Journal of Molecular and Genetic Medicine

Rozés-Salvador and Conde, J Mol Genet Med 2019, 13:1
DOI: 10.4172/1747-0862.1000397

Short Communication Open Access

Participation of Rabs during Neuronal Development and Disease

Rozés-Salvador V[1-3] and Conde C[1,2]*

[1]Universidad Nacional de Córdoba (UNC) Av. Haya de la Torre s/n, Ciudad Universitaria, Córdoba, Argentina
[2]Instituto Mercedes y Martín Ferreyra (INIMEC-CONICET), Friuli 2434, 5016, Córdoba, Argentina
[3]Instituto A.P. De Ciencias Básicas y Aplicadas, Universidad Nacional de Villa María (UNVM), Arturo Jauretche 1555, Ciudad Universitaria, Villa María, Argentina

Abstract

Membrane traffic has been widely studied in recent decades, and now it is clear that its participation in biological processes such as cellular migration, mitosis, and immune response, among others, is crucial and determinant. During the development of the nervous system, membrane trafficking organizes both the differential distribution and degradation of specific components, among others. Failures in these functions lead to the development of neurological pathologies that can be progressive, chronic or even lethal such as Alzheimer's, Huntington's and Parkinson's diseases. These pathologies have significant health and economic costs in many countries. For this reason, research is being focused on the study of those components (mainly proteins) involved in membrane traffic during health and disease. In this short communication, we summarize main findings and state of the art discussion about the functions of some membrane trafficking components during development, as well as the implications of their dysfunction into the progression of neurological pathologies.

Keywords: Membrane trafficking; Rabs; Smad anchor for receptor activation; Neuronal development; Neuronal diseases

Introduction

The cellular development begins with the growth and further differentiation of a cell, which are processes that involve differential expression of genes, synthesis, and sorting of specific proteins redistribution of cellular components and membrane addition, among others [1]. In order that these events occur through a synchronized and coordinated way, proper coordination between the endosomal trafficking machinery is crucial. In general terms, trafficking may be summarized in 3 main steps: Endocytosis, sorting, and exocytosis. Briefly, the intracellular membrane trafficking begins with endocytosis, which consists of the internalization of components within the cell, which are positioned inside endosomes (called early endosomes). Once there, the destination of this material is classified and sorted, which means that it is either returned to the plasma membrane (by recycling endosomes) or sent to degradation (by late endosomes and subsequently lysosomes). Finally, the externalization of material outside of the cell is called exocytosis [1,2].

One of the better characterized proteins linked to vesicular trafficking are the Rab-family proteins, which belong to the superfamily of the Related Proteins (Ras) GTPases. Rabs are a group of regulatory molecules that are in different subsets of membrane domains along the secretory and endocytic pathway. In the active state, that is, bound to GTP, their function is to recruit endosome membrane-specific effector proteins [3-5]. Some of these Rabs have a specific cellular location within the different types of endosomes and are used as markers for these. For example, Rab5 is commonly used as early endosome marker, Rab11 for recycling endosomes and Rab7 for late endosomes, among others. Other Rabs are located in the cell membrane and vesicles such as Rab8 [6-12]. Some of the regulatory functions described for Rabs include the interaction with different effector proteins that select the cargo, promote the movement of vesicles to different compartments and verify the correct fusion site [13].

Additionally, there are other proteins interacting with endosomes and associated with Rabs, linking trafficking with signalling such as the Smad Anchor for Receptor Activation (SARA), which represent a subpopulation of early endosomes [14]. Also, SARA suppression or overexpression modifies the endogenous distribution of specifics Rabs like Rab5 and Rab11 and whose contribution to the development of the nervous system will be discussed below [15].

Discussion

Participation of Rabs during neuronal development

The participation of proteins associated with membrane traffic during the process of formation and extension of neurites has been widely studied.

