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MINI-REVIEW

Key roles of Arf small G proteins and biosynthetic trafficking for animal development

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ABSTRACT

Although biosynthetic trafficking can function constitutively, it also functions specifically for certain developmental processes. These processes require either a large increase to biosynthesis or the biosynthesis and targeted trafficking of specific players. We review the conserved molecular mechanisms that direct biosynthetic trafficking, and discuss how their genetic disruption affects animal development. Specifically, we consider Arf small G proteins, such as Arf1 and Sar1, and their coat effectors, COPI and COPII, and how these proteins promote biosynthetic trafficking for cleavage of the *Drosophila* embryo, the growth of neuronal dendrites and synapses, extracellular matrix secretion for bone development, lumen development in epithelial tubes, notochord and neural tube development, and ciliogenesis. Specific need for the biosynthetic trafficking system is also evident from conserved CrebA/Creb3-like transcription factors increasing the expression of secretory machinery during several of these developmental processes. Moreover, dysfunctional trafficking leads to a range of developmental syndromes.

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Introduction

Biosynthetic trafficking builds and renews all cells. This general role can be viewed as constitutive. However, certain developmental processes require specific responses of the secretory system. For example, a particular developmental process may require a significant increase to total secretory output, as is the case when the *Drosophila* embryo increases its plasma membrane (PM) content by ~25-fold in a few hours,[1] or when the vertebrate embryo produces and secretes huge amounts of extracellular matrix (ECM) for bone development.[2] Alternately, the development of polarized cells requires specific proteins to enter the biosynthetic trafficking system and then be targeted to PM sub-domains.[3] Here, we review developmental processes with specific dependencies on biosynthetic trafficking and the molecular mechanisms involved. We focus on the Arf family of small G proteins, their upstream regulators and their downstream effectors. Implications for developmental diseases and disorders are also highlighted.

An overview of biosynthetic trafficking and its regulation by Arf family small G proteins

The biosynthetic pathway involves a complex network of membrane bound organelles that deliver macromolecules to the PM and extracellular space (Fig. 1A). The endoplasmic reticulum (ER) is an extensive, partially tubulated membrane network that is continuous with the outer nuclear membrane and spans a large volume of the cytosol.[4] Newly synthesized proteins translocate from ribosomes into the lumen of the ER, a process coordinated with protein folding and membrane integration.[5,6] From the ER, proteins are trafficked to the Golgi apparatus. The Golgi is a system of membrane compartments arranged in flattened stacks referred to as cisternae, with *cis* cisterna engaged in ER trafficking and *trans* cisterna directing transport toward the PM.[7-9]

Trafficking at the ER and Golgi is regulated by the Arf family of small G proteins. Anterograde vesicle transport from the ER to the Golgi is regulated by family member Sar1.[10,11] Sar1 organizes COPII coated vesicles for budding of cargo from ER exit sites.[9,12] Sar1 is activated at ER membranes by its guanine nucleotide exchange factor (GEF) Sec 12. Sar1-GTP then recruits the cargo adaptor complex of Sec 23 and Sec 24, which recruits the COPII coat components Sec 13 and Sec 31. Sec 23 is also a GAP for Sar1. In a negative feedback loop, coat assembly induces Sec 23 activity leading to Sar1 GTP hydrolysis and coat disassembly.

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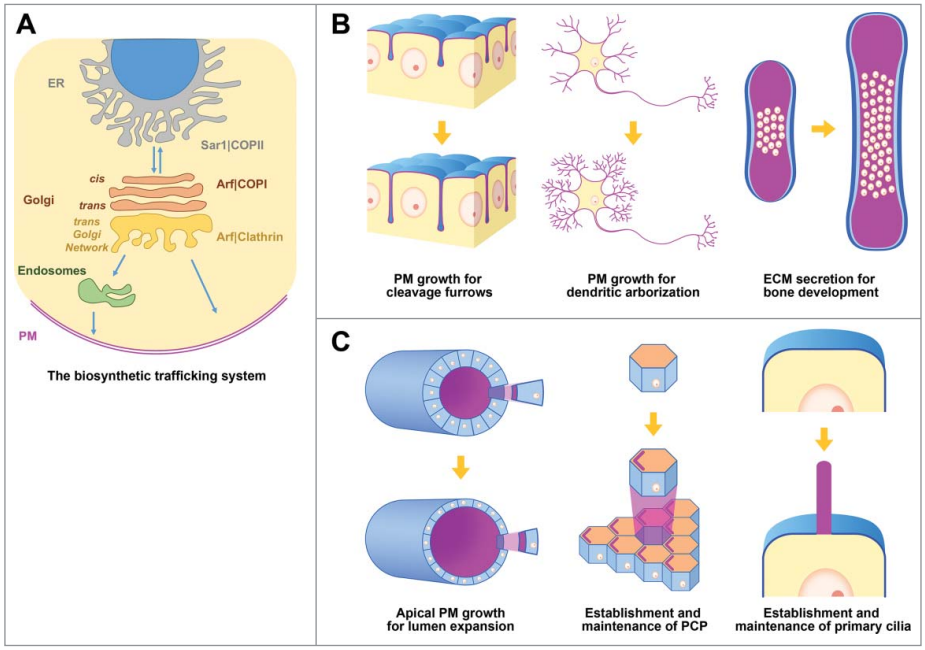

