosomes Are the Major Vesicular Compartment Undergoing Ca2+-Regulated Exocytosis from Cortical Astrocytes. J Neurosci. 2008; 28(30): 7648-7658
- Liu T, Sun L, Xiong Y, Shang S, Guo N, Teng S. et al. Calcium triggers exocytosis from two types of organelles in a single astrocyte. J Neurosci. 2011; 31(29): 10593-10601.
- Dou Y, Wu HJ, Li HQ, Qin S, Wang YE, Li J, et al. Microglial migration mediated by ATP-induced ATP release from lysosomes. Cell Res. 2012; 22(6):1022-1033.
- Shen K, Sidik H, Talbot WS. The Rag-Ragulator Complex Regulates Lysosome Function and Phagocytic Flux in Microglia. Cell Rep. 2016; 14(3): 547-559.
- Feldmann A, Amphornrat J, Schönherr M, Winterstein C, Möbius W, Ruhwedel T, et al. Transport of the major myelin proteolipid protein is directed by VAMP3 and VAMP7. J Neurosci. 2011; 31(15): 5659-5672.
- Jung J, Jo HW, Kwon H, Jeong NY. However, ATP Release through Lysosomal Exocytosis from Peripheral Nerves: The Effect of Lysosomal Exocytosis on Peripheral Nerve Degeneration and Regeneration after Nerve Injury. Biomed Research International. 2014; (3): 936891-936891.
- Chen G, Zhang Z, Wei Z, Cheng Q, Li X, Li W, et al. Lysosomal exocytosis in Schwann cells contributes to axon remyelination. Glia. 2012; 60(2): 295-305.
- 12. Parenti G, Andria G, Ballabio A. Lysosomal Storage Diseases: From Pathophysiology to Therapy. Annu Rev Med. 2015; 66(1): 471-486.
- 13. Faust PL, Kaye EM, Powers JM. Kaye Empowers, Myelin lesions associated with lysosomal and peroxisomal disorders. Expert Rev of Neurother. 2010; 10(9): 1449-1466.
- Marsden D, Levy H. Newborn screening of lysosomal storage disorders. Clin Chem. 2010; 56(7): 1071-1079.
- 15. Boustany RM. Lysosomal storage diseases--the horizon expands. Nat Rev Neurol. 2013; 9(10): 583-598.
- Aggarwal S, Yurlova L, Simons M. Central nervous system myelin: structure, synthesis and assembly. Trends Cell Biol. 2011; 21(10): 585-593.
- Baron W1, Hoekstra D. On the biogenesis of myelin membranes: Sorting, trafficking and cell polarity. Febs Lett. 2010; 584(9): 1760-1770.
- Bakhti M1, Winter C, Simons M. Inhibition of myelin membrane sheath formation by oligodendrocyte-derived exosome-like vesicles. J Biol Chem. 2011; 286(1): 787-796.
- 19. Trajkovic K1, Dhaunchak AS, Goncalves JT, Wenzel D, Schneider A, Bunt G, et al. Neuron to glia signaling triggers myelin membrane exocytosis from endosomal storage sites. J Cell Biol. 2006; 172(6): 937-948.
- 20. White R, Krämer-Albers EM. Axon-glia interaction and membrane traffic in myelin formation. Front Cell Neurosci. 2014; 7(1): 284-284.
- 21. Baron W, Ozgen H, Klunder B, de Jonge JC, Nomden A, Plat A. The major myelin-resident protein PLP is transported to myelin membranes vila a transcytotic mechanism: involvement of sulfatide. Mol Cell Biol. 2015; 35(1): 288-302.
- 22. Pavlos NJ, Grønborg M, Riedel D, Chua JJ, Boyken J, Kloepper TH, et al. Quantitative analysis of synaptic vesicle Rabs uncovers distinct yet overlapping roles for Rab3a and Rab27b in Ca2+-triggered exocytosis. J Neurosci. 2010; 30(40): 13441-13453.
- Cazares VA, Subramani A, Saldate JJ, Hoerauf W, Stuenkel EL. Distinct Actions of Rab3 and Rab27 GTPases on Late Stages of Exocytosis of Insulin. Traffic. 2014; 15(9): 997-1015.

- Jordens I, Westbroek W, Marsman M, Rocha N, Mommaas M, Huizing M, et al., Rab7 and Rab27a control two motor protein activities involved in melanosomal transport. Pigm Cell Res. 2006; 19(5): 412-423.
- Mrakovic A, Kay JG, Furuya W, Brumell JH, Botelho RJ. Rab7 and Arl8 GTPases are Necessary for Lysosome Tubulation in Macrophages. Traffic. 2012; 13(12): 1667-1679.