In this sense, experiments addressed in sensory neurons of dorsal root ganglion (DRG) shown that Rab7 controls the neurites growth by an endosomal trafficking-mediated mechanism involving neurotrophic tyrosine kinase receptor A (TrkA) signaling since the inhibition of Rab7 results in TrkA accumulation in endosomes [16]. Also, in DRGs, it has been reported that trafficking of integrin β1 (membrane receptor involved in cell adhesion and recognition) at the surface of the membrane during neurites growth, requires the participation of Rab11 and its effector Rab coupling protein (RCP). Changes in the expression of Rab11 modify the levels of integrin β1 at the surface and, as a consequence, alter axonal growth [17].

In hippocampal neurons, Rab5 suppression inhibits the morphogenesis of both axon and dendrites, whereas Rab17 suppression only affects the dendritogenesis, suggesting that the expression and function of Rabs during development is context-dependent [18]. Also, it has been recently identified that the guanine nucleotide exchange factor for Rab8, GRAB, promotes the transport of vesicles to the axonal

***Corresponding author:** Dr. Cecilia Conde, Universidad Nacional de Córdoba (UNC) Av. Haya de la Torre s/n, Ciudad Universitaria, Córdoba, Argentina, Tel: +90 312 442 74 04; E-mail: cconde@immf.uncor.edu

Received January 15, 2019; **Accepted** January 29, 2019; **Published** February 01, 2019

Citation: Rozés-Salvador V, Conde C (2019) Participation of Rabs during Neuronal Development and Disease. J Mol Genet Med 13: 397 doi:10.4172/1747-0862.1000397

membrane by mediating the interaction between Rab11 and Rab8, acting as a regulator of axonal growth in hippocampal neurons as well as *in vivo* corticogenesis [19,20]. In cortical neurons, both *in vitro* and *in vivo*, neuronal development could be regulated by the modulation of the protein lemur kinase 1 (LMTK1) expression, a protein that plays a role in the recycling of endosomal trafficking and up-regulates Rab11a. It has been shown that LMTK1 inhibition increases both the growth and branching of the dendrites [21,22].

Finally, it has been shown that neurons lacking SARA (either wild type-suppressed or isolated from the knockout mice), develop more than one axon, a phenotype that reports the inability to define the normal neuronal structure with one single axon, altering the polarity process of hippocampal neurons by changing the location of both Rab5 and Rab11 endosomes [15]. Furthermore, during the development of the cortex *in vivo,* SARA suppression produces a delay on the migration of the neurons from the ventricular zones, generating as a consequence that developing neurons arrive later to the outer cortical layers [23].

Involvement of Rabs during neurodegenerative disease

Considering the membrane trafficking role during neuronal development, a strong emphasis has been done on studying the participation of Rabs in pathologies affecting the nervous system.

Several studies associate changes on Rabs expression with neurodegenerative disorders. In Alzheimer disease (AD), the expressions of Rab4, Rab5, Rab7, and Rab27 are up-regulated [24-26]. In this context, high levels of Rab5 enhance the amyloid precursor protein (APP) expression, a central protein for the development of this disease, reproducing the morphology and endosomal phenotype found in AD [27].

Along the same line, the decrease in the number of Rab11-dependent synapses (caused by a decrease in Rab11 expression) could explain their participation in Alzheimer's, Huntington's and Parkinson's diseases [28-31]. In this regard, the loss of specific dendritic spines occurs at sites of huntingtin aggregate formation. Rab11 overexpression restores the number of spines around the aggregates in hippocampal neurons [32]. Moreover, the inhibition of Rab11 decreases the axonal localization of BACE (beta-secretase 1), a protein associated with the processing of APP; suggesting a relationship between Rab11 and APP dynamics [33]. However, a direct relationship between cellular processes alterations and cognitive dysfunction has not yet been defined.

Finally, the participation of proteins associated with Rabs in neuronal pathologies has also been reported. In this sense, endogenous SARA expression is increased in the hippocampus of rats subjected to pilocarpine-induced status epilepticus (SE). The SARA suppression by lentiviral infection delays the onset of SE through signalling dependent on Transforming Growth Factor (TGFβ), suggesting that SARA contributes to the development of the SE [34].