Figure 1. Roles of biosynthetic trafficking for animal development. (A) The biosynthetic secretory pathway and its molecular regulators. The Sar1 small G protein promotes anterograde traffic from the endoplasmic reticulum (ER) by promoting the assembly of COPII-coated vesicles. At the Golgi, Arf1, Arf4, and Arf5 regulate retrograde COPI vesicle trafficking. At the *trans* Golgi network (TGN), Arfs assemble clathrin-coated vesicles to deliver biomolecules to endosomal compartments and the plasma membrane (PM). (B) Developmental processes under high secretory demand. Left, delivery of membrane to cleavage furrows promotes their ingression for embryo cleavage. Middle, PM growth promotes dendritic growth and arborisation. Right, secretion of ECM promotes bone development. (C) Developmental processes regulated by biosynthetic trafficking in polarized epithelial cells. Left, increases in apical membrane and apical ECM secretion promotes lumen growth in epithelial tubes. Middle, trafficking of polarity determinants promotes the establishment and maintenance of planar cell polarity. Right, biosynthetic trafficking promotes the formation and maintenance of primary cilia. See main text for details.

Outward material flow is, in part, counterbalanced by retrograde transport within Golgi stacks and from the Golgi to the ER. This retrograde transport retrieves transport machinery for re-use. The COPI coat mediates the budding events involved and also contains adaptor proteins for recruiting cargo.[9] COPI is recruited to Golgi membranes by the small G proteins Arf1, Arf4, or Arf5. At the Golgi, the Arf GEFs GBF1 and BIG1/2 activate Arf small G proteins and interact with COPI subunits and cargoes. Similar to the regulation of COPII coats, Arf GAPs induce the GTP hydrolysis of Arfs for COPI coat disassembly and recycling.[10,11,13]

For trafficking to the PM, cargo-ladened vesicles exit the Golgi from the *trans* Golgi network (TGN), a dynamic membrane compartment associated with multiple clathrin adaptors responsible for the sorting of cargoes into secretory vesicles destined for endosomes and the PM.[8] Various classes of adaptors are found at the TGN, including the AP1 family, the GGA family, Epsin related proteins, and the exomer complex.[8] Under the regulation of different small G proteins from the Arf and Rab families, including Arf1, Arf4, Arf-like-1 (Arl-1), Rab6, and Rab8, adaptors connect cargo proteins to clathrin coated pits that bud from the Golgi.[10,11,14]

Membrane supply for cleavage of the Drosophila *embryo*

The early *Drosophila* embryo develops as a syncytium.[1,15,16] After 9 nuclear divisions at the center of the embryo, nuclei move to the embryo periphery and continue their synchronous nuclear divisions without cell division. At the periphery, the nuclear divisions become coordinated with phases of PM growth. From interphase to metaphase, partial cleavage furrows ingress around each nuclear compartment, providing anchorage for mitotic spindles and preventing the collision of neighboring spindles. From metaphase to telophase, the furrows regress, and for the next cycle, new furrows form around each daughter nuclei. This synchronized growth and dissolution of PM furrows occurs through cycles 10–13. At cycle 14, furrow ingression is dramatically increased and not reversed. Instead, the furrows become the lateral and basal PM of ~6000 columnar cells. These PM growth periods increase total PM area by ~25-fold to form the blastoderm (Fig. 1B).