- Kloer DP, Rojas R, Ivan V, Moriyama K, van Vlijmen T, Murthy N, et al. Assembly of the biogenesis of lysosome-related organelles complex-3 (BLOC-3) and its interaction with Rab9. J Biol Chem. 2010; 285(10): 7794-7804.
- Junaid M, Muhseen ZT, Ullah A, Wadood A, Liu J, Zhang H. Molecular modeling and molecular dynamics simulation study of the human Rab9 and RhoBTB3 C-terminus complex. Bioinformation. 2014; 10(12): 757-763.
- 28. Jin RU, Mills JC. RAB26 coordinates lysosome traffic and mitochondrial localization. J Cell Sci. 2014; 127(5): 1018-1032.
- Lu R, Johnson DL, Stewart L, Waite K, Elliott D, Wilson JM. Rab14 regulation of claudin-2 trafficking modulates epithelial permeability and lumen morphogenesis. Mol Biol Cell. 2014; 25(11): 1744-1754.
- Schardt A, Brinkmann BG, Mitkovski M, Sereda MW, Werner HB, Nave KA. The SNARE protein SNAP-29 interacts with the GTPase Rab3A: Implications for membrane trafficking in myelinating glia. J Neurosci Res. 2009; 87(15): 3465-3479.
- Shen YT, Gu Y, Su WF, Zhong JF, Jin ZH, Gu XS. et al. Rab27b is Involved in Lysosomal Exocytosis and Proteolipid Protein Trafficking in Oligodendrocytes. Neurosci Bull. 2016.
- 32. Pereira JA, Lebrun-Julien F, Suter U. Suter, Molecular mechanisms regulating myelination in the peripheral nervous system. Trends Neurosci. 2011; 35(2): 123-134.
- 33. Nave KA, Werner HB. Myelination of the nervous system: mechanisms and functions. Annu Rev Cell Dev Biol. 2014; 30(1): 503-533.
- 34. Court FA, Zambroni D, Pavoni E, Colombelli C, Baragli C, Figlia G, et al. MMP2-9 cleavage of dystroglycan alters the size and molecular composition of Schwann cell domains. J Neurosci. 2011; 31(34): 12208-12217.
- 35. Salzer JL. Schwann cell myelination. CSH Perspect Biol. 2015; 7(8).
- 36. Klein D, Martini R. Myelin and macrophages in the PNS: An intimate relationship in trauma and disease. Brain Res. 2015; 1641: 130-138.
- Hung HA, Sun G, Keles S, Svaren J. Dynamic regulation of Schwann cell enhancers after peripheral nerve injury. J Biol Chem. 2015; 290(11): 6937-6950.
- Zhou Y, Notterpek L. Promoting peripheral myelin repair. Exp Neurol. 2016.
- Medina DL, Fraldi A, Bouche V, Annunziata F, Mansueto G, Spampanato C, et al. Transcriptional activation of lysosomal exocytosis promotes cellular clearance. Dev Cell. 2011; 21:421-430.
- Spampanato C, Feeney E, Li L, Cardone M, Lim JA, Annunziata F, et al. Transcription factor EB (TFEB) is a new therapeutic target for Pompe disease. EMBO Mol Med. 2013; 5: 691-706
- 41. Izumi T. Physiological roles of Rab27 effectors in regulated exocytosis. Endocr J. 2007; 54: 649–657.
- Shimada-Sugawara M, Sakai E, Okamoto K, Fukuda M, Izumi T, Yoshida N, et al. Rab27A regulates transport of cell surface receptors modulating multinucleation and lysosome-related organelles in osteoclasts. Sci Rep. 2015; 5: 9620.
- 43. Fois G, Hobi N, Felder E, Ziegler A, Miklavc P, Walther P, et al. A new role for an old drug: Ambroxol triggers lysosomal exocytosis via pHdependent Ca(2+) release from acidic Ca(2+) stores. Cell Calcium. 2015; 58: 628-637.

- 44. Chandran V, Coppola G, Nawabi H, Omura T, Versano R, Huebner EA, et al. A Systems-Level Analysis of the Peripheral Nerve Intrinsic Axonal Growth Program. Neuron. 2016; 89: 956-970.
- 45. McNeill A, Magalhaes J, Shen C, Chau KY, Hughes D, Mehta A, et al. Ambroxol improves lysosomal biochemistry in glucocerebrosidase mutation-linked Parkinson disease cells. Brain. 2014; 137: 1481-1495.