Conclusion

The performance of central and peripheral neurons depends on proper development. Numerous evidences have shown the importance of membrane traffic during development and neuronal specification. In this regard, we wonder about the impact of aberrant trafficking on the development of both neuronal and non-neuronal pathologies. Currently, the biggest challenge in this field is to understand whether changes in the normal operation of trafficking are either a cause or a consequence for neuronal pathologies development. In this regard, many articles support the notion that alterations on endosomal trafficking represent an early event at the onset of nerve pathologies and treatments aimed at restoring endosomal function can be successful therapeutic strategies. However, further research is required to discriminate at which level trafficking-mediated events impact on physiological and pathological functions of both neural and non-neural cells.

Funding Information

Work in the author's laboratories is supported by grants (PICTs) from the Ministry of Science and Technology (MINCyT) and National University of Villa Maria (UNVM), Argentina. CC is staff scientists of the National Council of Research of Argentina (CONICET). VRS is postdoctoral fellows of CONICET.

References

1. Platta HW, Stenmark H (2011) Endocytosis and signaling. Curr Opin Cell Biol 23: 393-403.
2. Doherty GJ, McMahon HT (2009) Mechanisms of endocytosis. Annu Rev Biochem 78: 857-902.
3. Pfeffer SR (1994) Rab GTPases: Master regulators of membrane trafficking. Curr Opin Cell Biol 6: 522-526.
4. Novick P, Zerial M (1997) The diversity of Rab proteins in vesicle transport. Curr Opin Cell Biol 9: 496-504.
5. Panopoulou E, Gillooly DJ, Wrana JL, Zerial M, Stenmark H, et al. (2002) Early endosomal regulation of Smad-dependent signaling in endothelial cells. J Biol Chem 277: 18046-18052.
6. Bucci C, Parton RG, Mather IH, Stunnenberg H, Simons K, et al. (1992) The small GTPase rab5 functions as a regulatory factor in the early endocytic pathway. Cell 70: 715-728.
7. Stenmark H, Parton RG, Steele-Mortimer O, Lütcke A, Gruenberg J, et al. (1994) Inhibition of rab5 GTPase activity stimulates membrane fusion in endocytosis. EMBO J 13: 1287-1296.
8. Ullrich O (1996) Rab11 regulates recycling through the pericentriolar recycling endosome. J Cell Biol 135: 913-924.
9. Maxfield FR, McGraw TE (2004) Endocytic recycling. Nat Rev Mol Cell Biol 5: 121-132.
10. Feng Y, Press B, Wandinger-Ness A (1995) Rab 7: An important regulator of late endocytic membrane traffic. J Cell Biol 131: 1435-1452.
11. Huber LA (1993) Protein transport to the dendritic plasma membrane of cultured neurons is regulated by rab8p. J Cell Biol 123: 47-55.
12. Huber LA (1993) Rab8, a small GTPase involved in vesicular traffic between the TGN and the basolateral plasma membrane. J Cell Biol 123: 35-45.
13. Hutagalung AH, Novick PJ (2011) Role of Rab GTPases in membrane traffic and cell physiology. Physiol Rev 91: 119-149.
14. Rozes-Salvador V (2018) New player in endosomal trafficking: Differential Roles of Smad Anchor for Receptor Activation (SARA) protein. Mol Cell Biol 38: 1-2.
15. Arias CI, Siri SO, Conde C (2015) Involvement of SARA in axon and dendrite growth. PLoS One 10: e0138792.
16. Saxena S (2005) The small GTPase Rab7 controls the endosomal trafficking and neuritogenic signaling of the nerve growth factor receptor TrkA. J Neurosci 25: 10930-10940.
17. Eva R, Dassie E, Caswell PT, Dick G, Ffrench-Constant C, et al. (2010) Rab11 and its effector Rab coupling protein contribute to the trafficking of beta 1 integrins during axon growth in adult dorsal root ganglion neurons and PC12 cells. J Neurosci 30: 11654-11669.
18. Mori Y, Matsui T, Fukuda M (2013) Rabex-5 protein regulates dendritic localization of small GTPase Rab17 and neurite morphogenesis in hippocampal neurons. J Biol Chem 288: 9835-9847.
19. Kawauchi T, Sekine K, Shikanai M, Chihama K, Tomita K, et al. (2010) Rab GTPases-dependent endocytic pathways regulate neuronal migration and maturation through N-cadherin trafficking. Neuron 67: 588-602.