Exocytic trafficking is a major contributor to the inward PM growth of cleavage furrows. Although not cellularized, each nucleus of the syncytial embryo

organizes its own ER and Golgi membrane systems.[17] The activity of Golgi Arf-GEFs is needed for furrow ingression,[17] and Arf1 localizes to the Golgi and is needed for furrow ingression,[18] Golgi organization and Golgi COPI coats.[19] Additionally, Arl1 promotes the Golgi localization of the golgin Lava Lamp,[20] which is important for dynein-mediated translocation of Golgi elements toward the embryo surface where the PM is found.[21,22] Post-Golgi trafficking to the PM depends on the exocyst complex. The exocyst complex localizes to PM domains near the embryo surface,[23] where new membrane inserts.[24] The small G protein RalA localizes to the PM and is required for recruiting the exocyst complex.[25] Both RalA and the exocyst appear to recruit Rab8-positive Golgi vesicles and Rab11 vesicles to the PM.[25,26] These studies outline a biosynthetic pathway critical for this developmental stage of high plasma membrane growth.

Recently, the Arf GAP Asap was found to promote Arf1 localization at the Golgi for furrow ingression.[19] Although an Asap-Arf1 interaction site contributed to furrow biosynthesis, no evidence for Asap at the Golgi was found. Instead, Asap localized primarily to the PM, and thus may displace Arf1-GTP from this or other post-Golgi membranes for recycling to the Golgi. Such recycling may optimize Golgi output to meet the high demand of furrow biosynthesis. Intriguingly, Asap becomes sequestered to the nuclear region just before the onset of furrow regression, a period also marked by mild alterations to Golgi structure. Thus, cell cycle regulation of Asap localization may help couple Golgi output with the furrow ingression-regression cycles of the early embryo.

Membrane supply for dendrite and synapse growth

Neurons can gain a huge surface area to form axons and dendrites for cell-cell communication throughout the body. Most neurons develop multiple branched dendritic extensions that are capable of integrating various incoming signals.[27] The secretory pathway plays a significant role in dendritic growth and arborisation[28] (Fig. 1B). In particular, the Sar1-COPII axis is required for dendritic growth. Removal of Sar1 from either *Drosophila* neurons or cultured rat hippocampus neurons leads to Golgi morphology defects and reduction of dendritic extensions, without effects on axonal growth.[29] The position of the Golgi is normally polarized within neurons such that post-Golgi trafficking is directed toward growing dendrites.[30] Moreover, neurons differ from other cells in that they possess individual structures termed Golgi outposts that are enriched in dendrites versus axonal extensions.[29,30] Perturbations of Golgi Arf GEFs or Arf1 reduce dendritic growth.[30] Arf4 has also been implicated in dendritic growth of the hippocampus, as mice heterozygous for a Arf4 null allele have behavioral and cognitive disabilities that correlate with abnormal dendritic growth, and Arf4 loss or gain leads to reduced or increased dendritic growth, respectively, in culture.[31] Thus, similar to the syncytial *Drosophila* embryo, biosynthetic machinery is essential for the total membrane growth requirement of dendritic networks.

Additionally, biosynthetic trafficking contributes to neuronal synapses, the specialized membrane domains responsible for the release, detection and uptake of neurotransmitters.[32] In *Drosophila*, Arl1 and the Arf-GEF Gartenzwerg (Garz; a GBF-1 homolog) promote Arfaptin function at the Golgi, and the 3 proteins act together for the development of synapse numbers.[33]

ECM supply for bone development

Bones are essential for the structure and movement of vertebrates. Most bones develop through endochondral ossification.[2,34] Mesenchymal cells migrate to sites of bone development and differentiate into chondrocytes to deposit a cartilage template. Ossification is then mediated by osteoblasts, which mineralize the cartilaginous template. These steps require massive amounts of ECM secretion (Fig. 1B).

For the deposition of cartilage, chondrocytes secrete ECM components including specific collagens and proteoglycans.[2] Mutations affecting these ECM components are associated with developmental diseases such as skeletal dysplasias.[35,36] Significantly, disruptions to biosynthetic trafficking also leads to skeletal development defects.[36] For the ER, mutations affecting components of the COPII coat (Sec 13, Sec 23a, Sec 24d, or the small G protein Sar1b) are all associated with impaired skeletal development. In particular, the autosomal recessive syndrome cranio-facial-sutural dysplasia (CLSD) maps to a mutation affecting a conserved phenylalanine residue of Sec 23a.[37] Fibroblasts from CLSD patients display abnormally enlarged ER membranes that contain increased and often excessively tubulated ER exit sites.[37,38] *In vitro* experiments have also shown that the disease mutant of Sec 23a is unable to recruit members of the outer COPII coat, Sec 13 and Sec 31.[38] Moreover, a nonsense mutation producing an early stop codon in zebrafish Sec 23a leads to malformations of craniofacial cartilage associated with abnormal ECM deposition.[39] Similarly, depletion of Sec 13 in human fibroblasts impairs collagen secretion, and loss of Sec 13 in zebrafish leads to craniofacial abnormalities resembling those with Sec 23a disruption.[40] Sar1b knock-down in zebrafish embryos also leads to abnormal craniofacial skeletal development with retention of

