Regulation and Coordination of Intracellular Trafficking: An Overview

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Abstract

During the last two decades, efforts in the protein trafficking field have focused primarily on the identification of the machinery components of vesicular transport and mechanisms that underlie it. In addition, research has started to reveal how intracellular trafficking is regulated. Here, we summarize the current state of our knowledge about the regulation of vesicular transport and its coordination with other cellular processes. At the most basic level, individual transport steps are regulated spatially and temporally in two different ways. First, molecular switches of the Arf, Rab and Rho GTPase families regulate the assembly of components of the vesicular transport machinery on membranes, mediating the formation, targeting and fusion of vesicles that shuttle cargo between intracellular compartments. Second, reversible posttranslational modifications, like phosphorylation and ubiquitination, allow efficient cargo sorting and machinery component recycling. At a higher level, individual transport steps are integrated into whole pathways, with GTPases as a mechanism for this integration. Finally, intracellular trafficking pathways are coordinated with other cellular processes. Here too, GTPases appear to play a role by orchestrating coordination.

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Introduction

Eukaryotic cells have a complex array of exocytic and endocytic membrane systems. Movement of membranes and cargos between organelles must occur efficiently while maintaining the integrity and structure of the organelles. Such maintenance requires sorting of proteins for forward transport while retaining resident proteins, as well as recycling of membranes and resident proteins back to donor organelles. Our current knowledge of the intracellular compartments and pathways are the subject of the first section of this book.\(^1\) Transport between organelles is mediated by membrane-bounded vesicles, which move membranes and proteins in both directions. Identification of the machinery components of vesicular transport and the mechanisms by which they function, the major issue the field has dealt with during the last two decades, is summarized in Section II. The progress made in these studies has made it possible to embark on the next major challenge in this field: understanding the spatial and temporal regulation of vesicular transport and the integration of individual transport steps into whole pathways in the context of the cell. This topic is the subject of Section III.

Two different mechanisms regulate individual vesicular transport steps. The first involves monomeric GTPases that act as molecular switches. These proteins regulate all aspects of vesicle life, from formation at the donor compartment to fusion with the acceptor compartment and are the subject of Chapter 16.\(^2\) The second type of regulatory mechanism uses posttranslational modifications, i.e., phosphorylation and ubiquitination of proteins. The best-characterized examples of this type of regulation occur in the endocytic pathway, where both endocytic cargo and endocytic machinery components are modified in a reversible way to allow cargo sorting and machinery component recycling. This type of regulation is discussed in Chapter 17.\(^3\)

Individual transport steps require coordination to allow integration of the steps into whole pathways. Monomeric GTPases and their upstream regulators play a key role in this process too. GTPase cascades were shown to regulate other cellular processes,\(^4\) and there is growing evidence that such cascades act in intracellular trafficking as well.\(^5,6\)

It has become clear that intracellular trafficking needs to be coordinated with other processes to allow for proper cell function. Evidence of such coordination is beginning to emerge and the examples are discussed in Chapters 18-20. First, intracellular trafficking is important for polarized cell growth.\(^7\) Second, intracellular trafficking is crucial for proper signaling, with Rab GTPases playing a role in this coordination too.\(^8\) Finally, both exocytosis\(^9\) and endocytosis\(^10\) are required for development of multi-cellular organisms.

Here, we summarize what is currently known about the regulation of intracellular trafficking, its coordination with other processes and the importance of this regulation to human health, and we discuss future perspectives in this field.

Regulation of Individual Transport Steps

Components of the trafficking machinery cannot by themselves drive efficient vesicular transport. For example, specific SNARE combinations can drive synthetic membrane fusion; however, the fusion reaction is extremely slow.\(^11\) Two types of highly conserved regulations ensure that intracellular trafficking is a specific and efficient process: monomeric GTPases and posttranslational modifications of cargo and machinery components.

GTPases Regulating Individual Vesicular Transport Steps

Monomeric GTPases of the Arf, Rab, Rho and dynamin families control specific vesicular transport steps. GTPases in general act as molecular switches as they cycle between the inactive GDP-bound and the active GTP-bound forms. This switching is catalyzed by guanine-nucleotide exchange factors (GEFs) that activate the GTPases and by GTPase activating proteins (GAPs) that inactivate them. When in the active state, GTPases that regulate intracellular trafficking interact with downstream effectors. These effectors and their binding proteins mediate the various steps of vesicle life, from formation at the donor compartment to fusion with the acceptor compartment.\(^2\)