

Participation of Rabs during Neuronal Development and Disease

Rozés-Salvador V^{1,3} and Conde C^{1,2*}

¹Universidad Nacional de Córdoba (UNC) Av. Haya de la Torre s/n, Ciudad Universitaria, Córdoba, Argentina

²Instituto Mercedes y Martín Ferreyra (INIMEC-CONICET), Friuli 2434, 5016, Córdoba, Argentina

³Instituto 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 specific 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 $\beta 1$ (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 $\beta 1$ 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

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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 (TGF β), 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-neuronal cells.

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