collagen in intracellular compartments, abnormalities accompanied by additional multi-organ effects.[41] A second autosomal recessive skeletal disorder, osteogenesis imperfecta, has been linked to mutations of the COPII coat component Sec 24d.[42,43] Fibroblasts from patients with this disorder display enlarged ER membranes that retain ECM components,[42] and similarly, zebrafish and medaka mutants of Sec 24d display distended chondrocyte ER membranes, sub-cellular retention of ECM components, and skeletal malformations.[44,45]

As for ER machinery, Golgi trafficking machinery has been recently implicated in bone disorders.[46] Heterozygosity for a mutation of the ARCN1 gene, encoding the δ subunit of the COPI coatomer, was linked to human craniofacial syndromes. Knockdown of ARCN1 in fibroblasts induces the ER stress response and disrupts ECM transport, and Arf GEF inhibition phenocopies the ARCN1 knockdown, implicating COPI recruitment by Arf GEFs and Arfs.

Secretion for lumen development in an epithelial tube

The development of epithelial tubes is essential for animal physiology. The *Drosophila* tracheal system is an excellent model for tube morphogenesis *in vivo*. It is a segmented and hierarchical network of air-filled tubes that deliver oxygen throughout the body.[47,48] An essential element of a tube is its lumen. Polarized secretion of apical PM determinants, such as the transmembrane protein Crumbs, and lumen ECM materials plays an essential role in lumen expansion and regulation.[49,50] (Fig. 1C). In the *Drosophila* tracheal system, *sar1* mutants display ER and Golgi morphology disruptions, sub-cellular retention of tube lumen materials, and decreased tube lumen diameters.[51] Disruptions of COPII secretory machinery phenocopy these tracheal disruptions.[51,52] Thus anterograde trafficking via COPII vesicles seems to be required for lumen expansion. Whether the secretion of a specific COPII cargo or simply general trafficking is required remains unknown. However, mutations affecting the COPII component Sec 24 were shown to have cell autonomous effects on lumen development,[52] and ER export of the apical membrane determinant Crumbs requires Sar1 and COPII.[53]

At the Golgi, trafficking through Arf1 and the COPI complex also plays an essential role in lumen expansion. Without the COPI components γCOP or δCOP, Golgi and ER membrane organization becomes irregular, secretion of luminal proteins is disrupted, Crumbs levels at the apical PM are lower, and tube diameter decreases.[54] The Arf GEF Garz is also needed for tracheal tube development. Garz normally localizes to the *cis* Golgi of tracheal cells, and in the absence of Garz, Golgi localization of Arf1 and COPI coatomer are both dramatically reduced, and ER-Golgi organization is compromised.[55,56]

Exocytosis for notochord and neural tube development

In chordates, the notochord plays important structural and signaling activities. The notochord is derived from chordamesoderm which elongates along the anterior-posterior body axis through cell-cell intercalation and secretes ECM for its structural integrity.[57,58]

The cell-cell intercalation events that elongate the notochord depend on PM domains gaining distinct molecular composition polarized in the plane of the tissue (planar cell polarity; PCP)[59] (Fig. 1C). Recent work indicates that Arf1 and its effector AP-1 are required for controlling PCP in different tissues of *Drosophila* and zebrafish embryos. Disrupting Arf1 or AP-1 activity leads to PCP defects in the *Drosophila* wing. Arf1 and AP-1 colocalize to *trans* Golgi membranes of the cells involved and promote the biosynthetic trafficking of the PCP protein Frizzled.[60] Interestingly, expression of a constitutively active Arf1 construct in zebrafish embryos resulted in abnormal organization of the notochord and shortening of body length.[60] In addition to its elongation, the notochord must also secrete ECM to support body structure. In zebrafish, loss of COPI subunits or Arf GEF activity leads to notochord defects associated with disrupted ER-Golgi structure and defects in ECM secretion.[61] Thus, Arfs and biosynthetic trafficking may be important for both the PCP and the ECM of the notochord.

