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Review

The early secretory pathway in development: A tale of proteins and mRNAs

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ABSTRACT

The secretory pathway ensures the proper delivery of secreted proteins to the extracellular medium and of transmembrane proteins to almost all membrane cellular compartments. During their transport in the different compartments making up this pathway, newly synthesized proteins are modified and dispatched to their final destinations. So far, this pathway has mostly been studied in tissue cultured cells or yeast but recently, mutations in genes encoding key proteins of this pathway have been shown to lead to severe developmental defects in different model organisms.

In this review, we describe how specific steps of epithelial, cartilage, notochord and brain development as well as body axis formation are controlled by the early secretory machinery illustrating that it is as crucial as transcriptional programs.

Contents

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1. A short introduction to the early secretory pathway

Cell differentiation is mostly controlled at the transcriptional level but these programs need to be implemented and regulated by a number of cellular pathways, one of them being the secretory pathway.

Proteins destined for secretion to the extracellular space or delivery to the plasma membrane and most of the cellular membrane-bound organelles (except for mitochondria) travel through the secretory pathway, which is made up of a series of membrane compartments, whose identity is defined by a specific subset of resident proteins and unique morphological features [1].

Newly synthesized cargo proteins enter the exocytic pathway at the endoplasmic reticulum (ER) where they fold, may oligomerize and acquire oligosaccharide chains before exiting the ER. This takes place at specific sites called ER exit sites or tER sites that are characterized by the presence of COPII-coated vesicles [2]. The COPII coat machinery includes the small GTPase Sar1 and its transmembrane GEF (guanidine exchange factor) Sec12, as well as two protein complexes, Sec23/24 and Sec13/31 complex. Upon COPII coat assembly, newly synthesized proteins are sorted and enriched in the forming buds by means of cargo receptors or by interacting directly with COPII subunits (reviewed in [3]).

Upon exiting the ER, the newly synthesized proteins reach the Golgi apparatus. Although the way protein cargo moves through the Golgi is a matter of intense debate, what is clearly emerging is a role for the COPI-coated vesicles in this movement. The COPI coat comprises seven subunits that assemble on the Golgi membrane, generating COPI-coated vesicles. These vesicles have been shown to mediate the retrograde movement of resident Golgi enzymes within the Golgi stack, and of cargo receptors and ER resident proteins back to the ER [4]. In addition, a number of specific cargo molecules are reported to undergo anterograde transport in COPI vesicles (reviewed in [4]).

The Golgi apparatus is where proteins are further modified, proteolytically cleaved and sorted. One important Golgi-based modification is the maturation of complex oligosaccharides moieties attached on these proteins either through N- or O-linked glycosylation. Although not fully understood, protein glycosylation is crucially important for their biological function [5]. An emerging family of developmental disorders, the congenital disorders of glycosylation (CDG) that are characterized by mutations in genes encoding proteins affecting O- and N-linked glycosylation (http://www.euroglycanet.org/) exemplifies its importance [6]. Interestingly, a new CDG group has been recently associated with deficiencies in subunits of the conserved oligomeric golgi (COG) complex [7], a tethering complex involved in Golgi to ER transport [8].

Mirroring the multiple and complex functions that it carries out, the Golgi apparatus has a remarkable architecture. It is characterized by stacks of flattened membrane-bound compartments, the Golgi cisternae, a unique feature of this organelle. One group of proteins involved in this organization are Golgins that comprise long coiled-coil proteins, such as golgin-97 and GM130 [9,10]. Another class comprises GRASP55 and 65 that were originally identified as Golgi stacking factors in vitro and are now shown to control more aspects of the Golgi organization during interphase but also at the onset of mitosis (reviewed in [11]).

At the exit face of the Golgi (Trans Golgi Network), the modified proteins are dispatched toward their final destination. In polarized exocytosis, cargo carriers are tethered to specific plasma membrane sites by the exocyst, an octameric complex, both in epithelial cells [12] and yeast [13].

Transport within the secretory pathway involves a series of membrane targeting and fusion events between cargo-containing carriers and target organelles. Correct targeting is coordinated by Rab GTPases and tethering factors that are single coiled-coil proteins or multimeric complexes, such as TRAPP [14] and COG (see above). Membrane fusion is mediated by NSF (NEM sensitive factor) ATPase, SNAP (soluble NSF-attachment protein), and SNAREs (SNAP receptors) [15–17]. First, a very tight trans-SNARE complex is formed by α-helical bundles of the cytoplasmic domains of one vesicle (v)-SNARE and 3 target (t)-SNARE domains. This is thought to bring the two membranes close enough to allow their fusion. SNAP then binds to the trans-SNARE complex allowing the recruitment of hexameric ATPase NSF that dissociates the complex into its individual SNARE components, priming them for recycling and another round of vesicular transport.

An increasing number of mutations in genes encoding proteins functioning along the secretory pathway are associated with genetic diseases and developmental defects (summarized by [18,19]; and reviewed in [20]). Here, we will focus on how development of epithelia, skeleton, notochord and neurons as well as the body axis specification are affected by mutations in secretory pathway-related genes.

2. Epithelial development

2.1. Epithelial polarity, junctions and Golgi-based sorting

Animal bodies contain many epithelial tissues. Although epithelia acquire morphological and functional adaptations depending on the organ that are found, they share a number of characteristics, such as the fact that they are polarized and have physical cell–cell junctions.

Establishing epithelial cell polarity requires the interplay of at least three polarity complexes (Bazooka/PAR6/aPKC; Scribble/Lethal giant larvae/Discs large; and Crumbs/Disc lost/Stardust) [21,22] that polarize exocytic events by interacting with SNARES. However, this is beyond the scope of this review as thus far, the involvement of the early secretory pathway has not been shown [20,23].

On the other hand, the formation of epithelial cell junctions requires protein sorting at the TGN. One type of cell–cell junctions are the adherens junctions, whose formation depends on the deposition of E-Cadherin and Armadillo/β-Catenin [24] in addition to the membrane-associated Bazooka and Crumbs polarity