20. Furusawa K, Asada A, Urrutia P, Gonzalez-Billault C, Fukuda M, et al. (2017) Cdk5 Regulation of the GRAB-Mediated Rab8-Rab11 cascade in axon outgrowth. J Neurosci 37: 790-806.

21. Takano T, Tomomura M, Yoshioka N, Tsutsumi K, Terasawa Y, et al. (2012) LMTK1/AATYK1 is a novel regulator of axonal outgrowth that acts via Rab11 in a Cdk5-dependent manner. J Neurosci 32: 6587-6599.

22. Takano T, Urushibara T, Yoshioka N, Saito T, Fukuda M, et al. (2014) LMTK1 regulates dendritic formation by regulating movement of Rab11A-positive endosomes. Mol Biol Cell 25: 1755-1768.

23. Mestres I, Jen-Zen C, Calegari F, Conde C, Ching-Hwa S, et al. (2016) SARA regulates neuronal migration during neocortical development through L1 trafficking. Develop 143: 3143-3153.

24. Ginsberg SD, Mufson EJ, Counts SE, Wuu J, Alldred MJ, et al. (2010) Regional selectivity of rab5 and rab7 protein upregulation in mild cognitive impairment and Alzheimer's disease. J Alzheimers Dis 22: 631-639.

25. Ginsberg SD, Mufson EJ, Alldred MJ, Counts SE, Wuu J, et al. (2011) Upregulation of select rab GTPases in cholinergic basal forebrain neurons in mild cognitive impairment and Alzheimer's disease. J Chem Neuroanat 42: 102-110.

26. Kim S, Sato Y, Mohan PS, Peterhoff C, Pensalfini A, et al. (2016) Evidence that the rab5 effector APPL1 mediates APP-betaCTF-induced dysfunction of endosomes in Down syndrome and Alzheimer's disease. Mol Psychiatr 21: 707-716.

27. Grbovic OM, Mathews PM, Jiang Y, Schmidt SD, Dinakar R, et al. (2003) Rab5-stimulated up-regulation of the endocytic pathway increases intracellular beta-cleaved amyloid precursor protein carboxyl-terminal fragment levels and Abeta production. J Biol Chem 278: 31261-31268.

28. DiFiglia M, Sapp E, Chase K, Schwarz C, Meloni A, et al. (1995) Huntingtin is a cytoplasmic protein associated with vesicles in human and rat brain neurons. Neuron 14: 1075-1081.

29. Li X, DiFiglia M (2012) The recycling endosome and its role in neurological disorders. Prog Neurobiol 97: 127-141.

30. Udayar V, Buggia-Prévot V, Guerreiro RL, Siegel G, Rambabu N, et al. (2013) A paired RNAi and RabGAP overexpression screen identifies Rab11 as a regulator of beta-amyloid production. Cell Rep 5: 1536-1551.

31. Breda C, Nugent ML, Estranero JG, Kyriacou CP, Outeiro TF, et al. (2015) Rab11 modulates alpha-synuclein-mediated defects in synaptic transmission and behaviour. Hum Mol Genet 24: 1077-1091.

32. Richards P, Didszun C, Campesan S, Simpson A, Horley B, et al. (2011) Dendritic spine loss and neurodegeneration is rescued by Rab11 in models of Huntington's disease. Cell Death Differ 18: 191-200.

33. Buggia-Prevot V (2014) Axonal BACE1 dynamics and targeting in hippocampal neurons: A role for Rab11 GTPase. Mol Neurodegener 9: 1.

34. Yu W (2017) Smad anchor for receptor activation contributes to seizures in temporal lobe epilepsy. Synapse 71: e21957.