PCP, cell-cell intercalation and asymmetric cell division also organizes the neural tube in vertebrate embryos. The neural tube is derived from the neural plate, a portion of the ectoderm located dorsally to the notochord that gives rise to the central nervous system.[62] The COPII coat component Sec 24b is critical for the trafficking of the PCP protein Vangl2 and proper neural tube development in mice,[63,64] and 4 mutant variants of the Sec 24b gene have been linked to neural tube closure defects in humans.[65] Loss of Sec 23a in mice also causes severe neural tube opening and embryo lethality, although the neural tube defect observed in Sec 23a mutant embryos arises from a reopening of a closed neural tube rather than failure of primary closure.[66]

Exocytosis for ciliogenesis

Primary cilia are microtubule-based, PM protrusions with a specific membrane composition. Cilia mediate

developmental signaling, and mutations affecting cilia structure lead to a class of diseases called ciliopathies. Trafficking of specific cargo to the base of cilia is essential for ciliogenesis and cilia function.[67,68] (Fig. 1C). A clear example of trafficking from the Golgi to the primary cilium has been documented for rhodopsin transport in frog photoreceptor cells[69] At the Golgi, Arf4 and its Arf GAP ASAP1 help recruit rhodopsin as vesicle cargo.[70,71] Arf4 and ASAP1 directly bind rhodopsin through 2 different protein sequence motifs.[70,71] Moreover, ASAP1 acts as a scaffold to organize multiple proteins for rhodopsin trafficking. ASAP1 binds Rab11 and its interacting partner FIP3, and recruits the Rab GEF Rabin8 which in turn binds and activates Rab8.[70-72] Rab8 and Rab11 target rhodopsin-containing vesicles to the cilia, apparently by tethering of the vesicle to the cilium base through the exocyst complex component Sec 15.[69] Thus, an Arf-Rab cascade directs rhodopsin trafficking from the Golgi to the primary cilium of photoreceptor cells.

Transcriptional regulation of biosynthetic machinery during development

Biosynthetic trafficking must be linked to transcription and translation of the cargo being transported. Moreover, a conserved transcription factor family plays a widespread role in increasing the expression of the secretory machinery. The CrebA/Creb3-like transcription factors recognize a consensus motif within enhancer regions of genes for secretory machinery and promote their expression.[73] This expression is critical for animal development. As examples, CrebA drives expression of Sar1 and COPII components to promote dendritic growth in *Drosophila*,[74] Creb3l2/BBF2H7 promotes transcription of COPII coat genes for ECM secretion and skeletal development in mice and zebrafish,[75] and CrebA induces secretory gene expression for tube morphogenesis and secretion of the *Drosophila* salivary gland.[73,76] Widespread use of a conserved transcriptional mechanism for the expression of biosynthetic trafficking machinery indicates the importance of induced biosynthetic trafficking for specific developmental processes.

Concluding remarks

We have reviewed how specific developmental processes rely on increases to total biosynthetic output or on the biosynthetic trafficking of specific proteins. The membrane trafficking machinery involved can be upregulated for particular developmental processes, and is coordinated locally by Arf family small G proteins. Such trafficking is critical for major developmental processes, and abnormal trafficking results in developmental syndromes.

Numerous questions remain. For many developmental processes, it is unclear whether the biosynthetic trafficking of specific cargo is critical. In such cases, the phenotypes resulting from removal of trafficking machinery should mimic those resulting from removal of cargo. How such cargo finds its final destination would also require definition. For cases in which a general increase to biosynthesis is required the amount of biosynthetic machinery could become limiting. How widely used are CrebA/Creb3-like transcription factors for elevating expression of biosynthetic trafficking machinery, and do distinct transcriptional programs exist for such increases? How is the Golgi positioned for polarized secretion in different cell types? How prevalent are specific developmental roles of trafficking machinery isoforms, and are such roles due to tissue-specific expression or unique protein activities of the isoforms? Moreover, post-translation modifications and interactions with cargo can modify the behavior of biosynthetic trafficking machinery,[77] but have not been evaluated during animal development. Thus many avenues are open for pursuing a fuller understanding of the biosynthetic trafficking that underpins animal development.

Disclosure of potential conflicts of interest

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